THESIS

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METHYLPROPYLCARBINOL URETHANE

PHYSIOLOGICAL ACTION

IN

ANIMALS,

By

John Donald, M.D.

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Vol. I.

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FOREWORD and ACKNOWLEDGMENTS.

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Several years ago, when I held the position of Senior Anaesthetist in Glasgow Royal Infirmary, I was seriously impressed with the fatalities and dangerous conditions arising during general anaesthesia. These were more commonly met with during chloroform anaesthesia, and did not by any means occur only after, or mostly after long anaesthesias; they occurred as often during the induction period. There seemed to be a capricious element about chloroform which could not be accounted for. In some cases, the collapse came with surprise to the administrator and without warning. Trouble showed itself sometimes with the strongest men. In these latter cases, the cause may have been struggling during induction, exhausting the heart in a purely physical way; or the patient's dread of the ordeal may have been the cause. Ether was not so often accompanied by dangerous manifestations during the anaesthesia; but sometimes the patient took bronchitis or pneumonia thereafter.

Concluding, that in the main, dangers from chloroform were due to overdose, and those from ether were post-anaesthetic, I endeavoured to eliminate both dangers by using chloroform with a dosimetric machine, - that of Vernon Harcourt being selected. In this way, one could tell to a decimal at any moment the exact strength of the vapour of chloroform in the atmosphere breathed, and keep it at the same strength. This, however, was not always successful, although most useful in long abdominal operations, especially when a precursor of morphia had been administered. The anaesthesia was often too light, and shock impressions were experienced from insufficient anaesthesia.

There seemed to be a clamant need for a safer anaesthetic.

At this time Hedonal was being used, and I thought it promised better results. It seemed from reports and a limited personal experience, to have none of the evil effects of either chloroform or ether. I then determined to examine in a scientific way what the action of Hedonal was, particularly in the mammal, so that one might have definite information to go upon for use in the human subject. Fully two years were spent at this time in laboratory work and definite results obtained, which are here recorded.

Later, when holding a post as Surgeon for Diseases of the Throat, Nose and Ear, many of the nose operations were carried out with cocaine and adrenalin applied locally by pledgets; but even here, troubles arose. Reports of death from cocaine poisoning came from different centres. In my own experience, a patient sitting on a form with cocaine pledgets in the nostrils (5%), died before anything was attempted in the way of operation. An investigation by the authorities was made at this time, and surgeons who had experience with anaesthetics were asked for their opinion and for their suggestions as to how local anaesthetics - cocaine in particular - might be administered with greater safety. I then recorded my recommendations, which need not be detailed here. At this time further research on the subject was carried out, with special regard to the action of Hedonal on the frog.

The study which has now been completed embraces various investigations which I have not seen dealt with in any publication. It is the only experimental work on the subject which has been done in this country (Great Britain): I have at least seen no publications of this kind, nor could I hear of any such when inquiring through the medical press, the large German year-books of medicine, nor when asking the manufacturers themselves.

Upwards/

Upwards of one hundred original tracings or photographs are included in this study, the mathematical record of facts has been made a prominent feature, ahd the ground covered is extensive. In any scientific papers on this subject, I have never seen any tracings produced, - this has been unfortunate.

Apart from the anaesthetic field altogether, I feel that Hedonal has not been used medically as it might have been. If I have not been dogmatic in stating how it may be used by the clinician, I feel that by presenting to anyone who is interested, the actual tracings in considerable number, and under many different physiological conditions, the medical man will thus be able to see for himself in what ways Hedonal may be used, much better than he would if only a verbal report were placed in his hands. Thus I feel sure that the use of Hedonal in the clinical field might be much extended, especially for diseases of the nervous system, blood pressure, or of the heart.

I modestly hope that the great labour which has been expended may not have been in vain.

All the experiments have been carried out in the Physiological Department of Glasgow University. The work on Hedonal done by others, although limited, has here been recorded very accurately, and at some length, because occasionally the reports of different authors have seemed to be in conflict. The reports on Respiration for an example, are most confusing. When examining the reports of Dreser, Burkhardt and Kummel (see p.73), one cannot have a definite idea whether there is any dangerous effect on respiration or not.

As the original papers on Hedonal were mostly in the Russian language, and were then translated into German, with the advent of the Great War difficulties naturally arose in getting access to these.

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I have received much assistance from the Librarians of the Royal College of Surgeons, the Royal College of Physicians, and the Royal Society of Edinburgh, who courteously gave me every facility for consulting their works on this subject. I wish also to mention the library of the University of Munich, from which I got some references of the greatest importance in the work by Dreser.

Lastly I have to thank the Bayer Company who are the manufacturers of the drug; they gave me all their printed papers and made further inquiries for me in Germany regarding such literature.

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SECTION I.

Introduction.

Advent of Hedonal.

Work done by others:-

(1) Oré.
(2) Schmiedeberg.
(3) Krawkow.
(4) Dreser.
(5) Lampsakow.
(6) Burkhardt.
(7) Karlowitsch.
(8) Jeremitsch.
(9) Fedoroff.
(10) Sidorenko.
(11) C.M.Page.
(12) Rawden Veale.

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INTRODUCTION.

Scientific men have been for more than half a century seeking for an ideal anaesthetic; but it has not yet been found. Chloroform is comparatively easy to administer, but its great potency as a toxic agent in the action of the heart has made many workers afraid to use it. Many if not all cases of delayed chloroform poisoning show fatty degeneration of the liver, kidneys or heart, or all of them. Ref. 51. Ref. 44.

Ether is not so toxic, but it has some qualities of its own which are objectionable. Apart from the tendency to catarrh already referred to, it does not give such complete muscular relaxation as chloroform, and if deeper narcosis is necessary the "Clover" inhaler requires for its manipulation one having special experience in its use. The odour of ether is very pungent and disagreeable by inhalation. In the words of Felix Rood - "To anyone who has inhaled a breath of a stray vapour of ether, it must always be a source of surprise, that serious complications are not always produced by a long anaesthesia, as we know they are." These facts I have observed personally during five years' experience in Glasgow Royal Infirmary as Senior Anaesthetist. Ref. 62. Ref. 33. Ref. 40. Ref. 62.

To obviate the catarrhal danger which may result from the administration of ether, Dr Dudley Buxton used it mixed with olive oil as a rectal enema in the year 1893. This was quite suitable in most cases except abdominal operations, as it caused undesirable distension of the bowel, and sometims post-operative diarrhoea. The work of L.Burkhardt on intravenous chloroform and intravenous ether, was in his experience anything but a success. His work in this respect dates from the year 1909. In more recent years, Ref. 55. Ref. 45 Ref. 57.

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an attempt with intravenous ether was again made, with a view to getting quit of the catarrhal danger. The ether (5%) was dissolved in normal saline and was perfused through one of the veins of the arm. Ether is about 7 times weaker than chloroform, so that it was necessary to throw a fairly large quantity of total liquid into the vascular system. In large operations as much as 1500 c.c. might be required. This solution led to oedema in the pendulous parts of the body, such as the buttocks. The face would occasionally show oedema. A 10% solution was then used to obviate this difficulty, and make a smaller quantity of total liquid suffice. The result was that in some cases haemoglobinuria was produced. Finally a 7.5% solution of ether was used with better success. Ref. 57.

The medical profession still looked for a more perfect anaesthetic or a safer method of employing the known anaesthetics which were in their possession. A kind of compromise between a general and a local anaesthesia was arrived at. Lumbar puncture, (introduced by Bier in the year 1899), and the intraspinal injection of quite a number of drugs, was much practised for several years. Among such are cocaine, stovaine, alypine, novocaine and tropococaine. The method fell into disuse about 8 years ago, The drug sometimes passed too high in the spinal canal and not only anaesthetised the upper limbs, but in some instances stopped the muscles of respiration through the respiratory reflex centre in the medulla. Besides this immediate danger, there have been found more remote and lasting effects resulting from this method, for example, paralytic conditions which have remained more or less permanent in such regions as the bladder and bowel, and even in the lower limbs. Patients have died from the drug having passed direct to the medulla, the pelvis having been raised too high. Death has even occurred six months after the injection from softening of the brain. Ref. 66.

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I do not believe it is possible to obtain an ideal or perfect anaesthetic. As anaesthesia is contrary to nature, no form can ever be perfect. This, however, is no reason why the profession should not seek for one as near perfection as possible.

George Crile has gone into this subject very scientifically, when speaking of the kinetic theory of shock. In his paper, when defining ideal conditions for anaesthesia, he coins a word "anoci-association", by which he means a condition, not only whereby the voluntary movement and insensibility to pain are abolished, but where the brain does not receive such stimuli at all, even though not perceived by the patient. In this regard, Crile believes ether by inhalation is only a veneer. The patient does not feel, but stimuli reach the brain and actually cause material change in the nerve cells there, whether such stimuli be of the nature of fear (functional) or traumatic (physical). In both these forms Crile has shown microscope slides, in which are seen the changes mentioned. If the stimulus, or stimuli, (either functional or traumatic) be strong enough, there may result exhaustion or even death. Crile therefore proposed that, while the brain should be made unconscious of pain, stimuli should not be allowed to reach the brain. These conditions he considers are achieved (1) by removing fear, (2) by blocking all the sensory nerves in the surgical area by novocaine injection, and (3) by administering gas and oxygen by inhalation.

Ref. 49.
Ref. 50.

It has been the common experience with new discoveries in medicine or surgery that there has been an undue lauding of the virtues of such discovery at the beginning, before sufficient experience had been gained. Later it has often happened that there has been a change in the opposite direction like the swing of a pendulum. Such methods or discoveries have then fallen for some time into disuse, to/

to be again used after further experimentation. This has been the experience with the advent of chloroform, and of ether, with spinal analgesia and also with intravenous anaesthesia.

Hedonal has fallen very much into disuse. The purpose of the work here completed has been to let the profession see whether indeed it would not be worth while to introduce Hedonal again into anaesthetic practice. I personally think that the apparatus for its intravenous administration should be installed in all large hospitals, and that it should be used in the cases where chloroform and ether are obviously unsuitable.

I also strongly advocate its use by the physician in the strictly medical sense.

THE ADVANTAGES OF HEDONAL.

1. There is little or no excitement during the induction of narcosis. The patient does not experience the choking feeling so common with inhalational anaesthesia - especially ether; breathing continues as before unaffected, the patient falling into natural sleep.
2. There is great muscular relaxation, whereby it is possible to manipulate the under surface of the liver without shock resulting.

   I personally have always felt, particularly with chloroform, that whenever complete relaxation in the abdomen was obtained, the danger from cardiac collapse from overdose was not far distant. With ether, complete muscular relaxation is not so easily produced at all, apart from the question of danger.
3. The urine never shows albumen, haemoglobin, nor casts, and as Hedonal is a diuretic it is superior to morphia.
4. Fatty degeneration does not occur in the liver, kidneys nor heart: this is almost constantly found in delayed chloroform poisoning.
5. Hedonal does not irritate the respiratory tract: it is not excreted by the lungs and is in this way superior to ether.
6. In conditions following haemorrhage, either acute or long continued, when an operation must be carried out, Hedonal introduced intravenously is/

is in my opinion the safest anaesthesia known. The quantity of warm normal saline perfused as the drug-solvent, meets the condition of unfilled arteries.

With patients of this kind, when a severe operation must be carried out, it is common for surgeons first of all to begin the continuous introduction of warm normal saline by needles in both breasts before inhalation is started.

7. Hedonal is not so volatile as ether and can therefore be introduced at a higher temperature.

8. As a precursor to chloroform, it can reduce the quantity of chloroform required very considerably.

DISADVANTAGES OF HEDONAL.

1. In long operations of two hours or more, there may be too much liquid introduced (apart from its composition) when Hedonal is the anaesthetic chosen. This may be followed by oedema in pendulous parts of the body.

2. Plethoric patients, for the reason given above, are not suitable.

3.. The apparatus for continual dropping is not portable, and thus as an anaesthetic the intravenous use of Hedonal will be more restricted to institutions.

THE ADVENT OF HEDONAL.

Hedonal or Methylpropylcarbinol Urethane, which has the formula $C_6H_{13}O_2N$, was first investigated by Dreser and Bonhoeffer in company in 1899, the experiments being carried out primarily in fishes and frogs. It is a white powder occurring in needles like menthol, and is a derivative of Ethyl Urethane ($C_3H_2NO_2$) with the ethyl radicle displaced by the higher radicle Methylpropylcarbinol. It breaks up in the body into water, CO_2 and urea. Hedonal is not very soluble. Gwathmey states that one part dissolves in 120 at 98.6°Fah.. Naturally it is still less soluble in normal saline from which it readily crystallises out on cooling.

Ref. 20. Ref. 53. Ref. 54. Ref. 68. Ref. 43. Ref. 20.

Dose of Hedonal in the human subject:-

The dose by the mouth is usually stated to be 1 to 2 grammes.

Ref. 20.

Dreser in his early work put the dose as .5-1 gramme. Ref. 53.

Fedoroff in 1903 gave by the mouth 3-4 grammes of Hedonal as a precursor to the inhalation of chloroform, as was suggested to him by Krawkow. Ref. 39. In the first case of intravenous Hedonal narcosis in the clinic (7th Dec. 1909), Ref. 4. Fedoroff gave 2 grammes of Hedonal by the mouth as a precursor. In the greater number of such cases, however, he administered 3-4 grammes either by mouth or rectum, 1 to 2 hours before injecting. Fedoroff later on Ref 42. eliminated entirely this preliminary dose, as he considered the post-operative sleep unduly long, namely 17-20 hours. Ref. 10

The dose in very young children has been gone into quite recently (1923) by Paul Drevermann of Freiberg. Ref. 63. Up to 3 months he gives .75 to 1 gramme mixed in 30 c.c. of gruel per rectum. Children of 18 months might in some cases require 1.5 gramme. The patient is ready for operation in an hour; but some of the older infants were found to require a further aid to anaesthesia in addition, namely hypodermic injection of 5-6 c.c. of a .5% solution of Novocaine-Suprarenine.

Intravenously the dose has been stated by Sidorenko to be .04 gramme Ref. 2. per kilogramme of body weight to establish narcosis clinically.

In a case reported by Harold Upcott of Hull, the patient (an adult) Ref. 17. required 420 c.c. of a .75% solution of Hedonal in normal saline intravenously to establish narcosis for operation during 16 minutes. This represents approximately 3 grammes of Hedonal; or supposing the patient to weigh 10 stones, the quantity was at the rate of .04 gramme of body weight, as used by Sidorenko.

All the clinical workers with Hedonal (both British and Continental) have made use of the same solution - .75% in normal saline - for intravenous use. The solution as prepared by C.M.Page in this country (St.Thomas' Ref. 41. Hospital) had the following composition:-

Hedonal	7.5 grammes.
Sodium chloride	9.0 "
Distilled water	1000 c.c.

WORK ALREADY DONE BY OTHERS.

On reviewing the work which has been done on Hedonal, the subject naturally divides itself into two sections - that done clinically and that done experimentally, or work with the human subject and work with animals in the laboratory. The clinical work is naturally much more in evidence as regards quantity. The experimental has been limited to a comparatively small number of investigators, and these almost entirely Russian.

Dreser of Munich, as already mentioned, was the pioneer. Ref.53. The bulk of all the experimental work was done in the laboratory of Dr Krawkow (Petrograd) by himself and others such as Fedoroff, Jeremitsch, Lampsakow, and Karlowitsche.

In this country (Britain), as already stated, there seems to be no literature whatever relating to experimental work on this subject.

After the clinical use of Hedonal intravenously was begun Ref.5. in Russia, it was tried in this country clinically, the pioneer here being C.M.Page, of St.Thomas's Hospital, London.

ORÉ.

The advent of intravenous anaesthesia does not belong to modern times. It dates from 29th May, 1872, when the French Surgeon Oré published his experiments with Chloral Hydrate in animals. He injected from 2-6 grammes in water according to the weight of the animal, and obtained a deep narcosis from 2-5 hours, from which the animal could not be awakened, even by electric currents. Ref. 34.

Oré then applied his method in the human subject, reporting his results in 1874. He employed it in the case of a man, giving 9 grammes chloral with 10 grammes of water, divided into two injections with 5 minutes between them. There was great muscular relaxation and no bad symptoms, the accelerated pulse becoming slower and steadier. Ref. 69.

Again he reported in the same year a case where, by one injection of Chloral Hydrate, an operation for partial resection of the calcaneum was carried out. The anaesthesia was absolute and yet after the operation, the patient was wakened up immediately by currents of electricity. Ref. 35.

SCHMIEDEBERG (STRASSBURG).

Oswald Schmiedeberg was the first to propose Urethane, Ethyl Urethane, or Ethyl Carbamate as a hypnotic. This was in 1885. It was found to be very safe. The heart and lungs were not affected by it because of a group in its composition which acted like ammonia, and which opposed the narcotic group. The amino element was found to be too strong relatively to the other, making it, while very safe, ineffectual. Experiments in his own laboratory in Strassburg were carried out on the frog, rabbit, dog and pigeon. Ref. 36.

Regarding its action on the frog, Schmiedeberg states "Indeed it/

it appears scarcely possible to kill a frog with it, unless we absolutely embalm him therewith". As much as 6 grammes have been given without harm. Ref. 36. page 208. line 5.

In the dog it was found that, beginning with 1 gramme by the mouth for medium-sized animals, and increasing the dose, the animal showed staggering and a tendency to sleep when 2.5 grammes had been reached. Strange to relate, when the dose was further increased to 3 or 4 grammes, the animal did not become more drowsy - on the contrary it became more active. Evidently the amino group had been too powerful. For this reason it was considered that if the stimulating group were displaced by some higher alcohol radicle, the combination would act more powerfully as an hypnotic. Several substances were tried, such as Propyl and Isobutyl and the result hoped for by Schmiedeberg was obtained, namely, the narcotic effect was increased. There was this inconvenience, however, that the new substances formed were far too insoluble. Ref. 36. page 208. line 12. Ref. 6. page. 12. line 1.

A large report was written by Professor Krawkow in Petrograd, embracing the experimental work of Schmiedeberg, and dedicated to him on his 70th birthday. Ref. 4.

PROFESSOR KRAWKOW.

In 1908 Professor Krawkow published a long paper on the subject of Hedonal-Chloroform narcosis. In this paper he mentioned the circumstances which led him to think of such a sequence. There were several surgeons working under him in his laboratory in Petrograd, namely Fedoroff, Jeremitsch, Lampsakow, Sidorenko, Glagolen, Blagoweschenski and Karlowitsch. Experiments were carried out mainly on the dog and rabbit, - the frog has not been mentioned in this work. The experiments of Blagoweschenski dealt with the effect of combinations of poisons such as Phenocoll and Antipyrine and others. Then the experiments of Karlowitsch on the effect of doubling the strength of chloroform/ Ref. 4. Ref. 65.

chloroform vapour were ~~xkxa~~ of great interest as well.

The Hedonal-Chloroform narcosis is an anaesthetic sequence in which the patient receives 3 grammes of Hedonal by the mouth and in one hour inhales chloroform from an open mask. It was claimed for it that in this way the quantity of chloroform required for narcosis was reduced to one-third. The sequence was carried out by Krawkow in the laboratory and was for many years the routine method of preparing animals for other experiments. He had seen how very difficult it was to chloroform a dog: the animal thereafter was miserable and often sick.

After observing the effect of Hedonal intravenously in the rabbit and dog, Krawkow considered it might be useful in the clinic. It was thought, however, that the quantity required would be disproportionately large and thus inconvenient. The sequence above referred to, therefore, promised to be better, and it was proposed by him as a method fit to be used in the clinic. Krawkow states "Narcosis of this character was first employed in the year 1903 by Professor Fedoroff in his clinic." Ref. 4.

Regarding the circulation in Hedonal-Chloroform narcosis, Professor Krawkow states as a result of personal and direct observation of Fedoroff's cases in the clinic, "It is specially to be remarked the regular and full pulse which persisted right up to the termination of a protracted operation of 2½ hours." Referring to anaemic patients and those with myocarditis under this sequence, he also says "It was a source of wonder that with some of these sick persons, the pulse during narcosis was more regular and fuller than before." Ref. 4. Ref. 4.

Concerning the blood pressure in animals from the use of Hedonal intra-venously, we have the following opinion:- "Accordingly it appeared to me uncommonly interesting and significant that the blood pressure, thanks to the latent effect of the amino group on the heart,

is/

is little reduced." Ref 4

It was found that the vaso-motor centre in animals was paralized with large doses of Hedonal but he states "The heart functions remain thereby so strong, that despite the dilatation of the vessels, it keeps the pressure to almost usual and works almost unexhausted until the animal's death."

LAMPSAKOW.

Probably the major portion of all the experimental work which had been done on Hedonal up to 1912 was carried out in the laboratory of Professor Krawkow in Petrograd, by himself and several others, among whom was Dr Lampsakow.

Lampsakow published a treatise on "Effects of Hedonal on the Animal Organism" in the Russian language in Petrograd in 1902, but it does not seem to have been published in any other language. The results of his experiments, however, have been reported at some length by Krawkow in 1908. Ref 5 In the rabbit a dose of .2 gramme by the mouth causes 2 hours' sleep. There is heavy sleep for 7 hours from .5 gramme and the corneal reflex does not disappear. The animal can be wakened by prodding, after which it goes to sleep. Injection of 10 c.c. of a 1 % solution of Hedonal in water into the vein in a rabbit's ear, causes sleep at once, lasting 40 minutes.

In the dog, .3 gramme Hedonal per 1 kilogramme of body weight causes deep sleep for 7 hours. The pupil is contracted: the temperature falls 1.8° Fah.. During the sleep there was copious flow of urine. A dose of .5 gramme to the dog per kilogramme causes sleep for 15 hours.

Ethyl Urethane has no such hypnotic effect on dogs. Even 8 grammes of Sulphonal has no effect.

The dog in light sleep by Hedonal showed a very slight reduction in blood pressure. During the heavy sleep, however, blood pressure falls 20-30 millimetres. Large doses paralize the vaso-motor centre, the/

the blood vessels are dilated, and yet the heart remains very steady to near the end.

Hedonal ultimately breaks up into CO_2, water and urea.

DR.KARLOWITSCH (WARSAW).

Dr Karlowitsch published in 1905 a very large treatise comprising 135 pages, upon the Hedonal-Chloroform narcosis of Krawkow. The experiments were carried out on animals in Professor Krawkow's laboratory. There was apparently used an instrument for measuring the density of the chloroform vapour accurately, similar to the one introduced by Dr Vernon Harcourt. An indicator travelled round an arc, which was divided into tenths. With this dosimetric machine, then, Dr Karlowitsch found, regarding the duration of induction of narcosis, that the narcosis was complete in 30-40 minutes, if chloroform alone was administered, the indicator standing at a certain point, namely 2/10ths. On the other hand, if Hedonal had been given as a precursor under the same conditions of density of vapour, the induction occupied only 5-8 minutes. Dr Karlowitsch found that in the Hedonal-Chloroform narcosis, the quantity of Chloroform necessary was reduced to a third. The induction period was much shortened and free from excitement. The blood pressure remained steady, even in the deepest narcosis. Heart contractions remained full and strong and there was no arythmia. Respiration was hardly altered at all. Under certain conditions, the respiration might cease and artificial respiration be of no avail when chloroform alone was given. On the other hand, when Hedonal had also been given, respiration might cease with strong doses of chloroform, but there was this difference that artificial respiration was always successful.

Ref. 63.

Ref. 64.

Ref. 4.

Ref. 65.

Again, if the animal had been under Chloroform alone for 1-2 hours and the strength of the Chloroform vapour had been then more than doubled (namely with the indicator pointing to 8/10ths) the animal in 6-8 minutes thereafter showed sudden cessation of respiration

and/

and heart. The animal invariably died, notwithstanding all the artificial respiration and heart massage, etc.. With previous use of Hedonal, however, under the same conditions of the experiment, and with the same dose of Chloroform, when the indicator for the strength of Chloroform vapour stood at 8/10ths, suspension of the respiration came on in 10-12 minutes, but the heart worked with similar energy and the pulse did not lose its tension. Artificial respiration was invariably successful after a few minutes. This experiment was carried out even to three times in succession in the same animal with restoration each time.

BURKHARDT.

Ludwig Burkhardt carried out many experiments in the laboratory with intravenous Chloroform and intravenous Ether. He introduced this method into the clinic and reported his results in 1909. Ref. 45.

The patient received first of all Scopolamine and Morphine and in an hour the injection of a saturated solution of Chloroform (.97%) in normal saline was started by the median vein.

In the first case the narcosis lasted 30 minutes, there having been injected 1100 c.c. of the solution.

Burkhardt reported in detail his early cases. The narcosis was good, the heart and respiration apparently everything which could be desired, but the urine quite frequently showed in the early days following operation, haemoglobin, albumen, leucocytes and casts. He adds, however, that even with inhalation narcosis there has been found albumen in the urine in 33% of the cases, so that in his opinion the irritation to the kidneys was not greater by the intravenous method.

In his intravenous Ether narcosis, the precursor above-mentioned was also required, and it was found that some of these cases did not remain narcotized by the ether, and Burkhardt recommended that in such/

such cases a little chloroform should be applied on an open mask. Ref. 57.

From what we read in his own reports at the 17th International Congress of Medicine, one is inclined to the conclusion that these methods do not seem to have impressed even their introducer too favourably. The intravenous Ether, however, was more successful than the intravenous Chloroform.

In reference to Burkhardt's intravenous ether method, Jeremitsch and Fedoroff jointly reported in 1910 "According to our opinion, it is quite evident that intravenous narcosis with ether alone is no sure method, and that to attain a complete narcosis, ether narcosis with the Scopolamine-Morphine narcosis becomes rather dangerous." Ref. 38.

H.DRESER. (MUNICH)

Dreser continued experimenting on animals on lines similar to those of Schmiedeberg, making use of his suggestion regarding new substances. Thus several new drugs allied to Ethyl Urethane were tested by him conjointly with Bonhoeffer. These drugs had the Ethyl Alcohol displaced by higher secondary or even tertiary alcohols. Experiments were thus carried out with Di-ethylcarbinol and Di-ethylmethyl-carbinol (Amyl Hydrate), but without success. At last there was tried Methylpropylcarbinol Urethane, commonly known as Hedonal. A report of the immediate results of his experiments with this substance was read by Dreser at the 71st Assembly of German Natural Philosophers and Physicians in Munich and published in that city in 1899. Ref. 53. Ref. 4. Ref. 53. Ref. 54. Ref. 53.

In fishes and in the frog, Hedonal was found to be 10 times as strong as Ethyl Urethane and 3 times as strong as Chloral Hydrate in hypnotic power.

In the rabbit and dog it was found to have double the strength of Chloral Hydrate, and this also held good in the human subject, (.5-1 gramme). Respiration was somewhat less active than in natural sleep. There/

There was great muscular relaxation. The oxygen used was diminished by 20%. Rabbits in deep sleep showed a reduction of temperature equal to 1° Cent. which Dreser seems to have considered was due to the decreased combustion in the tissues consequent upon the muscular relaxation and diminished respiration. In the human subject there was no specific effect on the respiration. Ref. 53. Ref. 53.

The excretion of urine in the rabbit and dog was increased in deep sleep more than four-fold and as was explained, the solids remained as before, only the water-absorbing portion of the kidneys being stimulated. In this respect Hedonal was considered superior to Morphia.

The blood pressure in rabbits in deep sleep showed no change or only a fall of a few millimetres. This was recorded by Ludwig's kymographion and mercury manometer. Ref. 53.

Finally there was estimated the latency time of the reflex action, when a frog's leg was stimulated by an electric current. A normal latent period was found to be .13 and .14 of a second. After injecting .005 gramme of Hedonal, Dreser was much astonished to find that the period was increased to .79 of a second, and later, when the effect was passing off, .52 of a second. It was thought that this result might be due to the relaxation of the protoplasmic dentritic appendages of the nerve cells during the Hedonal sleep and that in this way a longer cycle was brought about in the reflex action. Ref. 54.

Dreser concludes his report in these words "In the literature, I can find no measurement of that time in reference either to Chloral Hydrate or to any other hypnotic." Ref. 53.

DR. A. P. JEREMITSCH (PETROGRAD).

The experimental work on Hedonal was carried out in the laboratory of Professor Krawkow in Petrograd. Much of it was done in conjunction with Dr. Fedoroff. Hedonal was applied by Jeremitsch to animals first by the stomach alone. Then it was given to animals by the mouth as a precursor to chloroform by inhalation. This was by the suggestion of Krawkow. This Hedonal-Chloroform narcosis was then introduced into the clinic with good results by Fedoroff. The next advance was by Jeremitsch. He,in animals,tried the effect of eliminating the Chloroform and introducing the Hedonal intravenously by itself. It then remained for Jeremitsch and Fedoroff to use the Hedonal intravenously in the clinic. This in the first cases was carried out with a primary dose of Hedonal by the mouth one hour before operation. It was due to Fedoroff, however, that the first intravenous anaesthesia by Hedonal was carried out in the clinic in 1909. A report of the work was then published jointly by Jeremitsch and Fedoroff in 1910. Ref 4. Ref 39.

Technique of Jeremitsch:- In the clinic the solution injected intravenously was .75% in normal saline. It was warmed, placed in a 2 litre jar and sterilized for 15 minutes at 100°C. A needle, bent at a right angle was used. In the early cases injection was made in the central direction, namely, with the stream and at a temperature of 104°F.. Latterly the injection into the vein was made in the peripheral direction, - against the stream. Before injecting, some of the solution was run out, as the temperature was too low. The rate of introduction was 70 c.c. per minute. When induction of narcosis was complete, the needle was removed and a saline compress was applied. The solution was propelled by means of an air ball pressed by the foot. When more solution was required,/ Ref 10. Ref 3.

required, the same pierce opening was used; but Jeremitsch suggested that the surgeon should first assure himself that no coagulum was present. The injection being in the peripheral direction did not prevent the possibility of thrombosis, but it made embolism a very unlikely thing to occur, more especially when the central end had been ligatured. If coagulum was found, a new opening in the peripheral end of the vein was made. Ref. 10.

Dose:- The quantity administered was based on the results in the laboratory. There was given intravenously .1 to .2 of a gramme Hedonal per kilogramme of body weight in the human subject, the same as a dog had received. Ref. 5.

The effects:- There was good heart action and peaceful, regular breathing. Acceleration of the circulation (10 - 30 in the minute) was sometimes observed on starting the injection; but when narcosis was complete, the rate became as before the operation. Too rapid introduction caused cyanosis. The time for the induction was from 3 to 8 minutes. Regarding blood pressure Jeremitsch stated: "The introduction of the liquid has no effect upon the blood pressure worth mentioning." Ref. 3. In animals (the dog) the pressure was recorded by Jeremitsch in Professor Krawkow's laboratory. It showed not more than 5 m.m. of a fall. Ref. 2. It may be mentioned here that with intravenous ether in the dog, there were obtained great fluctuations in the blood pressure.

The after effects commonly experienced with inhalation narcosis were absent. The urine was not affected pathologically and there was great muscular relaxation.

It was found that with the dose of Hedonal by the mouth, before injection, the post-operative sleep was far too prolonged - 17 to 20 hours. Ref. 42. It was concluded that this dose could be done without.

It/

It was then observed that the patient wakened up quite soon after the operation.

FEDOROFF.

Fedoroff carried out much of his work on Hedonal, both experimental and clinical, in conjunction with Jeremitsch in Petrograd. Probably all of the experiments were done in the laboratory of Professor Krawkow. The name of Fedoroff probably stands out more prominently than that of any other on this subject. The introduction of Krawkow's Chloroform-Hedonal narcosis in the clinic was due to Fedoroff in 1903. In the same year he reported 100 cases of this sequence. Ref. 39. The first case in the clinic where Hedonal was used intravenously was on the 7th December, 1909. A few days later, on the 11th December, 1909, Fedoroff showed the intravenous Hedonal narcosis (in tabula) before the 9th Congress of Russian Surgeons in Moscow. Ref. 39.

Fedoroff (in common with Jeremitsch) injected the Hedonal at first in the central direction of the vein, latterly in the peripheral direction. His technique was described under the name of Jeremitsch.

In 1911 a list of 530 cases of intravenous Hedonal narcosis in the human subject was published by Fedoroff. Ref. 2. The interrupted system of injection was used. This was the method of all the Russian surgeons and indeed of all surgeons on the Continent.

Speed of introduction and dose:- Weak patients received 50-60 c.c. per minute; strong patients 100c.cs. The quantity was on a basis of .1 - .2 gramme per kilogramme of body weight - the dose found suitable in the laboratory. The original precursor of 3-4 grammes of Hedonal per rectum gave too long a sleep - 17 to 20 hours - and it was latterly left out. Ref. 10. The solution used was .75% Hedonal in normal saline. This solution has been the only one used clinically, both in/

im Britain and on the Continent. The average operation required 600 c.c., the shortest 400 c.c., and the longest 1800 c.c.. Fedoroff used 3 to 13.5 grammes of Hedonal intravenously for operations in the clinic. Sometimes the needle had to be inserted a fourth time for additional injections. The time from the beginning of injection until complete narcosis was obtained, took 3 - 8 minutes. Ref. 10. Ref. 42.

Regarding the circulation, Fedoroff states:- "In very difficult cases with small and frequent pulse before the operation, it became so much better during the narcosis". Again we have this remark by the same surgeon:- "The sometimes very difficult to be counted filiform pulse became during the narcosis easily countable and much stronger." Ref. 2. Ref. 2.

The blood pressure in dogs taken in Professor Krawkow's laboratory by Jeremitsch, showed either no change or only a fall of 5 m.m. In 60 of the published cases of Fedoroff, the blood pressure was recorded by Sabotkin. The pressure showed very little change - a little sinking at the beginning - but it soon returned to what it was before the operation. Sabotkin stated that the curves of systole, diastole and blood pressure lie parallel. Ref. 2. Ref. 2.

Safety:- Fedoroff considered that its safety lies in its property of not weakening the heart, this being due in his opinion to the presence of the amino group in its composition. The formation of thrombi was attributed to extra injections. Referring to the injection towards the periphery, Fedoroff states:- "I am of the opinion there is no cause to fear from thrombus of that kind." There is neither the excitement during induction nor the post-anaesthetic effects usually found with inhalation narcosis. The urine contained neither albumen nor casts after operation. Fedoroff states regarding safety:- "As to whether or no this system is without danger, I can pass no decided opinion; but it is certainly less dangerous than chloroform or ether narcosis." (presumably inhalational). Ref. 39. Ref. 42. Ref. 39. Ref. 10.

Chloroform/

Chloroform and ether are excreted by the lungs and kidneys. Both irritate the kidneys, especially chloroform. Ether specially irritates the lungs. Hedonal is excreted by the kidneys only but does not irritate them. Ref. 39.

For these reasons, Fedoroff considered that Hedonal intravenously was better in every way than intravenous Chloroform or Ether - the method carried out by Burkhardt. Regarding this latter method Fedoroff was not favourably impressed, nor did he think Burkhardt believed much in it himself. Ref. 45. He (Fedoroff) considered intravenous Ether by itself was no sure method, because its introducer suggested that when it failed a little Chloroform might be added by the open mask. Ref 39. The precursor of Morphine and Scapolamine was another poison to be considered. Fedoroff concludes:- "We therefore think it may be taken for granted that from our experimental researches and observations in the clinic, the interesting main point has been established for the first time,that by the introduction of hypnotic doses of Hedonal into the blood a deep and permanent narcosis can be obtained." Ref. 39.

DR. A.T.SIDORENKO.

Dr Sidorenko used the intravenous Hedonal method shortly after it was introduced by Fedoroff in the clinic. Ref. 1. He published a report in 1910. His method was a little different from that of Fedoroff. The vein was dissected out, the peripheral end was ligatured, the central end was cut open with scissors and a cannula inserted, connected with the tank which was placed at a height of 60-70 centimetres. When narcosis was induced, the cannula was removed, and a saline compress applied. Extra injections were given by placing the cannula in the same opening, first having massaged out of the mouth of the vein any small clot, and having run off some

of/

of the cold liquid. At the end the central portion of the vein was ligatured and the wound sutured.

The best rate of introduction was 50-60 c.c. per minute. When 100 c.c. were given per minute, it was found to be too fast and caused cyanosis. The dose required in the clinic to establish narcosis was .04 gramme per kilogramme of body weight; but this quantity does not seem to refer to maintenance of narcosis for operation. Ref. 2.

Blood pressure was found to fall a little at the beginning, and then became as before the operation. It was recorded by Sabotkin in the clinic. There was no alteration in the urine.

MR.C.M.PAGE. (LONDON).

Mr Page in 1912 reported 200 cases of intravenous Hedonal anaesthesia carried out in St Thomas's Hospital. He really introduced the method into this country. Ref. 5. The continuous infusion was adopted, as was common with all British surgeons. In this way embolism from thrombosis was much less likely to occur. The site of injection was in most of the cases in the veins of the leg, and injection was in the peripheral direction = against the stream. Ref. 7. The temperature of the solution, when infused into the vein was at first 115 - 120°F.. Ref. 18. This was believed to account for the cases of thrombosis resulting and latterly the temperature was Ref. 72. reduced to 105°F.. When narcosis was complete, the liquid was allowed to enter drop by drop... Page administered 3 grammes of Hedonal by the mouth 2 hours before operation. It was considered that fatalities had been due to an overdosing of the patient.

The urine showed no haemolysis, albumen nor casts, when these were absent before operation. Ref. 72.

During

During the narcosis the corneal reflex was found to be absent or sluggish, the light reflex usually present, and the pulse full and steady.

Regarding the blood pressure we are told that it drops slightly and then remains steady. The lowest pressure recorded was 90 m.m., and was usually due to a large quantity being injected - 1000 c.c. - 1700 c.c. In his report there are 6 cases given regarding the blood pressure as types of what might be expected; but the fall seems to be quite a substantial one. Ref. 5.

Case (1) Cystoscopy. Pressure at the beginning 170 m.m. (likely excitement). Quantity used 750 c.c. In 10 minutes it had become 115 m.m., then rose to 120 m.m., and during the last 5 minutes the pressure was 130 m.m.

(2) Appendicectomy. Quantity 1750 c.c.. Pressure fell from 110 m.m. to 90 m.m..

(3) Strangulated hernia. Pressure of 135 m.m. fell to 95 m.m..

(4) Ileo-sigmoidostomy. Pressure of 145 m.m. became 90 m.m..

(5) Appendicectomy. Pressure of 130 m.m. became 100 m.m..

(6) Excision of lower jaw. Pressure of 140 m.m. became 98 m.m..

The percentage of reduction of blood pressure in the above 6 cases is therefore as follows:- 32,18,29, 37, 23, 30 respectively.

RAWDEN VEALE (LEEDS).

Rawden Veale wrote a paper in 1912 on the complications following the intravenous administration of Hedonal. Oedema may occur in the lumbar and gluteal regions, and bedsores may form. Blisters sometimes form on the heels and other parts owing to the patient having been too long in one position. Ref. 12.

Pulmonary oedema may arise as a result of the large quantity of liquid injected, apart altogether from the drug dissolved in it. "In the majority of the cases there has been thrombosis in the vein selected for the infusion." One thrombus extended as far as the junction with the axillary vein. These seemed to give no trouble. Thrombosis in the femoral vein seems to have occurred occasionally, even when Hedonal was injected by the arm veins.

Pulmonary infarction has taken place as a result of an embolus having been carried from the site of injection 14 days later.

SECTION II.

ANAESTHETIC EFFECT.

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ANAESTHETIC EFFECT.

This has been tested in the rabbit.

To ascertain the power of Hedonal as a general anaesthetic in the rabbit, there were two long experiments of one and two hours respectively, carried out, the details of which are given in the present Section.

It has, however, been considered that before going into the details of these experiments, for the convenience of the reader, the total results should be placed in tabular form. In this way a mathematical record can readily be obtained of the power of Hedonal as an anaesthetic.

	Hedonal .75%.	Pure Hedonal.	Duration of Anaesthesia.	Weight of rabbit.
First experiment.	83 c.c. 41 c.c. 20 c.c.	9.5 grain 4.7 grain 2.3 grain	120 minutes. 1 hour. 1 hour.	2000 grammes. 2000 grammes 1 kilogramme.
Second experiment.	36 c.c. 40 c.c. 19 c.c.	4.1 grain 4.6 grain 2.19 grain	54 minutes. 1 hour. 1 hour.	2100 grammes 2100 grammes 1 kilogramme.

The important fact to be taken from the above table is, that a rabbit for maintenance of anaesthesia requires per kilogramme of body weight and by perfusion into the vein, 2.2 grains of Hedonal per hour.

After studying the conditions of anaesthesia due to Hedonal as they occur in the present experiments, it appears to me suitable to consider them under four headings:-

1. The anaesthetic dose.
2. The effect on the eye.
3. The nature of the anaesthesia.
4. The cause of death.

The effect on the vagus as seen in the heart tracings has also been considered.

The anaesthetic dose:-

In the first experiment the animal was under the anaesthetic influence of Hedonal (.75%) for 2 hours. It received in this time 17 doses, consisting of from 3 c.c. to 10 c.c., having had in all 83 c.c. or 9.5 grains of Hedonal. This quantity represents 4.8 c.c. (.5 grain Hedonal) every seven minutes, or at the rate of .25 grain Hedonal per kilogramme of body weight at the same intervals. It was found that the abdominal wall as tested by a needle, and even by actual incision, became very readily insensitive to pain, so that a relatively small dose such as 3 c.c. (.34 grain Hedonal) equal to .17 grain per kilogramme of body weight permitted painful manipulations to be made in this region without the slightest movement. (Experiment 1.) This is in accordance with the experience in the clinic, as one of the chief advantages of Hedonal as experienced by surgeons has been stated to be the great muscular relaxation produced, more particularly in the abdomen. On the other hand a fairly large dose such as 10 c.c. (i.e. $\frac{5}{9}$ c.c. per kilogramme or .57 grain) was necessary to abolish the plantar response to the needle when pressed firmly into the tissues.

Ref. 53. Ref. 41. Ref. 73.

When we examine the experimental work of Fedoroff and Jeremitsch, we find that in animals such as the rabbit and dog, there was required a dose of .1 gramme to .2 gramme (1.5 to 3 grains) of pure Hedonal per kilogramme of body weight for operations. This is in agreement with the quantity found necessary per hour in the present experiments.

Ref. 10. Ref. 39.

Effect on the eye:-

The action seemed to be very similar to what obtains with chloroform narcosis. Of course the changes come on much more rapidly, as the drug is sent directly into the blood stream. Chloroform on the other hand being given by continuous inhalation, shows its effects more gradually. A small dose of 1.5 c.c. per kilogramme (.17 grain Hedonal) was followed almost immediately by dilatation of the pupil from 5 millimeters to 7 millimeters, (see first dose in Experiment 1.) Large doses such as 5 c.c. per kilogramme (.57 grain Hedonal) made the pupil dilate up to 11 millimeters. My explanation of these phenomena is as follows:- The small dose dilated the pupil by stimulation of the cervical sympathetic nerves. The action was on the radiating fibres of the iris. At the same time, as might be expected, the seventh cranial nerve was seen to be active, the orbicularis palpebrarum closing the eye. When the large dose was administered, the dilatation resulting was due to paralysis of the third cranial nerve, which acts on the circular fibres of the iris. There was noticed that the eyelids fell apart as if from paralysis of the seventh nerve.

Regarding the corneal reflex, the experience varies very much with different rabbits. This may be the reason why different observers have given different reports on this point, some stating that Hedonal abolishes the corneal reflex, while others have found that it does not.

In Experiment II all the doses from 2 c.c. up to 10 c.c. abolished the corneal reflex every time;

The actual quantities are here shown.

2 c.c. Hedonal (.75%) = .23 grain Hedonal or .11 grain per kilogramme.

10 c.c. Hedonal (.75%) = 1.1 grain Hedonal or .52 grain per kilogramme.

In Experiment I, the corneal reflex was not abolished until the 12th dose of Hedonal, so that in this experiment a dose of even 8 c.c. of Hedonal failed to affect this reflex. By consulting the following table it may be seen that several doses of moderate strength were administered in close succession before the reflex was abolished.

EXPERIMENT I.

Dose.	Time.	Quantity.	
1	10.30	3 c.c. (.75%).	
2	10.39	5 c.c.	
3	10.54	6 c.c.)	No Hedonal for 33 minutes.
4	11.27	8 c.c.)	
5	11.44	3 c.c.	
6	11.48	3 c.c.	
7	11.51	3 c.c.	
8	11.58	3 c.c.	
9	12.1	3 c.c.	
10	12.4	4 c.c.	
11	12.7	4 c.c.	
12	12.10	4 c.c.	Corneal reflex abolished for the first time.
13	12.15	4 c.c.	
14	12.19	4 c.c.	
15	12.23	8 c.c.	
16	12.28	8 c.c.	
17	12.33	10 c.c.	

The rabbit referred to above weighed 2000 grammes.

It may be of interest to quote here the words of Professor Krawkow when he refers to the dose of .5 gramme by the mouth in a rabbit having procured 7 hours' sleep:-

> "The reflex to pain-irritation, and corneal reflex are analysed with greater difficulty; but do not completely disappear." Ref. 4.

Again, Cataldi of Rome states:-

> "When the dose exceeds .25 gramme per kilogramme of body weight an anaesthetic effect begins as shown among other symptoms by a weakening of the corneal reflex." Ref. 47.

Dr Mennell states that the corneal reflex is valueless in Hedonal anaesthesia. Ref. 61. The skin reflex on the sole is more important.

The Nature of the Anaesthesia.

If we examine closely a long anaesthesia due to Hedonal, it will be found that such anaesthesia is not exactly of the same nature as, for in-stance, that of chloroform of ether. Hedonal behaves rather like the pure hypnotics. Thus, looking at the table of doses in Experiment I, after the 3rd dose there was a period of 33 minutes without any Hedonal being given. The animal was in a deep sleep and yet the corneal reflex was present, and deep insertion of a needle into the sole of the foot elicited a response. Under similar conditions, with chloroform or ether, the animal would have been awakened, moving within 8 minutes. Hedonal causes an increasing drowsiness which continues for a time without any more Hedonal being required, even when the corneal reflex is present. In the clinic, this feature of drowsiness has been regarded in opposite ways by different surgeons, some deeming the post-operative sleep(which may last for 17 hours) an advantage; but others looking upon this characteristic as prejudicial to its use. Ref. 48.

Cause of death:-

This has been definitely ascertained. Respiration stops before the heart.

After the last dose (10 c.c.) in Experiment I, the respiration ceased in 30 seconds. The heart continued to beat feebly for another 2½ minutes and then ceased to all appearance. The whole of the anterior thoracic wall was then opened, when it was found that the heart was still beating, although there was no respiration. The heart then ceased in a few seconds later.

The order of disappearance of functions was as follows:-

Sensation in the abdominal wall.

Right hind leg - deep plantar response to needle.

Corneal reflex.

Left plantar response to needle.

Respiration.

Circulation.

Fedoroff in the clinic more especially watched the respiration rather than the circulation. Ref. 2.

Experiment I.

The following experiment was made on a rabbit weighing 2000 grammes. The animal was first etherized and the venous cannula was inserted into the left common jugular vein. After the ether had been stopped for 10 minutes, the rabbit received the first dose of Hedonal. The details are here stated.

9.55 a.m. Ether was started.

10.20. Ether stopped.

10.20. Condition of the animal:-

Light reflex absent,
Corneal reflex absent,
Pupil 4 m.m. in diameter - measured by the pupillometer.
Eyelids wide apart, suggesting deep anaesthesia.

10.25. Effect of the ether passing off.

Respiration faster. This is often a precursor of superficial state.
Pupil larger - 5 m.m.
Eyelids closer together - from returning activity of 7th cranial nerve.

10.27. Eyeballs beginning to roll.
Corneal reflex returning.

10.29. The left hind leg moved. The animal was returning to consciousness.

10.30. First dose:-

3 c.c. Hedonal (.75%)
1 c.c. Normal Saline.

The effect was seen almost at once.

The pupil dilated from 5 m.m. to 7 m.m.
The abdominal wall was quite insensitive to the needle when well inserted.
Eyelids opening widely, due to paralysis of the 7th cranial nerve acting on the orbicularis palpebrarum.
The corneal reflex was still present.

10.36. The eyes were beginning to close from returning function of the 7th nerve.

10.38½. Right hind leg twitched when the needle was applied.

Corneal reflex present.

The animal was passing into a superficial state.

The second dose was now given:-

5 c.c. Hedonal.
1 c.c. Saline.

The effect was seen in 10-15 seconds.

Slight dilatation of the pupil.
Eyelids more widely opened.

10.54. Eyeball rolling and a limb moved.

Corneal reflex more sensitive.

Anaesthesia passing off.

10.50. Needle deeply inserted into the skin of the abdominal wall produces no response.

Needle deeply piercing the sole of the foot causes response.

The eyelids became more tightly closed.

10.54. Third dose given.

6 c.c. Hedonal.
1 c.c. Saline.

The pupil at once dilated.

11.2. Needle in the abdomen gives no response.

Eyelids becoming more tightly closed again.

Response got from inserting a needle into the sole of the foot.

11.8. Corneal reflex active.

Eyelids closing still more from action of the 7th nerve.

Up to this point, the right hind leg has never failed to respond to the needle; it had disappeared with ether.

11. 15. No abdominal response to needle.

Corneal reflex active.

Response got from both plantar surfaces.

It is now 26 minutes since the last dose was given, and no movement of the animal (apart from interference) has indicated that it was waking out of sleep.

11.20. No abdominal response to the needle.

Corneal reflex very sensitive.

The eye is opening, due to the returning activity of the 3rd cranial nerve, this nerve acting on the levator palpebrae superioris.

11.27. The fourth dose was administered.

8 c.c. Hedonal.
1 c.c. Saline.

This was a large dose and the pupil in eight seconds was seen to dilate up to 11 millimeters.

11.31. No response while incision was made in the abdominal wall.

Response still obtained from the plantar surface.

11.54. The fifth dose was now given, although there were no signs of superficial state observed.

3 c.c. Hedonal.
1 c.c. Saline.

11.47. Corneal reflex has never yet in this experiment disappeared.

11.48 Sixth dose given.

3 c.c. Hedonal.
1 c.c. Saline.

Plantar response to the needle, and the corneal reflex became more sluggish.

11.51. Seventh dose.

3 c.c. Hedonal.
1 c.c. Saline.

The pupil at once dilated from paralysis of the circular fibres of the iris.

Plantar response still obtained when needle was deeply inserted.

11.58. Eighth dose given.

3 c.c. Hedonal.
1 c.c. Saline.

Corneal reflex and plantar response still active.

12.1. Ninth dose given.

3 c.c. Hedonal.
1 c.c. Saline.

Plantar response sluggish.

Corneal reflex sluggish.

12.4. Tenth dose given.

4 c.c. Hedonal.
1 c.c. Saline.

12.7. Eleventh dose given.

4 c.c. Hedonal.
1 c.c. Saline.

12.8. Response from the sole of the right foot for the first time is not obtained.

The pupil is 11 m.m.

12.10. Twelfth dose given.

4 c.c.Hedonal.
1 c.c. Saline.

Right plantar response to needle is absent.

Left plantar response is present.

Corneal reflex abolished for the first time.

12.15. Thirteenth dose.

4 c.c. Hedonal.
1 c.c. Saline.

No corneal reflex.

No right plantar response.

Left plantar response still obtained.

12.19. Fourteenth dose.

4 c.c. Hedonal.
1 c.c. Saline.

Conditions still the same as after last dose.

12.23. Fifteenth dose.

8 c.c. Hedonal.
1 c.c. Saline.

Corneal reflex absent.

Left plantar response absent for the first time.

12.28. Sixteenth dose.

8 c.c. Hedonal.
1 c.c. Saline.

12.31. Respiration slow and shallow.

12.33. Seventeenth dose.

10 c.c. Hedonal.
1 c.c. Saline.

Respiration ceased in 30 seconds after this last dose. The heart continued to beat feebly. The pupils were large and eyes wide open. In 2½ minutes after respiration ceased, the heart to all appearance ceased.

On now opening anteriorly the thorax, the heart was found to be still beating. The animal died.

In this long experiment of 120 minutes, it may be observed that the rabbit received 17 doses of Hedonal, ranging in quantity from 3 c.c. to 10 c.c. - a total of 83 c.c.

The functions disappeared in the following order:-

Sensation in the abdominal wall.
Right hind leg - deep plantar response to the needle.
Corneal reflex.
Left plantar response to needle.
Respiration.
Circulation.

Experiment II.

This experiment was originally carried out with a threefold purpose:-

(1) To ascertain the effect of Hedonal upon the cavities of the heart.

(2) To ascertain whether and to what extent Hedonal influences the action of the vagus nerve.

(3) To find out the power of Hedonal as a general anaesthetic.

The first two have been dealt with in detail elsewhere: it is mainly the anaesthetic property of Hedonal which is now under consideration.

The animal weighed 2100 grammes.

The following operations were carried out:-

Etherization.
Tracheotomy.
Venous cannula inserted in left jugular vein.
Thorax opened, and the necessary connections made for recording the action of the auricle and ventricle.
Vagus nerve on either side was also isolated ready for stimulation.

The blood pressure was not recorded.

The experiment lasted for 54 minutes, during which time the animal received 36 c.c. of .75% solution of Hedonal, or 4.1 grains of active ingredient. There were 6 doses of from 2 c.c. to 10 c.c., on an average of 6 c.c. each time, or .68 of a grain of Hedonal every six minutes, for an animal weighing 2100 grammes. This is .32 grain per kilogramme every 6 minutes. The anaesthesia was perfect. By "perfect anaesthesia" in this case is meant

(1) No voluntary movements.

(2) No involuntary or reflex movements.

(3) The vital automatic movements only in action.

(4) Corneal reflex abolished.

This was not a light anaesthesia: the animal could probably have done with less anaesthetic. In the earlier doses, however, any succeeding dose was only administered at the moment when the corneal reflex returned.

The/

The later doses were given without waiting for the corneal reflex to return. Hence the duration of anaesthesia recorded for the later doses is underestimated. A table giving the doses will show at a glance what has been done:-

Time.	Dose.	Quantity.	Anaesthesia.
10.41.	1	10 c.c.	18 minutes.
10.59	2	8 c.c.	9 minutes.
11.8.	3	4 c.c.	3 minutes.
11.11	4	2 c.c.	9 minutes.
11.20	5	6 c.c.	9 minutes.
11.29	6	6 c.c.	6 minutes.

The first dose is important, because the cornea was sensitive to touch at the beginning.

Details of the Experiment.

10. 35 a.m. At this time all dissection which had been carried out under ether was completed, the ether was stopped and artificial respiration continued all through.

Corneal reflex absent.

10.41. Right corneal reflex beginning to return after 6 minutes without any further anaesthetic having been given.

10.41. The revolving drum was started.

First dose:-

10 c.c. Hedonal (largest dose of all).
1 c.c. Saline.

Response of the right cornea disappeared in a few seconds.

10.43. Drum was stopped.

10.48. Both corneal reflexes absent. Eyelids of both eyes closing.

10.50. Drum started and a tracing taken.

10.51. Drum stopped.

10.55. Left corneal reflex present.

Right corneal reflex absent.

*The reason of the difference may be that the left is more sensitive because it was less interfered with, the head having been lying to the side.

10.59. Both corneal reflexes are now present.

The animal is now awake, but is about to pass into a superficial state of anaesthesia.

The first dose (10 c.c.) has therefore kept the corneal reflexes absent for 18 minutes. There has therefore been complete anaesthesia during this period.

10.59. Drum started.

10.59. Second dose:-

8 c.c. Hedonal.
1 c.c. Saline.

Corneal reflex was abolished in a few seconds.

11.1. Drum stopped.

11.8. Corneal reflex was again apparent.

The second dose has given 9 minutes anaesthesia.

11.8. Drum started.

11.8. Third dose:-

4 c.c. Hedonal.
1 c.c. Saline.

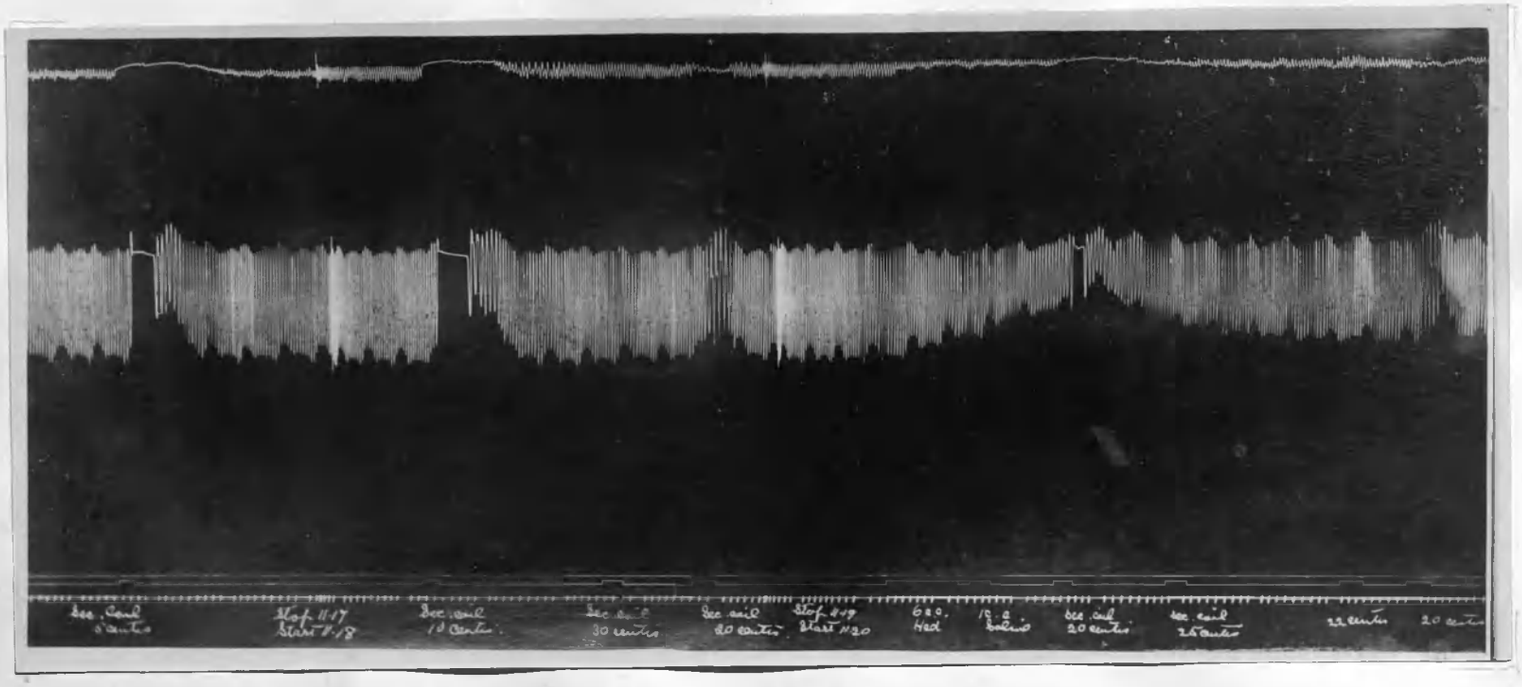
Corneal reflex was abolished.

11.10. Drum stopped.

11.11. Corneal reflex returned. This dose has given 3 minutes' anaesthesia

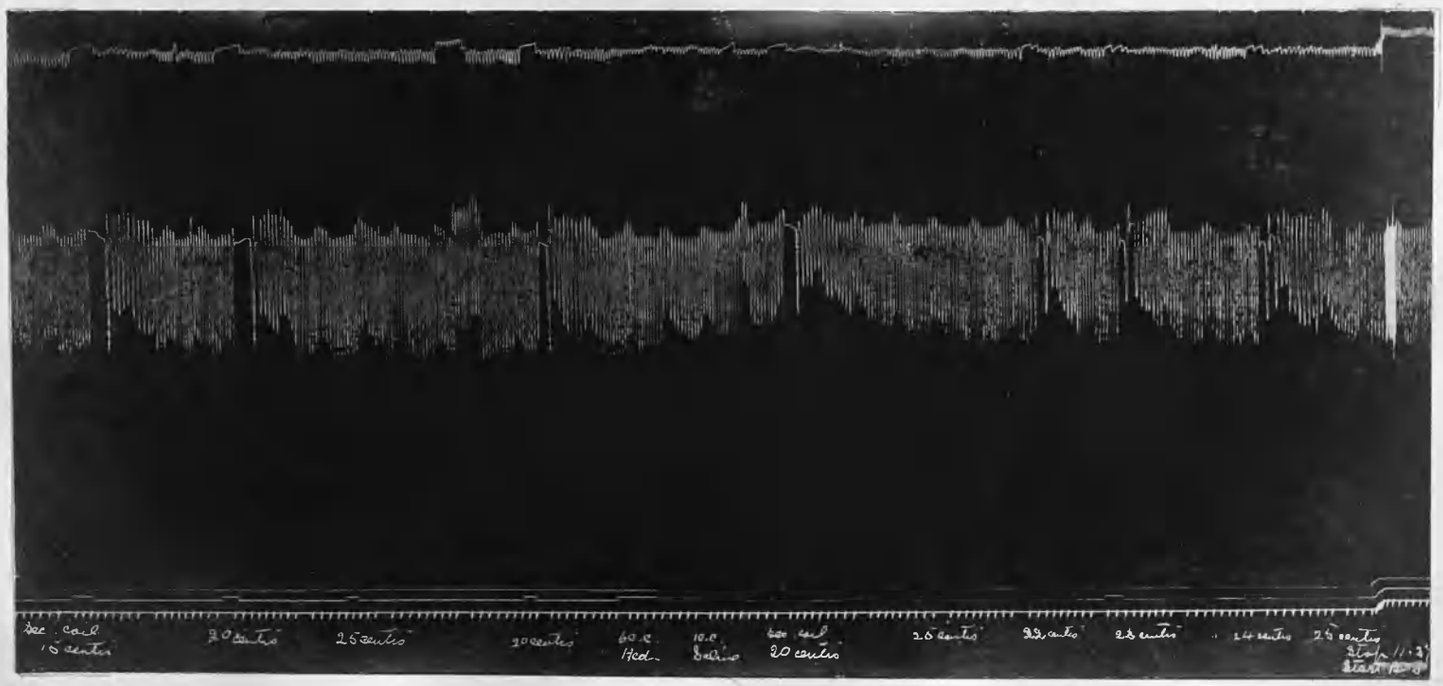
* My experience has been that the left side of the body is usually more sensitive than the right, both as to touch and electric stimuli.

Figure LXXXIX.



·44 Natural Size.

Figure LXXXI.



·47 Natural Size

11. 11. Drum started.

11.11. Fourth dose:-

2 c.c. Hedonal (.23 grain or .11 per kilogramme.
1 c.c. Saline.

Corneal reflex even with this dose was immediately abolished.

11.12½. Drum stopped.

11.13½. Drum started.

Left vagus was now cut and a thread attached.

Corneal reflex still absent, the animal being anaesthetised.

From this point the tracing can be followedin Figure LXXXIX.

11.16. Stimulation of the left vagus nerve with the secondary coil standing at 5 centimeters. During the stimulation the ventricle ceased in diastole. The heart had quite stopped. Whenever the current was withdrawn, the heart resumed action; but its rate was reduced for a few seconds, after which it became normal.

11.17 to 11.18. Drum was stopped.

11.18. Stimulation of distal extremity of left vagus with coil at 10 centimeters.

The heart stopped in diastole again and then resumed beating. Vagus was stimulated with the coil standing at 30 and also at 20 centimeters. This shows the minimum effect of the induced current. There is no cessation in diastole. There is no diminished amplitude. There is only the retarding of the heart rate. It is 9 minutes since the last dose of Hedonal and the animal is still anaesthetised.

11.19 to 11.20. The drum was stopped.

11.20. Fifth dose:-

6 c.c. Hedonal.
1 c.c. Saline.

At the moment of maximal effect of this dose upon the heart, the left vagus was stimulated with the coil at 20 centimeters. This is the same current as before when no diastolic cessation was seen - only retardation of the cardiac rate. In the present conditions, however, the result was "stand-still" of the heart in diastole for 2 seconds. When the immediate effect of this Hedonal dose had passed off, stimulation of the vagus with the coil at 25 and 22 centimeters respectively, had no effect. The heart then fully recovered. The vagus was now stimulated when the maximum effect of Hedonal on the heart had passed off, using the same current as when the heart was most affected by Hedonal, viz. with the coil standing at 20 centimeters. There was no cessation in diastole, but only slowing of the heart rate, which shows the "organ-pipe" appearance in the tracing.

11.29. Although the animal was still anaesthetised, more Hedonal was administered.

Sixth dose:-

6 c.c. Hedonal.
1 c.c. Saline. (see Figure LXXXI).

The effect lasted at least for 6 minutes, the animal being still asleep, and corneal reflex not having returned at 11.35.

SECTION III.

EFFECT ON THE HEART OF THE RABBIT WITH SPECIAL REFERENCE TO

(a) Amplitude of contraction of the auricle,

(b) Amplitude of contraction of the ventricle,

(c) Cardiac rate.

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The effect has always been, that there was marked decrease in the amplitude of contraction of the auricle and of the ventricle, when Hedonal was perfused.

No appreciable change was observed in the cardiac rate.

The effect on the ventricle was always greater than that on the auricle.

It was usually found that complete recovery after a dose more readily followed in the case of the auricle than in that of the ventricle: although the reverse was seen in Figure 26, when a dose of .25 of a grain per kilogramme was given. In this instance the ventricle fully recovered: the auricle did not fully recover.

The greater the dose the more marked was the reduction in amplitude of contraction. The time taken to recover from any one dose was found, as a rule, to be greater than the time required to bring about the maximum effect after beginning to perfuse the drug.

A moderate dose for a rabbit is .16 grain of Hedonal per kilogramme of body weight. In the present case by the term "a moderate dose" is meant one after which complete recovery took place to the prevailing conditions immediately before perfusion. This is the quantity given in Figures 30 and 28, from which there was complete recovery in the auricle and ventricle as regards amplitude of movement. It was represented by a dose of 4 c.c. (.46 grain) of Hedonal solution (.75%), the rabbit weighing 2800 grammes.

When a dose of .2 grains per kilogramme (Figure 30) was given, complete recovery to the former conditions was not always observed.

There were twelve experiments made. The average results may be seen in Figures 26, 27, 28, 30 and 32, which are here produced. The solution employed was .75% in saline, expept in one case (Figure 26) where a 1% solution was used.

Some of the Figures also show a blood pressure tracing; but this

effect/

effect has not been considered here, as it has been dealt with elsewhere.

The operations carried out in each experiment were as follows:-

Anaesthesia. The animal was anaesthetised by ether.

Tracheotomy. The trachea was exposed in the usual way. A glass tube, or one of McColl's brass tracheal tubes was inserted, and the connection was made with the ether bottle, artificial respiration being carried out by an electric air pump.

Insertion of venous cannula. A glass tube filled with normal saline was inserted into the left common jugular vein. Thereafter it was connected with a double burette stand for holding normal saline and Hedonal solution respectively.

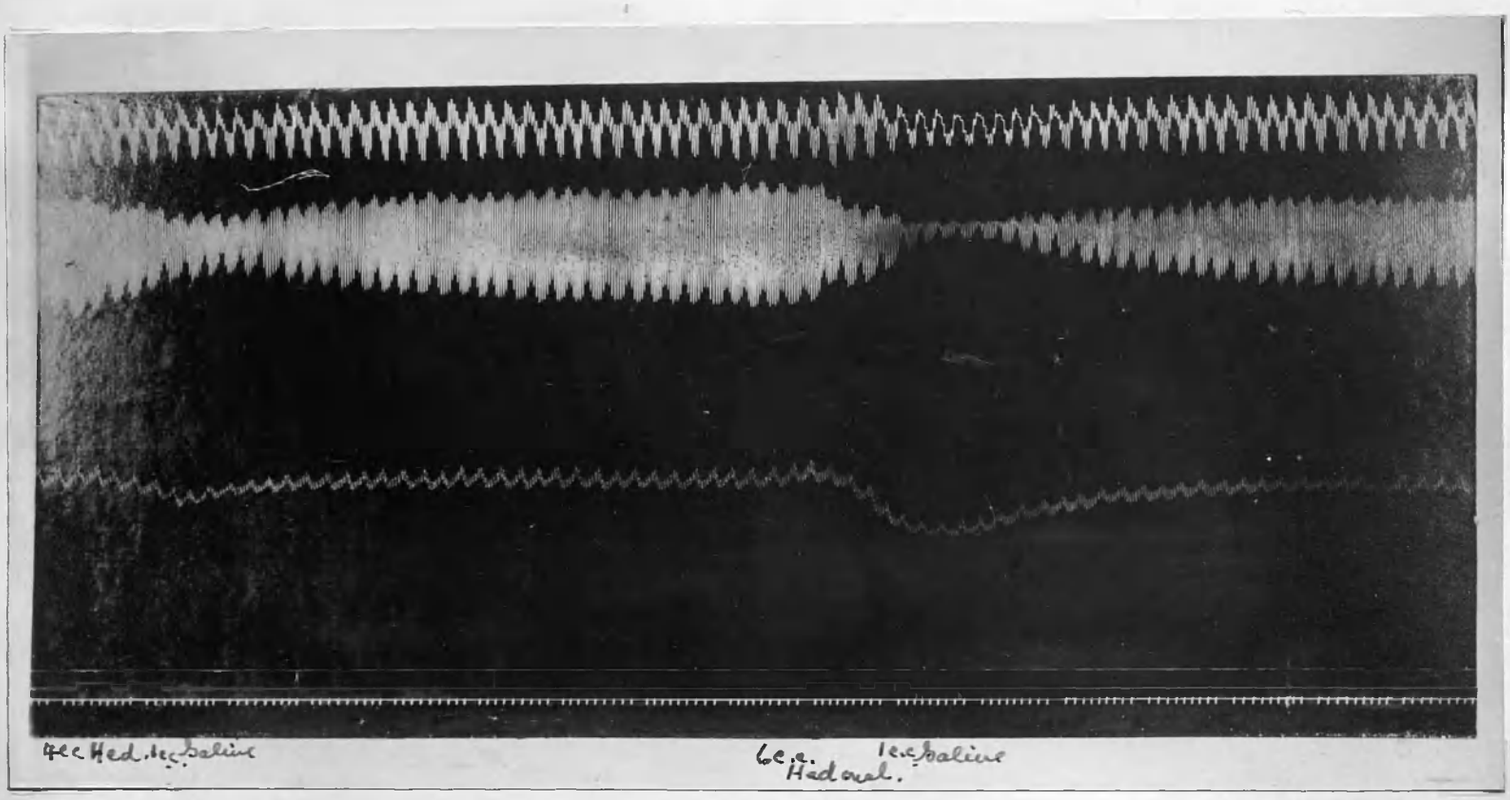
Insertion of the arterial cannula. A glass cannula was inserted into the right carotid artery and the connection was made with the blood pressure recording apparatus.

Dissection of the anterior thoracic wall. When the sternum and a portion of the ribs were removed, the pericardium was opened and fixed on each side by bull-dog clips, to the remaining thoracic wall. The heart was thus slung in a cradle formed by the pericardium posteriorly. A small metal clip was attached to the anterior surface of the auricle and one to the ventricle, threads being led from there to the travelling smoked paper which in the present experiment was 12 ft.long x 1 ft.deep.

Each figure shows six lines from top to bottom as follows:-

Tracing from the auricle.
Tracing from the ventricle.
Blood pressure (when present).
Abscissa line.
Signal line.
Time line in seconds.

Figure XXX.



·52 Natural Size.

FIGURE XXX.

In Figure XXX the rabbit weighed 2800 grammes.

The tracing is a selected portion from one of 10 feet long and shows three lines. The top one is taken from the auricle, the middle one from the ventricle, and the lowest one represents the blood pressure. The blood pressure has not been considered in this section.

A dose of 4 c.c. (.46 grain) and one of 6 c.c. (.69 grain) were administered by the jugular vein and the results are tabulated below.

In this experiment the heart recovered its previous amplitude of contraction of both auricle and ventricle after the smaller dose: after the second dose the auricle quite recovered its former amplitude, but the ventricle after recovery recorded only 28 millimeters, being a loss of 10 millimeters in amplitude, equal to 26%. The dose of 6 c.c. therefore, appears to be rather large.

The cardiac rate has not been altered by either dose.

TABLE I.

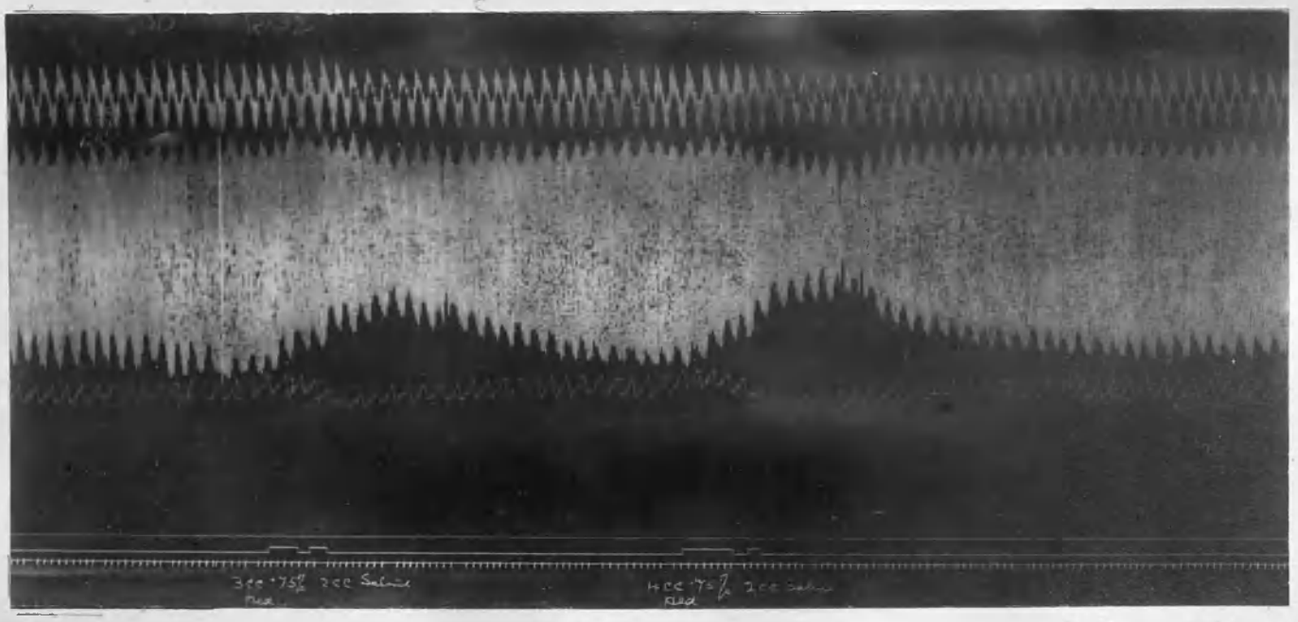
	Amplitude before Hedonal was given.	Dose given.	Amplitude after Hedonal dose.	Time to show maximum effect.	Time of recovery after full effect.	Loss in amplitude.	Percentage of loss at time of dose.	Recovery.
Auricle	19 m.m.	4 c.c.	14 m.m.	20 secs.	25 secs.	5 m.m.	26	Complete
	19 m.m.	6 c.c.	10 m.m.	18 secs.	30 secs	9 m.m.	47	Complete
Ventricle	38 m.m.	4 c.c.	18 m.m.	20 secs.	60 secs.	20 m.m.	52	Complete
	38 m.m.	6 c.c.	5 m.m.	18 secs.	40 secs.	33 m.m.	86	Incomplete.

Note:- Incomplete recovery means, that the heart had not returned fully to its previous condition at the time a subsequent dose was administered.

Figure XXXII.

·47 Natural Size.

Figure XXVIII.



·41 Natural Size.

FIGURE XXXII.

Figure XXXII is a tracing taken from the heart of a rabbit weighing 2100 grammes. It represents the effect of a large dose administered six minutes after the ether was withdrawn and when anaesthesia was passing off, as was shown by the corneal reflex returning.

The dose administered was:-

*10 c.c. Hedonal and

1 c.c. Saline.

The usual result was obtained as in other experiments. This is very marked in the ventricle. The amplitude of contraction of the ventricle which was 58 millimeters, became only 12 millimeters, a loss of 79%: it did not fully recover. The auricle has been affected similarly but in a lesser degree.

The cardiac rate has been unchanged.

*10 c.c. of Hedonal (.75%) contains 1.1 grain or .52 grain per kilogramme.

FIGURE XXVIII.

Figure XXVIII is produced to show the effect of a very moderate dose of Hedonal on a large rabbit weighing 2800 grammes. The effect was quite marked with a dose of 3 c.c. and of 4 c.c.. It was greater in the ventricle than in the auricle, and recovery was complete in each case. Recovery was found to take place sooner than with the larger doses such as 6 c.c. or 8 c.c.

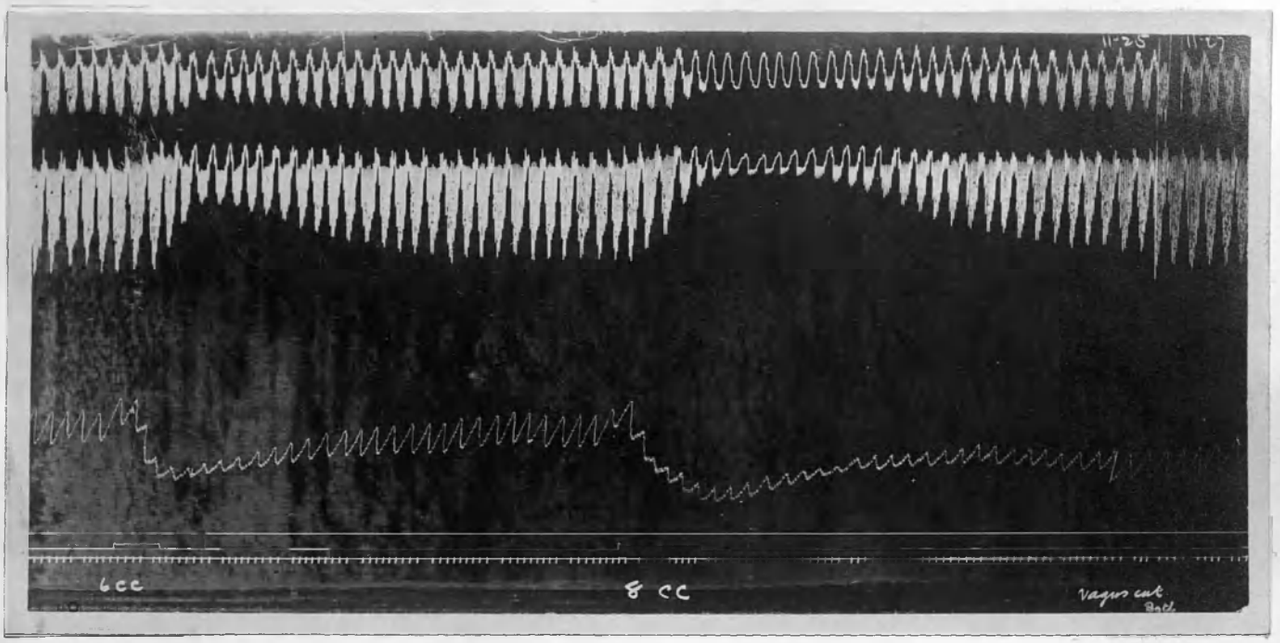
Note:- 3 c.c. Hedonal (.75%) contains .34 grain = .12 grain per kilogramme.
4 c.c. " " " .46 grain = .16 grain "
6 c.c. " " " .69 grain = .23 grain "
8 c.c. " " " .92 grain = .32 grain "

The above estimations have been made on the assumption that a 1% Solution is represented by 1 grain in 110 minims, seeing that 1 oz.water weighs 437½ grains.
By the equational method we have:-

$$\frac{16.9 \text{ minims}}{1 \text{ c.c.}} \quad \frac{8 \text{ c.c.}}{110 \text{ minims}} \quad \frac{.75 \text{ grains}}{x \text{ grains.}} = .92 \text{ grain.}$$

(See Table II.).

Figure XXVII.



·41 Natural Size.

TABLE 2.

(Referring to Figure XXVIII.).

	Amplitude before Hedonal was given.	Dose.	Amplitude after Hedonal.	Time to show maximum effect.	Time taken to recover.	Loss in amplitude.	Percentage of loss.	Extent of recovery.
Auricle	22 m.m.	3 c.c.	18 m.m.	20 secs.	30 secs.	4 m.m.	18	Complete
	22 m.m.	4 c.c.	16 m.m.	25 secs.	35 secs.	6 m.m.	27	Complete
Ventricle	78 m.m.	3 c.c.	58 m.m.	20 secs.	30 secs.	20 m.m.	25	Complete
	78 m.m.	4 c.c.	46 m.m.	30 secs.	40 secs.	32 m.m.	41	Complete.

FIGURE XXVII.

The above figure is a tracing taken from a rabbit weighing 2300 grammes. Two large doses of Hedonal were perfused and the effects are recorded in tabular form. The result shows that the effect of such doses even in a large rabbit is very marked; but that recovery is good. Further - the relative effect on the ventricle is much greater than that on the auricle, and the auricle recovered sooner than the ventricle its former amplitude of contraction.

TABLE III.

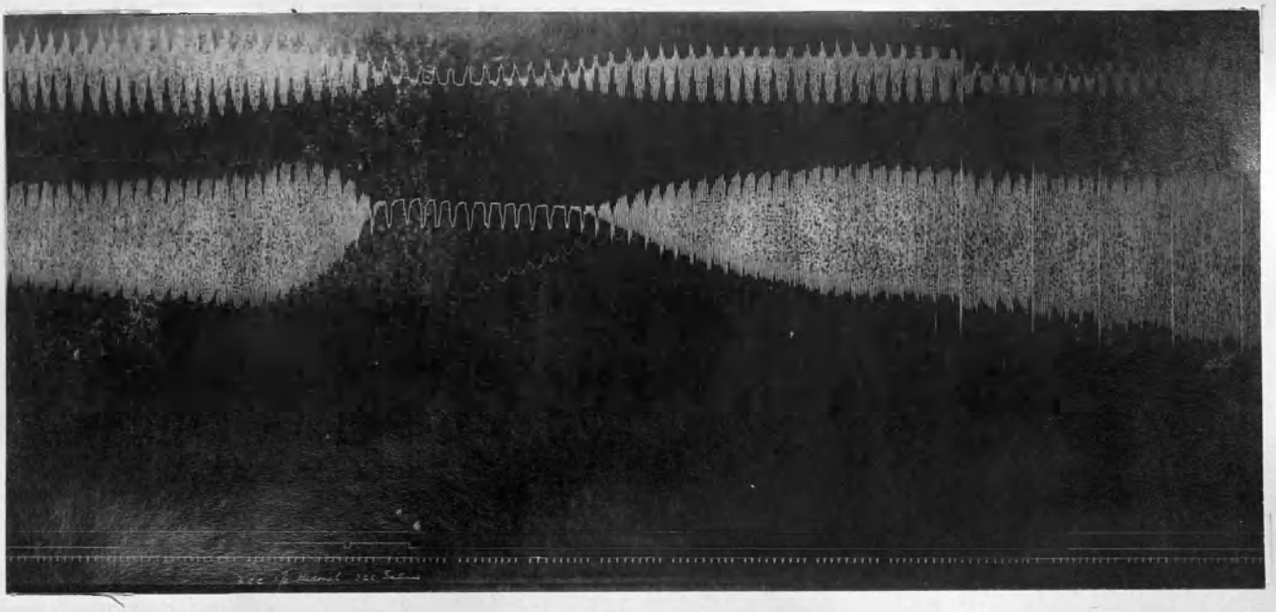
(referring to Figure XXVII.)

	Amplitude before Hedonal was Dose. administered.	Amplitude after Hedonal.	Time to show maximum effect.	Time of recovery after maximum effect.	Loss in amplitude.	Percentage of loss at time of maximum effect.	Extent of recovery.
Auricle	22 m.m.	6 c.c. 16 m.m.	18 seconds.	20 Seconds.	6 m.m.	27	Complete.
Auricle	22 m.m.	8 c.c. 12 m.m.	22 seconds.	30 Seconds.	10 m.m.	45	Complete.
Ventricle	46 m.m.	6 c.c. 20 m.m.	16 Seconds.	40 seconds.	26 m.m.	56	Incomplete. Loss of 4 m.m.
Ventricle	42 m.m.	8 c.c. 8 m.m.	20 Seconds.	40 seconds.	34 m.m.	80	Incomplete. Loss of 8 m.m. *

*In 40 seconds after the maximum effect of 8 c.c., the amplitude of contraction of the ventricle was 34 m.m., representing a loss of 8 m.m. There was then a pause of 2 minutes in the movement of the smoked paper, when it was found that the amplitude had been fully restored to 42 m.m.

It is likely that if the heart had been given more time after the first dose, the ventricle would have also been fully restored.

Figure XXVI.



·4 Natural Size.

FIGURE XXVI.

Figure XXVI is taken from the heart of a rabbit weighing 1800 grammes, and shows the effect of one dose of Hedonal. The Hedonal solution was 1% in saline. The dissection took a long time and the animal became moribund, the blood pressure registering only 6 m.m.. There was therefore administered by hypodermic needle into the rubber tube of the venous cannula, a dose consisting of

.5 c.c. Adrenalin (1 in 1000)
.5 c.c. Saline.

These were mixed in the syringe. The tracing starts with the effect of this dose still acting.

The amplitude of contraction of the auricle was 28 m.m. and in 30 seconds it had become 32 m.m..

The ventricle line was 38 m.m. and in 30 seconds it had become 48 m.m.

The following dose was then given:-

3 c.c. Hedonal (1%.)
3 c.c. Saline.

The result in the auricle line:- In 3 seconds after beginning to perfuse the drug (3 c.c. of 1% Hedonal or .46 grain Hedonal) and before it had all been introduced, the contraction of the auricle began to diminish in its amplitude. In 30 seconds the maximum effect was obtained - 6 m.m. The auricle in 35 seconds later had recovered, but not to its former amplitude. It became 20 m.m.

The result in the ventricle line:- In 45 seconds the maximum effect was obtained, the amplitude of contraction being 8 m.m.. For 30 seconds it had remained about 10 m.m.. In 40 seconds after the maximum effect the ventricle had recovered its former amplitude of contraction - 48 m.m.. Recovery was therefore complete.

At the end of the tracing the drum was stopped on five occasions, the time being marked on the chart. Though this section is not dealing with blood pressure, it may be remarked that the blood pressure line has passed into the ventricle line and has become lost to view.

In the above experiment, there is a marked effect upon the auricle and ventricle, even with what has been considered in other experiments a moderate dose for a rabbit; but the strength of the solution in this single instance has been greater and explains the more profound effect.

TABLE IV.

	Amplitude before Hedonal.	Dose.	Amplitude after Hedonal.	Time for maximum effect.	Time for recovery.	Loss in amplitude.	Percentage of loss.	Extent of recovery.
Auricle	32 m.m.	3 c.c. of 1%.	6 m.m.	30 secs.	35 secs.	26 m.m.	81	Partial
Ventricle	48 m.m.	3 c.c. of 1%.	8 m.m.	45 secs.	40 secs.	40 m.m.	83	Complete.

SECTION IV.

EFFECT OF HEDONAL ON THE HEART OF THE FROG.

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Effect of Hedonal on the excised heart of the frog:-

(a) Amplitude of heart's movement.

(b) Cardiac rate.

Seven experiments were carried out by perfusion where the drug-solvent and restorative were identical, viz., "Sherrington."*

One experiment was made where the solvent was .5% normal Saline and the restorative was "Sherrington."

There was one experiment with the solvent and the restorative both saline but of different strengths, viz., .9% and .75% respectively.

Lastly, one experiment is included where the Hedonal solution was dropped on the heart's surface.

Dealing collectively with the experiments produced in this section, the general results are now reported.

In the first eight tracings (seven experiments) the strength of the Hedonal solution used was 1 in 2000, 1 in 1000, and 1 in 250 respectively. The drug solvent was the same as the control or restorative solution in each of these, viz., "Sherrington."

Effect on amplitude of cardiac contraction.

The most prominent and constant effect upon the heart was a diminution in the amplitude of the contraction.

A solution of 1 in 2000 sometimes failed to affect the amplitude of contraction as in Figure 6, arrow 5 on page 66. This is the weakest solution which has produced any diminution in amplitude of contraction. The effect is seen in Figure 1, arrows 3, 9, 11 and 13, on page 60. The strongest solution used (1 in 250) has frequently stopped the action of the heart entirely, as can be seen in Figure IV, page 63, and in Figure III, arrow 5, on page 63.

* For composition see p. 18, Vol. II.

A solution of 1 in 1000 has even caused stoppage of the heart, as in Figure 1, arrow 7. In this case "Sherrington" perfused before the heart had entirely stopped, failed to avert the final change.

Effect on cardiac rate:-

Weak solutions, such as 1 in 2000 increased the rate at first; in Figure II, arrow 3, the increase was 18%. Subsequent doses increase the rate less than at first; in Figure II, arrow 5, the reduction was only 11 per cent. This result was important as it was near the beginning of the experiment and the heart was less affected by other doses. This result can also be seen in Figure 1, arrows 9, 11 and 13, on page 60.

Solutions of 1 in 1000 also increased the rate at first, to be followed sooner by retardation. This is very striking in Figure II, line 1, where the rate is increasingly reduced, even though the restorative has been perfused - see arrows 1 and 2. The exact figures are here recorded. The rate at the beginning of line 1 was 20 in 60 seconds. Hedonal 1 in 1000 was perfused and the rate immediately became 23 - an increase of 15%. In the next period of 60 seconds, the rate was 16,-a reduction of 20%. Next period, notwithstanding that "Sherrington" was being perfused, the rate became 7, equal to a loss of 75% as compared with the normal 20. This is not a "Sherrington" effect as the restoration due to "Sherrington" was shown later. It was a continued Hedonal effect.

Strong solutions, for example, 1 in 250, may increase the rate at the beginning but much sooner show the reduction than the weaker solutions, and may stop the heart altogether. This is well seen in Figure III, arrows 1, 3 and 5.

In Figure VI, arrow 1, an increased rate is followed by cessation.

When the heart has ceased to beat it can be readily restored in many cases by "Sherrington". This is seen in Figure IV and in Figure III, arrow 8, at the beginning of line 3.

In one case where the heart had stopped with 1 in 250 solution of Hedonal and "Sherrington" failed to restore it, the action was quite recovered by gently touching the surface of the heart with a smooth glass rod, Figure VI, arrow 9.

The heart stops in diastole.

This can be plainly seen in Figures VII and VIII.

In addition to the group of experiments above mentioned, other three have been included here for different reasons.

When the drug solvent and the restorative differ a result may be constantly obtained, no matter how dilute the solution of the drug may be. It is then not a Hedonal effect at all. This can be seen in Figure IX. The dilutions of Hedonal were made up to 1 in 100 millions in ,5% saline but the restorative was "Sherrington" containing Ca Cl_2. The drug solution cut down the amplitude every time - no less with the extreme dilutions - and the "Sherrington" always restored the amplitude.

Then again, a tracing is shown where the drug solvent was normal saline .9 % and the restorative was saline .75%. This is seen in Figure X on page 60. The dilutions were as great as 1 in 20 millions. The effect was not decreased by this great dilution. The diminution of the sodium ion in the restorative allowed a relatively greater amplitude of contraction. This was not a Hedonal effect. The tracing shows a marked reaction like what is found in the hypodynamic heart of the frog referred to by Clark. Ref. 26. Such a heart is very sensitive.

In this experiment, much perfusion had already taken place before the very dilute solution was used.

Lastly it has been shown in Figure XI that Hedonal solution .37% dropped on the heart's surface can stop all movement, which movement can again be restored by normal saline applied in the same manner.

Method adopted.

In the present 10 experiments the following method was carried out:- The pithed frog was placed on its back on the frog-board and the apex was suspended by a clip after the necessary dissection. A glass cannula was then placed in the truncus venosus and tied there: it had a branch for overflow so that the liquid could always remain at the same level. The severed heart was then placed on a second stand, the heart being suspended by the glass cannula above, and the apex held by a clip pointing downwards and held by a thread. The thread was attached to the long arm of the myograph lever whose arrow point made a tracing on a slowly revolving drum. A third stand then supported the solution of Hedonal and the restorative solution placed 10 inches higher than the heart. These two vessels were fitted with rubber tubes from below, each being supplied with a spring clip and at the end a piece of glass tubing. This was easily inserted into the upper end of the heart's cannula when perfusion was to take place.

FIGURE I.

In Figure I is shown the effect on the frog's heart of Hedonal solution 1 in 2000 and 1 in 1000. The estimation was made from a period approximately 60 seconds and taken from 15 millimeters of the time line as the waves were rather close for accurate counting. The total results of this experiment are seen as follows:-

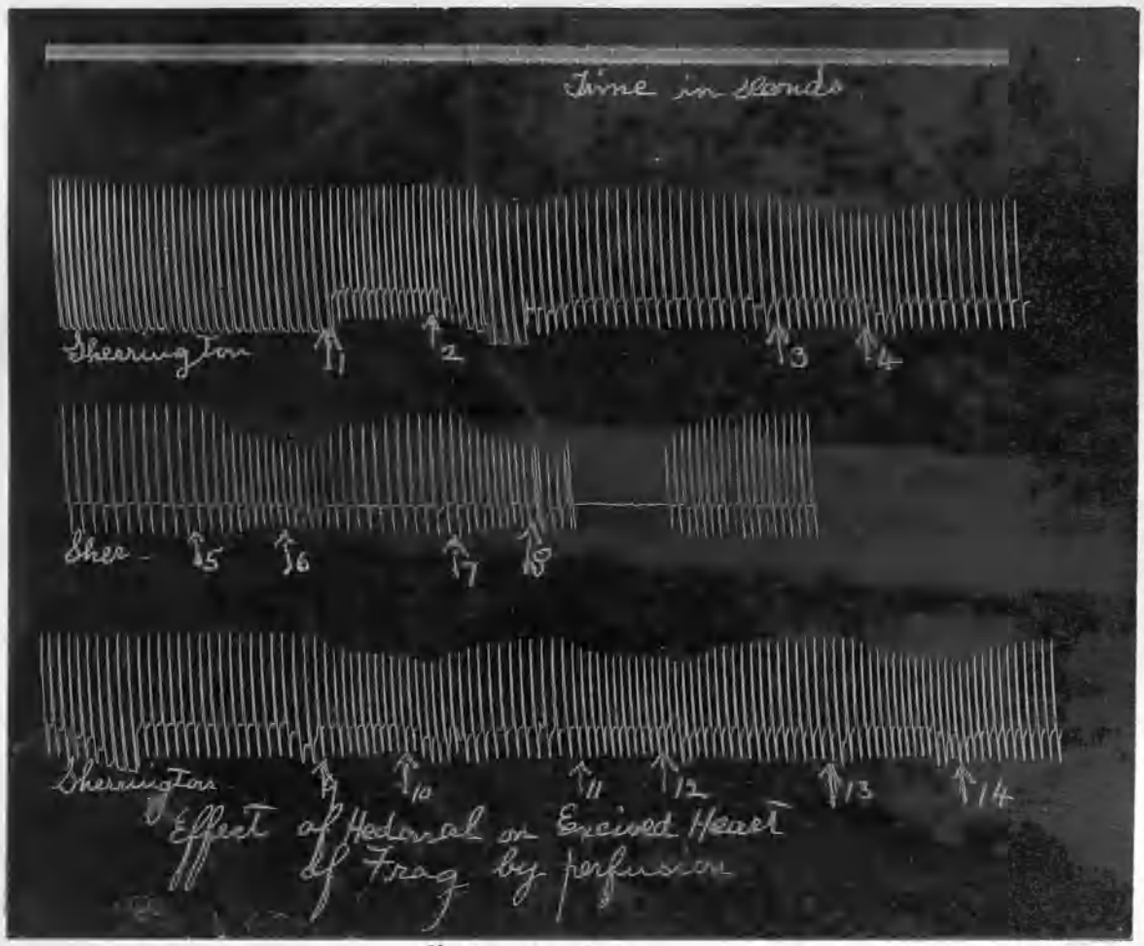
Hedonal Solution 1 in 2000.

1. The amplitude of the heart's movement was reduced on an average taken of 5 doses by 20%.
2. The cardiac rate was increased on an average taken of 5 doses by 22%.

Hedonal Solution 1 in 1000.

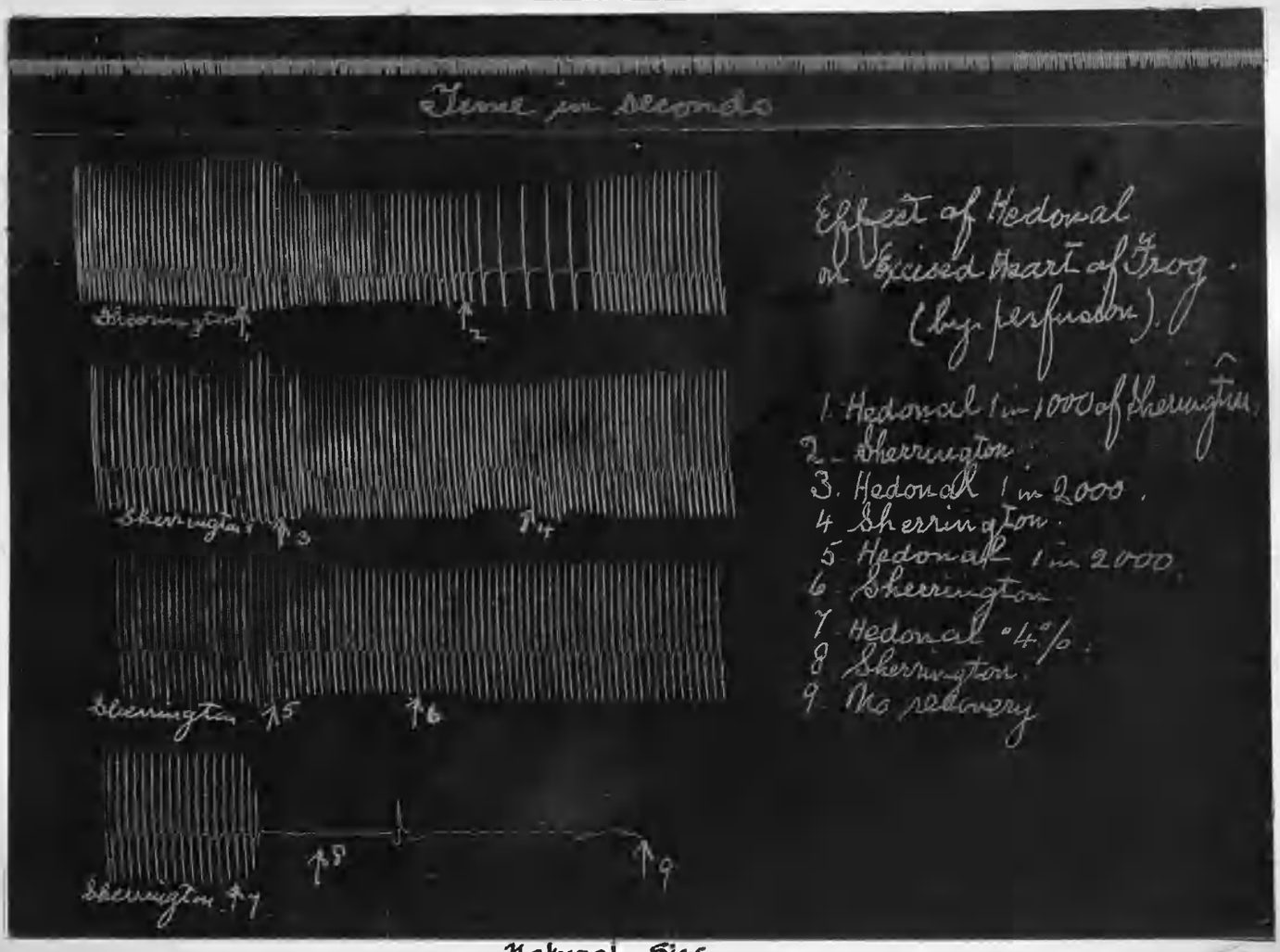
1. The amplitude of contraction was reduced on an average by 38%.
2. The rate was increased on an average by 28%.

Figure I.



Natural Size.

Figure II.



Natural Size.

Details of the perfusions made in this tracing.

1. Hedonal 1 in 2000 of "Sherrington".
2. "Sherrington".
3. Hedonal 1 in 2000.
4. "Sherrington".
5. Hedonal 1 in 1000.
6. "Sherrington".
7. Hedonal 1 in 1000.
8. "Sherrington".
9. Hedonal 1 in 2000.
10. "Sherrington".
11. Hedonal 1 in 2000.
12. "Sherrington".
13. Hedonal 1 in 2000.
14. "Sherrington".

Details of measurement of amplitude of contraction and cardiac rate by each dose.

First line:-

"Sherrington", Amplitude of contraction 20 m.m.

cardiac rate 12. . .

Hedonal, 1 in 2000. Amplitude of contraction 18 m.m. Reduction 10%.

Rate 15. Increase 25%.

"Sherrington", Amplitude of contraction 19 m.m.

Rate 12.

Hedonal, 1 in 2000, Amplitude of contraction 15 m.m. Reduction 21%.

Rate 13. Increase 8%.

"Sherrington", Amplitude of contraction 18 m.m.

Rate 11.

Second line:-

"Sherrington", Amplitude of contraction 17 m.m.

Rate 10.

Hedonal, 1 in 1000, Amplitude of contraction 11 m.m. Reduction 35%.

Rate 13. Increase 30%.

"Sherrington", Amplitude of contraction 17 m.m.

Rate 11.

Hedonal 1 in 1000. Amplitude of contraction 10 m.m. Reduction 41%.

Rate 14. Increase 27%.

"Sherrington" - The heart continued to contract for 3 pulsations, when it stopped as if from the continued effect of Hedonal. The heart then began to respond to the "Sherrington".
Amplitude of contraction 16 m.m. Rate 15.

Third line:-

"Sherrington,"	Amplitude of contraction 17 m.m. Rate 11.	
Hedonal, 1 in 2000.	Amplitude of contraction 13 m.m. Rate 15.	Reduction 23%. Increase 36%.
"Sherrington,"	Amplitude of contraction 17 m.m. Rate 11.	
Hedonal, 1 in 2000.	Amplitude of contraction 13 m.m. Rate 15.	Reduction 23%. Increase 36%.
"Sherrington,"	Amplitude of contraction 17 m.m. Rate 13.	
Hedonal 1 in 2000.	Amplitude of contraction 13 m.m. Rate 14.	Reduction 23%. Increase 7%.
"Sherrington,"	Amplitude of contraction 17 m.m. Rate 13.	

NOTE:-
The estimation in each Hedonal perfusion has been compared with the immediately previous restorative dose.

FIGURE II.

In Figure II the time line represents seconds, and periods of the tracing representing 60 seconds have been considered each time. The general effect in this experiment has been reduction in the amplitude of contraction with every Hedonal perfusion, and initial increase of the cardiac rate in each case except with the strongest solution, which stopped the movement of the heart; this last is a very strong effect (see arrow 7).

Table of Doses and Effects.

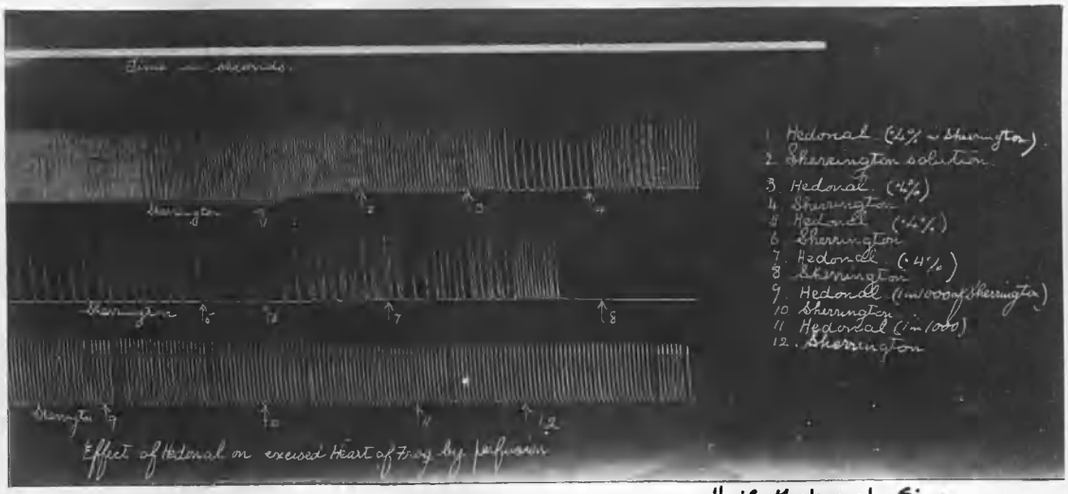
Hedonal solution.	
1 in 2000 (arrow 3)	Amplitude of contraction reduced 20%. Rate increased 18%.
1 in 2000 (arrow 5)	Amplitude of contraction reduced 21%. Rate increased 11%.
1 in 1000 (arrow 1)	Amplitude of contraction reduced 32%. Rate increased 15%.
1 in 250 (arrow 7)	All action of the heart ceased after 3 beats.

Detailed account of doses in Figure II.

"Sherrington"	Amplitude of contraction 22 m.m. Rate 20.	
Hedonal 1 in 1000.	Amplitude of contraction 15 m.m. Rate 23.	Reduction 32%. Increase 15%.
"Sherrington" (first period)	Amplitude of contraction 18 m.m. Rate 7.*	
"Sherrington" (second period)	Amplitude of contraction 22 m.m. Rate 18.	

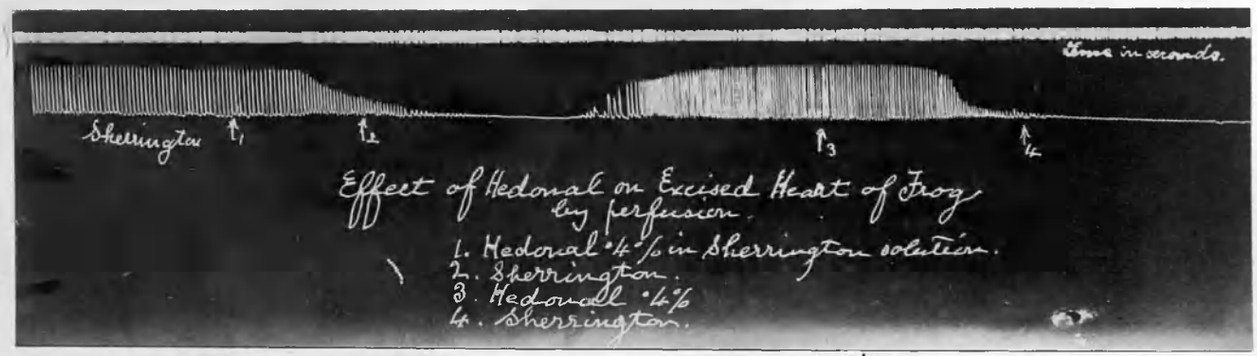
* This rate is a prolonged Hedonal effect.

Figure III.



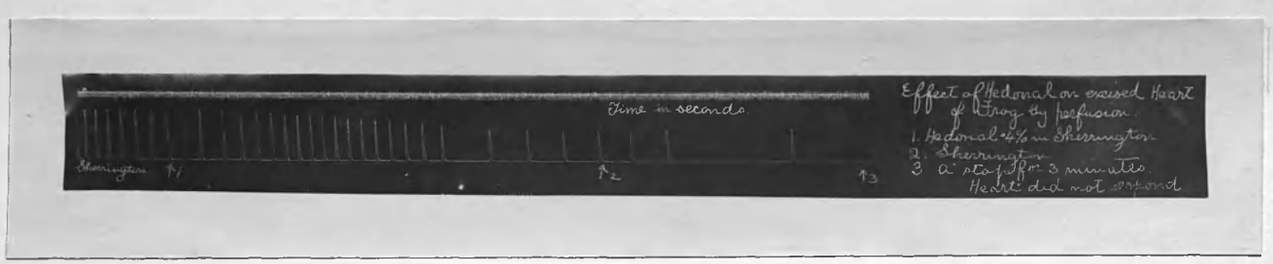
Half Natural Size.

Figure IV.



⅔rds. Natural Size.

Figure V.



Half Natural Size.

Second line:-		
"Sherrington"	Amplitude of contraction 25 m.m. Rate 17.	
Hedonal, 1 in 2000.	Amplitude of contraction 20 m.m. Rate 20.	Reduction 20%. Increase 18%.
"Sherrington"	Amplitude of contraction 23 m.m. Rate 20.	
Third line:-		
"Sherrington"	Amplitude of contraction 23 m.m. Rate 17.	
Hedonal, 1 in 2000.	Amplitude of contraction 18 m.m. Rate .19.	Reduction 21%. Increase 11%.
"Sherrington"	Amplitude of contraction 20 m.m. Rate 18.	
Fourth line:-		
"Sherrington"	Amplitude of contraction 20 m.m. Rate 16.	
Hedonal, 1 in 250,	After 3 pulsations heart ceased. No restoration.	

FIGURE III.

The tracing in Figure III shows the effect of .4% solution of Hedonal and 1 in 1000 solution, on the excised frog's heart by perfusion.

It has been observed in most experiments of this kind, that Hedonal at first increases the cardiac rate, more especially with weaker solutions, after which increase, the rate is reduced. This has been the experience even with the stronger solutions (1 in 250), although the initial increase has not been so marked nor has it been so constantly seen.

In the present case, Hedonal (1 in 250) was perfused four times at the beginning. At arrows 1 and 3, the increased rate can be seen. In the second line this solution has twice stopped the action of the heart, which was again restored by "Sherrington".

The two perfusions of the weaker solution have neither of them showed the initial increase, because the heart had already been so much under the influence of the drug; only a reduction in rate is observed.

FIGURE IV.

The tracing in Figure IV shows marked effect from two separate perfusions of Hedonal (1 in 250). This strong solution has caused to all appearance complete cessation of the heart after perfusion for 80 seconds, to be followed by complete restoration by "Sherrington".

At the beginning of the tracing the cardiac rate was 31 in 80 seconds and the amplitude 10 m.m. Hedonal was introduced at arrow 1. In 42 seconds the effect began. The rate then became 35, an increase of 13%. The amplitude of contraction became 4 m.m. - a loss of 60%. At this point "Sherrington" was again perfused. The amplitude still rapidly fell to zero in 80 seconds. The heart stopped for the next 60 seconds. The "Sherrington" then began to restore the heart.

At arrow 3 another dose of Hedonal (1 in 250) was perfused with exactly the same kind of result.

The reason why the Hedonal solution was slow in taking effect in this experiment was that there was a different perfusing cannula used, which had the overflow tube at a higher level. Some of the previous liquid was still acting when the second solution was introduced.

FIGURE V.

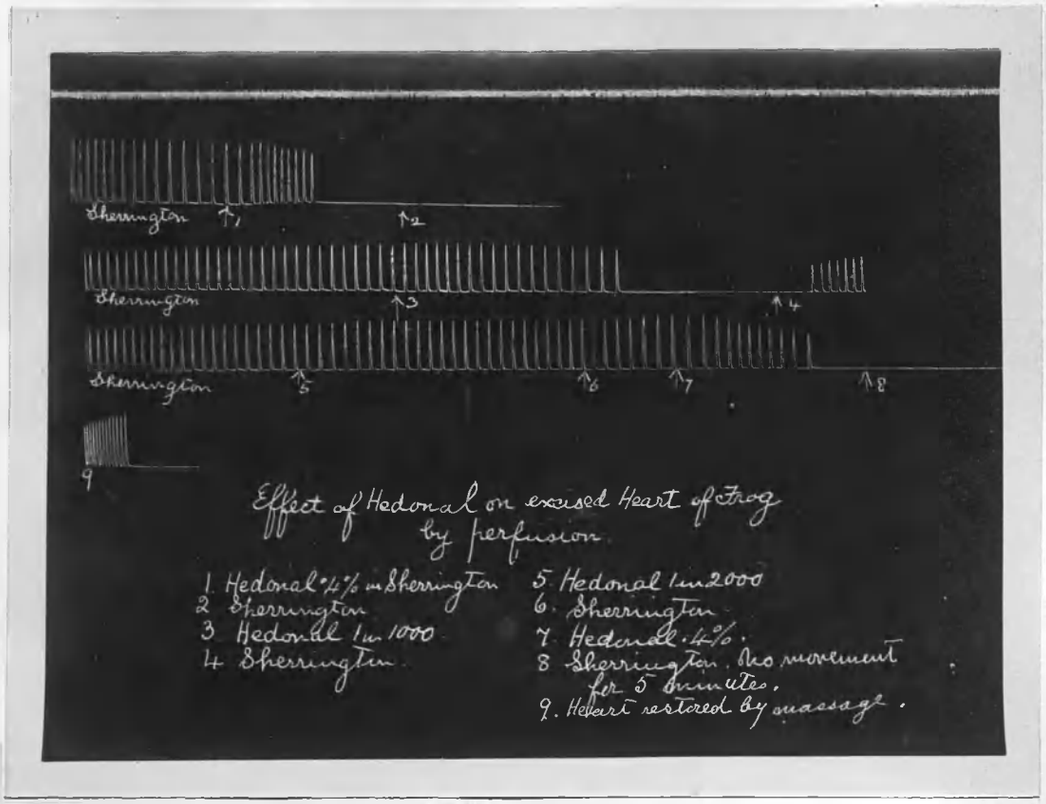
In Figure V there is seen the effect of a strong solution of Hedonal on the frog's heart when perfused. The drug was introduced for 400 seconds and "Sherrington" failed to restore it.

The tracing starts on the left with perfusion of "Sherrington". The cardiac rate here was 8 beats in 80 seconds. When the drug was being perfused the rate became 5, 7, 6, 2, 2, in similar periods. The strength of the Hedonal was 1 in 250.

The total loss in amplitude of contraction from arrow 1 to arrow 2 equals 40%.

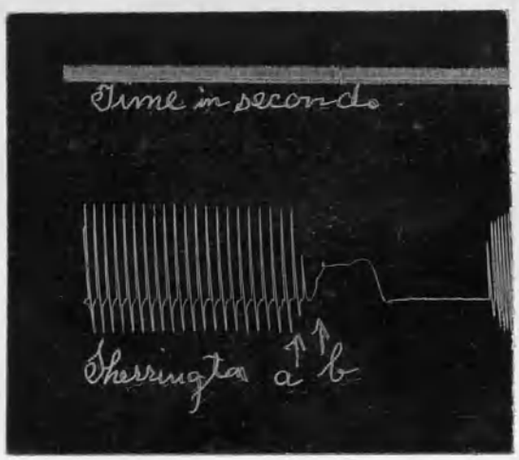
Loss in cardiac rate in this period was equal to 75%.

Figure VI.



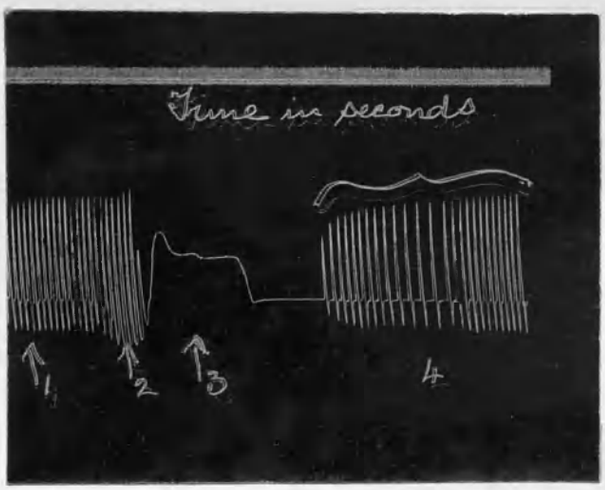
Scale 2/3rds Natural Size.

Figure VII.



Natural Size.

Figure VIII.



Natural Size.

FIGURE VI.

The tracing in Figure VI shows the effect of Hedonal in three strengths on the excised heart of the frog by perfusion.

The solution 1 in 2000 made no change in the amplitude or rate - see arrow 5.

The solution 1 in 1000 led to stoppage of the heart which was restored by "Sherrington" - see arrow 3.

The strong solution 1 in 250 was used at the beginning and the end. The amplitude of contraction was reduced 23% and 33% respectively. Both doses led to stoppage of the heart. In the first case "Sherrington" restored the cardiac action; in the second no restoration took place until the organ was gently touched with a glass rod.

NOTE:- The time line was in seconds.

FIGURE VII. and FIGURE VIII.

These small tracings (Figures VII and VIII) represent the same thing, and are taken from the same frog. The heart stopped in diastole. Good restoration was obtained by "Sherrington". The heart responded to Hedonal in 2 beats, the amplitude being quickly cut down. One lesser but prolonged contraction then took place after which the heart stopped in diastole.

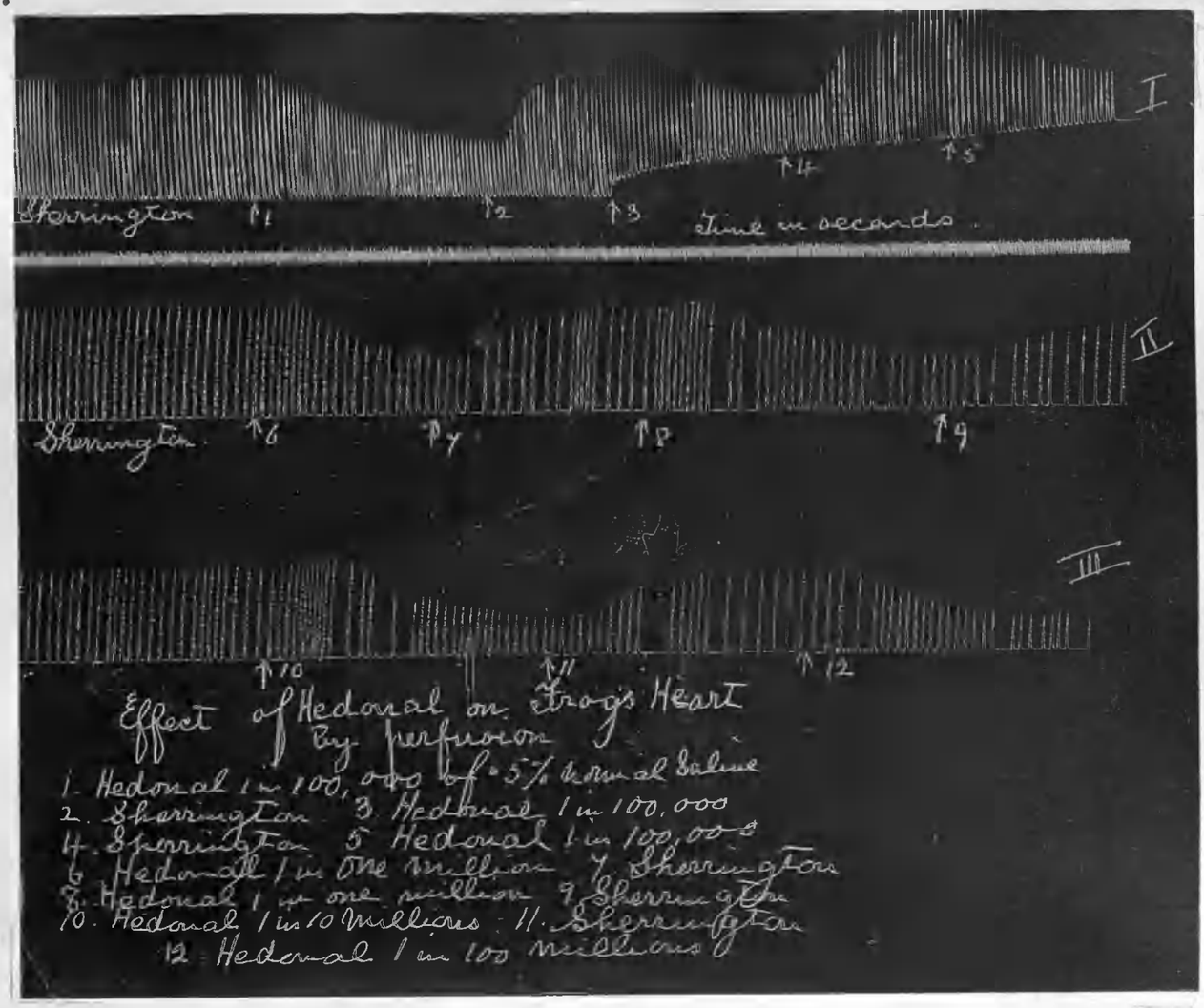
Figure VII.

Arrow a = Hedonal .4% in "Sherrington".
b = "Sherrington" - effect much delayed.

FIgure VIII.

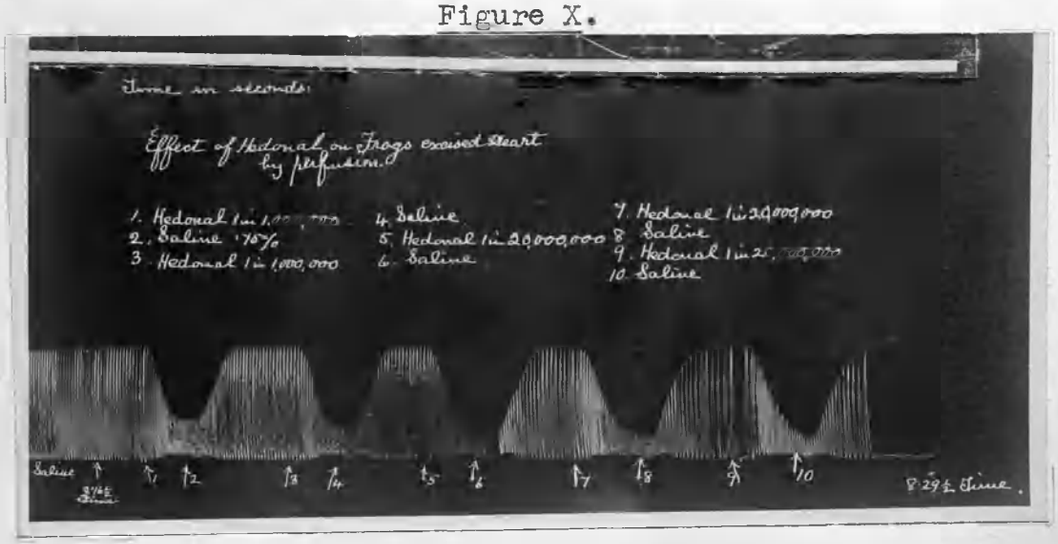
Arrow 1 = "Sherrington" being perfused.
2 = Hedonal .4%.
3 = The lesser but prolonged cardiac contraction.
4 = Restoration due to "Sherrington" after complete cessation.

Figure IX.



Natural Size.

Figure X.



Half Natural Size.

Figure XI.

Scale.
2/3rds
Natural Size

FIGURE IX.

The tracing in Figure IX is an interesting one. The Hedonal solution was diluted by .5% normal saline until a solution of 1 in 100 millions was obtained. The control used was "Sherrington" containing $CaCl_2$. Each dose of the Hedonal reduced the amplitude of contraction as much as at first, even with the weakest solution. The drug solvent and the control should have been identical. It is not a Hedonal effect which is shown; it could have been obtained without any Hedonal at all.

FIGURE X.

In Figure X the drug solvent and the control were both saline but of different strengths. The drug solvent was .9% saline and the restorative was .75% saline. The diminished quantity of the sodium ion tended to increase the amplitude every time. This then was not a Hedonal effect. The dilutions were made until 1 in 20 millions strength was obtained. The amplitude was as great at the end as with a weaker solution used at the beginning.

In this experiment the heart had undergone many perfusions previously, so that it resembled the hypodynamic heart in being very responsive.

FIGURE XI.

In Figure XI the effect is recorded after applying a few drops of Hedonal solution (.37%) over the outer surface of the excised heart of the frog.

The heart ceased after 3 beats, although the amplitude of the heart's movement had been 30 m.m. previously. Normal saline restored the movement again fully, and then the heart ceased.

SECTION V.

EFFECT OF HEDONAL ON THE RESPIRATION IN THE RABBIT.

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The following three experiments have been carried out, to ascertain in the first place, in what way Hedonal administered intravenously to a rabbit might affect its respiration, and secondly, to find out whether and to what extent stimulation of the vagus, when the animal is narcotised by Hedonal, would bring about a normal physiological response, as seen

(a) on the Respiration tracing, and

(b) on the blood pressure tracing.

The effect of Hedonal on the blood pressure is not discussed in this section.

The three experiments differ somewhat from each other.

Experiment A:- In this case a small dose of 1 c.c. (.11 grain) was given every 10-30 seconds to obtain a uniform narcosis without any ether being administered and with artificial respiration withdrawn. The condition then approached to the modern continuous method of anaesthesia, as against the older interrupted style. The tracing shows a respiration line and a blood pressure line (see Figs. 76 and 77).

Experiment B:- This one has been carried out to show the effect on respiration alone. There was much time lost in this case preparing a sensitive tambour, so that the effects are those found in an animal which was almost moribund. The results in this case, while instructive, may not be typical of an animal of average strength.

Experiment C:- In this experiment it has been ascertained in what way Hedonal affects the respiration, and also during the Hedonal narcosis, how the vagus nerve reacted to faradic stimulation, as seen in the tracings of the respiration and blood pressure.

GENERAL STATEMENT OF RESULTS OBTAINED.

Hedonal affects the respiration rate. A rabbit which had received 2.8 grains of Hedonal per kilogramme of body weight in an experiment lasting 17 minutes, showed a reduction in the rate equal to 58% (See experiment A, figs 76 and 77).

In another case (experiment C), it was found that the respiration rate was reduced 53% in the same time, the animal having received .9 grain of Hedonal per kilogramme.

A single dose of 3 c.c. (.34 grain) of Hedonal solution caused a reduction of the respiration rate equal to 21.7% (Experiment C).

Hedonal affects the amplitude of movement of the respirations.

In one experiment lasting 17 minutes, the reduction was 28% (Experiment A. Figs 76 and 77.). In another case, it was 38% in the same time (Experiment C.)

A single dose of 3 c.c. (.34 grain) of Hedonal caused a reduction of the amplitude equal to 25% (Experiment A.). In another case where the animal was moribund, the reduction was 50%. (Experiment B.).

Recovery of the amplitude to the previous normal takes place in 10 seconds.

Hedonal has no appreciable effect on the Vagus nerve, as has been ascertained by observing the respiration tracing, and blood pressure tracing, when the nerve has been stimulated during Hedonal narcosis, the secondary coil standing at 10 centimetres and even 20 centimetres from the primary. Respiration is almost stopped by these faradic stimulations: the blood pressure is also much affected. There is therefore no paralysis of the vagus observed.

It may be interesting to quote here the opinion of other observers on this subject of respiration.

Dreser in his own words states:- "The effects of the new urethane (Hedonal) Ref 54

on/

on the respiration was similar to that of urethane, namely, for the most part a slight depression."

Dreser again states:- "Neither Ethyl Urethane nor Hedonal in the human subject showed any specific effect on respiration. As in natural sleep, respiration was less active." Ref. 53

Fedoroff states that if the flow of the Hedonal solution be too rapid during administration, respiration stops. Ref. 11.

Burkhardt (of Nurenberg) in 1913 said, when referring to Hedonal, that he deprecated its use clinically, because of the fall of blood pressure, the difficulty of regulating the dose, the prolonged sleep, and the danger of respiratory paralysis. Ref. 48.

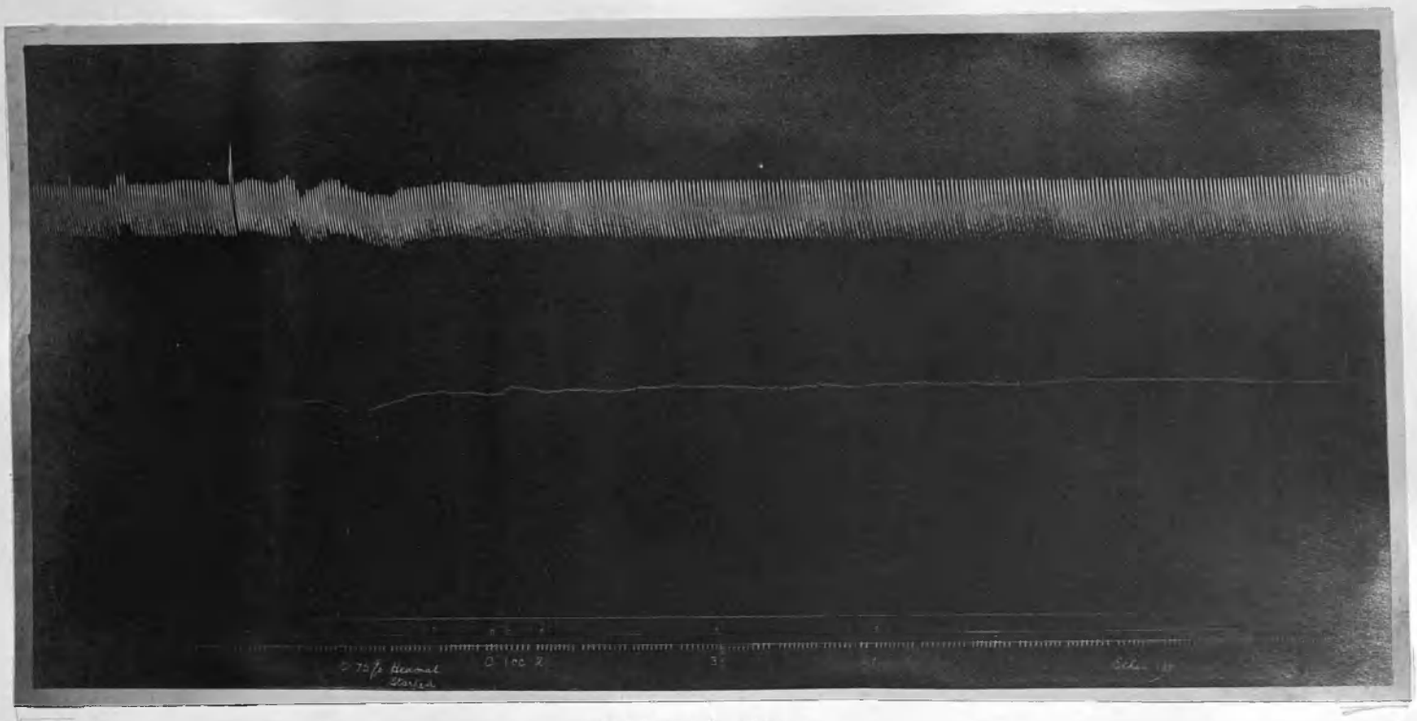
An early death was reported from Hull. In this case respiratory paralysis occurred without any warning, except a gradual diminution in the volume of breathing. Ref 45a and Ref. 17.

Dreser states, that Hedonal lowers blood pressure, but does not interfere with respiration. Ref. 11.

Dr Kummel at the International Medical Congress (1913) spoke of respiratory paralysis being an ever-present danger of Hedonal infusion. Ref 45a.

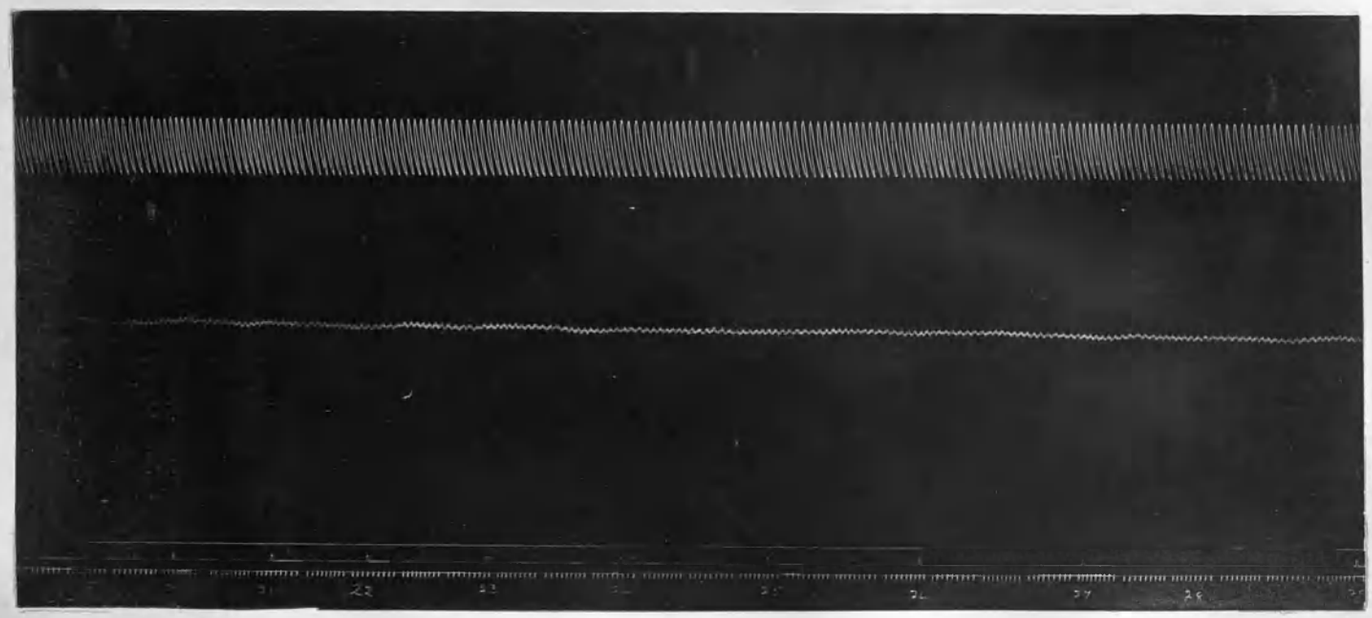
In considering such reports as the above, one may feel that it is just possible that in any experiments on this part of the subject, the observations may not have been scientifically recorded, only a rough idea being conceived of the conditions. As already stated, practically no tracings whatever on Hedonal have been published, at least in the German or English language - only the literature. Even when cursorily examining the present respiration tracings, one might easily come to the conclusion that there was no change.

Figure LXXVI.



·47 Natural Size

Figure LXXVII.



·44 Natural Size.

DETAILS OF EXPERIMENT A.

In this experiment (figs 76 and 77), Hedonal solution (.75%) was administered in a fairly regular manner, to keep up a uniform narcosis. Every 10-30 secs. 1 c.c. was perfused until 48 such doses were given. The operation lasted 17 minutes. The rabbit weighed 1950 grammes.

There is seen an upper broad respiration line and a lower thin blood pressure line. The time line is in seconds.

The following steps were carried out:-

Etherization.

Tracheotomy.

The venous cannula was inserted into the left common jugular vein and connected with one burette only, - containing Hedonal solution.

The arterial cannula was placed in the right carotid artery and connected to the blood pressure recording apparatus.

A balloon was applied to the abdomen, and connected by a tambour and pointed lever to the revolving drum.

The stopcock of the single burette was turned so that a very slow rate of flow could be obtained. Figure 76 shows the beginning of the experiment. While the animal was under ether narcosis the tracing was started. The Hedonal was then perfused as above stated and after four doses the ether was stopped and the animal allowed to breathe air through the tracheotomy tube. The signal line marked the beginning of every dose of 1 c.c.. The doses were recorded by numerals placed under the time line.

There were no visible fluctuations in respiration and there were no signs of superficial state coming on, so that the animal was in an anaesthetic state purely due to Hedonal all the time. The respiration rate/

rate very steadily became reduced from the first dose. When 36 c.c. had been introduced, the respiration began to show diminished amplitude of movement, or shallow breathing, but was very regular.

In estimating the effects in the present case, it has been found convenient to consider the number of respirations occurring in periods of 20 seconds. The conditions at every sixth dose have been tabulated below:-

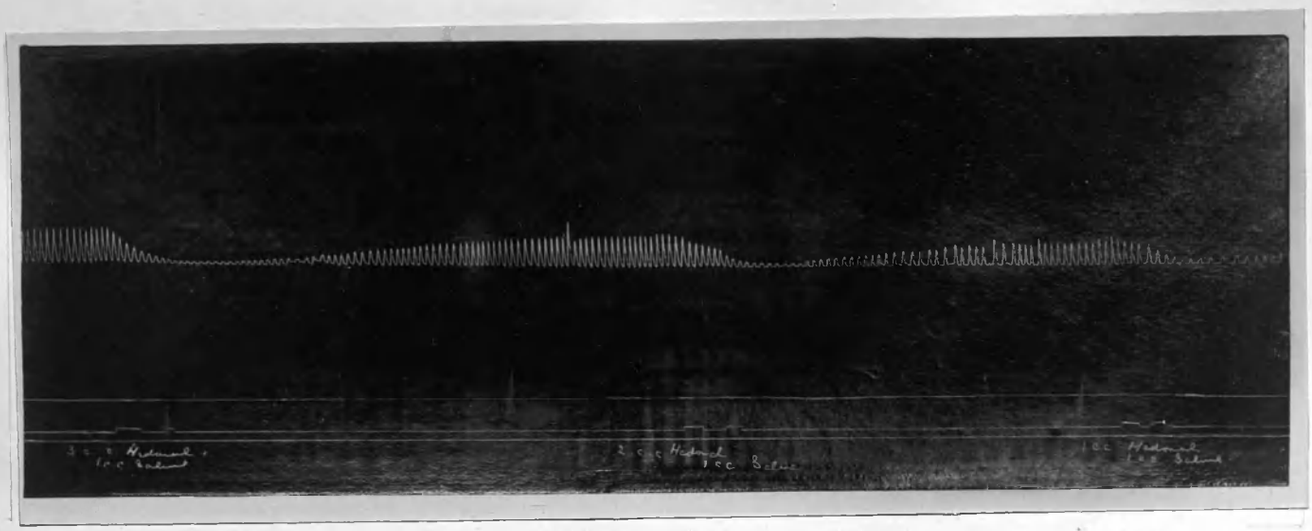
Number of the dose.	Respirations in periods of 20 secs.	Amplitude of respiration waves.
1st	29	18 m.m.
6th	22	20 m.m.
12th	18	18 m.m.
18th	17	18 m.m.
24th	15	18 m.m.
30th	15	18 m.m.
36th	12	16 m.m.
42nd	12	14 m.m.
48th	12	13 m.m.

The above occurred during 17 minutes.

There is thus a loss in the respiratory rate equal to 58% and a loss in amplitude of 28%. The tracing was a very long one; but the portions in figures 76 and 77 show what is necessary.

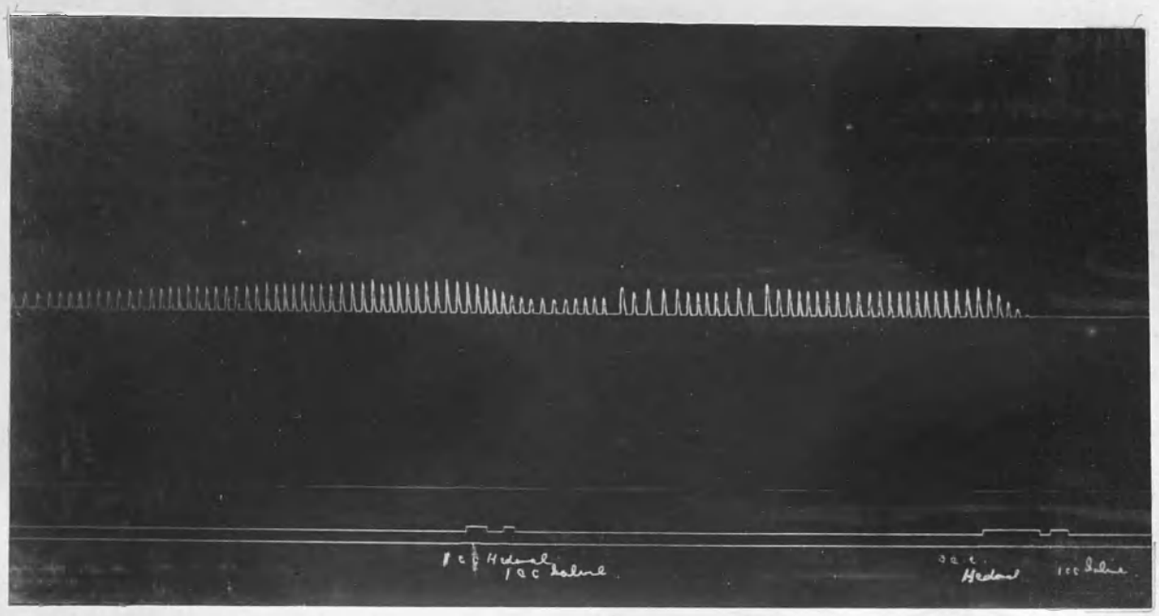
The animal received 5.5 grains of pure Hedonal or 2.8 grains per kilogramme.

Figure XC.



·42 Natural Size.

Figure XCI.



·55 Natural Size.

DETAILS OF EXPERIMENT B.

A rabbit weighing 1600 grammes was used. The animal was etherised until the venous cannula had been inserted in the left common jugular vein. No tracheotomy was necessary. A balloon was slightly distended and placed over the abdomen, being fixed there by a towel passed round the body. The connection was then made for a tracing, as in experiment A. The rubber tubing from the balloon had a hand-ball introduced by a glass T-shaped tube. This allowed the balloon to be distended or reduced in size, and also made it possible to place the pointer at the proper level on the travelling paper. As there was no time record taken, a portion of the tracing, measuring 40 millimetres in length, and representing 30 seconds, was considered each time. The doses given were:-

3 c.c. Hedonal and no Saline. The drug, not having been washed into the vessel, showed no effect.

3 c.c. Hedonal and 1 c.c. Saline.

Immediately, the amplitude of the respirations was reduced from 10 m.m. to 5 m.m. (50%). The respiration rate was reduced from 23 to 18 (21.7%). When the respiration recovered, the rate reached only 20; but the amplitude of the respirations was fully restored. This result may be the effect of the two doses of 3 c.c. as they were probably both washed in at the same time.

The experiment may now be followed in Figs. 90 and 91.

3 c.c. Hedonal and 1 c.c. Saline (1st dose in Fig.90).

This dose had a profound effect. Respiration became extremely shallow. The amplitude of the respirations was reduced from 12 m.m. to 1.5 m.m., equal to a loss of 87%. The respiration rate was reduced from 20 to 19, equal to a loss of 5%. The amplitude of the respirations was fully restored.

2 c.c. Hedonal and 1 c.c. Saline.

An immediate effect was again observed. The respiration rate fell from 21 to 19, equal to a loss of 9%. The amplitude again fell from 12 to 1.5 m.m. equal to a loss of 87%.

At the end of the tracing, (Fig.90) there is seen the effect of 1 c.c. Hedonal and 1 c.c. Saline.

This smaller dose has reduced the respiration rate from 18 to 14, equal to a loss of 22%. The amplitude fell from 10 to 2 m.m., equal to a loss of 80%.

The rest of the experiment can now be traced in Fig.91.

1 c.c. Hedonal and 1 c.c. Saline.

The respiration rate was reduced from 17 to 15, equal to a loss of 11%. The amplitude was reduced from 8 to 4 m.m., equal to a loss of 50%.

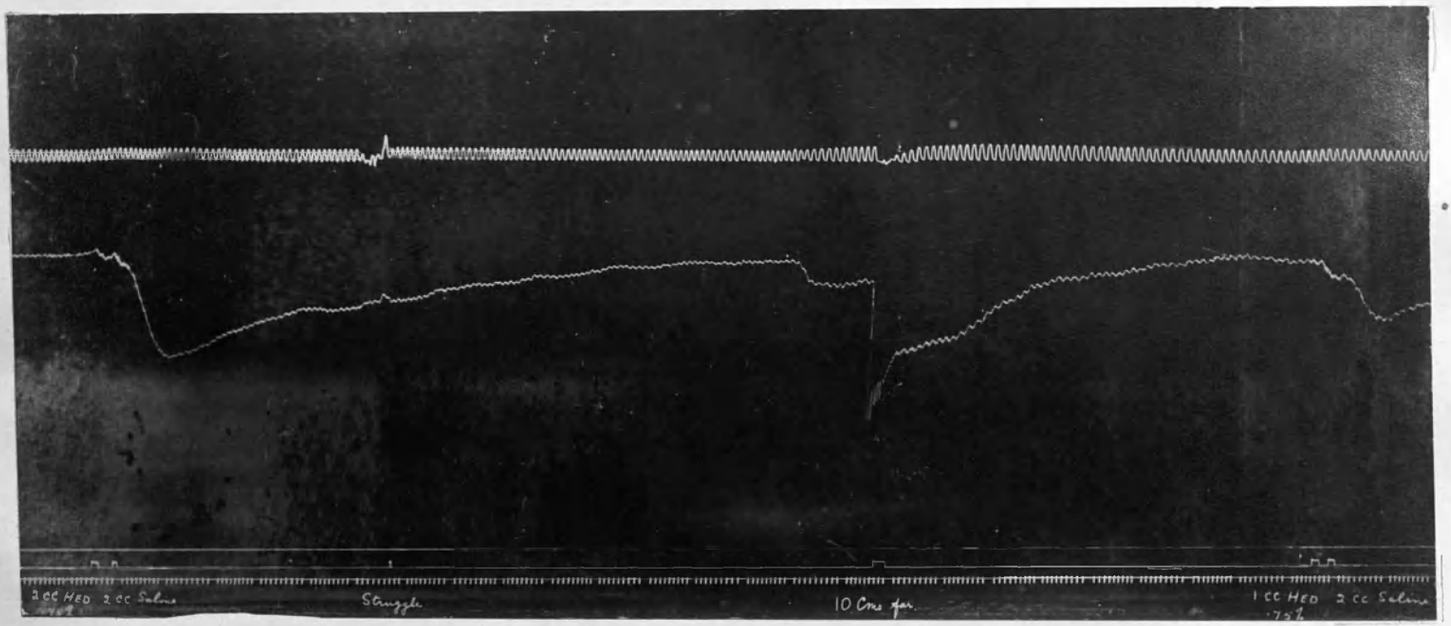
3 c.c. Hedonal and 1 c.c. Saline.

This dose stopped the respiration. The animal did not recover.

The animal used in this experiment was a small one and there was much time lost before the tracing was taken, preparing the sensitive tambour. The results recorded therefore, are likely more than the average. There was given in this experiment 1.8 grains of Hedonal altogether, or 1.1 grain per kilogramme of body weight.

A dose of 3.c.c. (.34 grain) caused a reduction in the respiration rate of only 5%,the amplitude being, however, reduced by 87%.

Figure LXXV.



·47 Natural Size.

DETAILS OF EXPERIMENT C.

This experiment shows the effect of Hedonal on the respiration of a small rabbit weighing 1300 grammes. It also shows the effect upon the respiration and blood pressure obtained by stimulation of the vagus nerve while the animal was narcotised by Hedonal. A portion of the tracing is seen in Fig.75.. There are two lines, the upper being that of the respiration and the lower being the blood pressure.

The following steps were carried out:-

Etherization.

Tracheotomy.

Venous cannula inserted in the left common jugular vein.

Arterial cannula inserted in the left carotid artery.

Left vagus nerve isolated.

A balloon placed over the abdomen and connected with the travelling smoked paper.

The time was recorded in seconds.

In this experiment, the vein, artery and nerve chosen were all on the same side. This is not desirable, as there is then more chance of interfering with the nerve by touching.

When all the dissection was completed, the ether was withdrawn, artificial respiration by the electric pump was continued for 8 minutes only so as to clear away all ether from the lungs, and the animal was allowed to breathe by the tracheal tube as it required. A normal tracing was then taken.

The following are the doses given during the experiment.

2.5 c.c. Hedonal (.75%) and 2 c.c. Saline.

3 " " " "

*2 " " " "

*This dose is seen at the left side of Fig.75.

Faradic stimulation, the secondary coil standing at 10 centimeters.

1 c.c. Hedonal and 2 c.c. Saline.

Faradic stimulation at 15 centimeters.

" " 20 "

2 c.c. Hedonal, and 2 c.c. Saline.

Results of the above doses in detail.

Conditions before starting:-

Respiration rate 28 - always counted in periods of 20 seconds.

Amplitude of the respirations 4 millimeters.

Dose 2.5 c.c. Hedonal.

Respiration rate became 25, 23, 23.

Amplitude of the respirations unaltered.

Dose 3 c.c. Hedonal.

Respiration rate 23, 19, 19, 18, 18 (loss 21.7%).

Amplitude of the respirations 3 millimeters during perfusion, and then returned to 4 millimeters, (loss 25%).

Dose 2 c.c. Hedonal (first dose marked in Fig.75).

Respiration rate from 19 became 19, 18, 18, 19, 19.

Amplitude of the respirations remained 4 millimeters - unchanged.

In 40 seconds later, there may be seen in the tracing a small irregularity, due to a movement of the animal, and marked "struggle."

Then in 80 seconds later, prior to using electricity, the vagus nerve was manipulated mechanically, during 20 seconds. The result of this is shown more particularly in the blood pressure line.

The blood pressure was reduced from 85 to 78 millimeters, equal to a loss of 8%.

The respiration rate was reduced from 18 to 15, a loss of 16%, (in 20 seconds).

The amplitude of the respirations was increased from 4 to 6 millimeters, or 50%.

The vagus was then stimulated for 3 seconds, the secondary coil standing at 10 centimeters.

The effect:-

Respiration almost ceased during stimulation.

Immediately stimulation was stopped, the respiration improved, so that the former rate was recovered in 10 seconds.

The blood pressure at the moment of stimulation fell vertically from 78 to 40 millimeters, - a loss of 48%. In 30 seconds it had fully recovered to 78 millimeters.

The next dose given was

1 c.c. Hedonal.

Respiration rate 14, remained 14, - no change.

Amplitude 4 millimeters became 3 millimeters, equal to a loss of 25%.

When the effect had passed off, there were given two separate stimulations of the vagus:-

Secondary coil at 15 centimeters.

Secondary coil at 20 centimeters.

Both of these showed an effect similar to that at 10 centimeters, but less. It is thus seen that the reduction in the respiration rate varies inversely with the distance of the secondary coil from the primary, when the vagus is stimulated and the animal under the anaesthetic influence of Hedonal.

Complete recovery of the respiration rate from these stimulations of the vagus, took place in 5 seconds after the current ceased to pass. The blood pressure took much longer to recover after vagus stimulation as may be seen below.

Coil at 10 centimeters took 75 seconds to recover.

Coil at 15 " " 32 " "

Coil at 20 " " 15 " "

Conclusions from Experiment C.

The respiration rate by a dose of 3 c.c. (.34 grain) was reduced 21.7%.

This is not a sudden change, the respiration continuing very uniform.

The amplitude of movement by a dose of 3 c.c. was reduced 25%. Doses of 1 c.c. and 2 c.c. showed little change.

Total result for the whole experiment of 17 minutes.

Respiration rate was reduced from 28 to 13 in 20 seconds - a loss of 53%.

The amplitude was reduced from 4 to 2.5 millimeters, - a loss of 38%.

There was given in the 17 minutes 1.2 grain Hedonal, equal to .9 grain per kilogramme.

SECTION VI.

EFFECT OF HEDONAL
UPON THE
VAGUS NERVE-ENDINGS
OF THE HEART.

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To find out whether the vagus nerve endings on the heart were affected by Hedonal, the nerve was exposed and stimulated, before and after administering a dose of the drug, and also at the time when the maximum effect of the drug was most apparent.

The effects were recorded with electric stimulations of varying intensity.

In the rabbit the result may be seen on the tracings of the auricle and ventricle and blood pressure: in the dog the heart was not dissected out but the effect is shown on the blood pressure line.

The effects on the rabbit may be seen in Figures XXIX, XCIII, LXXXVII, LXXXI and LXXXIX, and in the dog in Figure LXXXVIII.

Speaking generally the action of the vagus is retained during the Hedonal narcosis.

In Figure LXXXI stimulations were made with the secondary coil standing at positions varying from 15 to 25 centimeters. It was found that at 25 c.m. no effect at all was apparent. When stimulations were made at 15 up to 24 centimeters, in all cases there was seen "stand-still" of the heart as observed in the auricle and ventricle line.

In Figure LXXXIX the effect of vagus stimulation in the rabbit is further illustrated. It was observed when the secondary coil stood at 20 c.m. from the primary and the effect of a Hedonal dose was passing off, that the result of stimulation of the distal extremity of the divided right vagus in the neck was as follows:-

(1) Diminished amplitude of contraction of the auricle and ventricle.

(2) Reduction in the cardiac rate.

(3) Reduction in arterial tension as recorded from the carotid.

The above results are seen in Figure LXXXIX as an "organ-pipe" appearance.

When the same electric stimulation (Figure LXXXIX) was again applied to the nerve during the maximum effect of a dose of Hedonal, instead of only retardation of the cardiac rate there was seen "stand-still" of the heart in diastole. This effect remained during the time of stimulation. The pulsations then returned (but slowly) for 10 seconds, and then they became normal.

From the above it is apparent that the heart is more sensitive to vagus stimulation at the height of a Hedonal effect.

The weight of the rabbit also modifies the effect of vagus stimulation.

In Figures XXIX, LXXXVII and XCIII, which are taken from the same rabbit, we find that as the animal was of greater weight, stimulation of the vagus with the secondary coil even at 10 c.m. did not produce "stand-still" of the heart, but only marked retardation of the rate, with marked diminution in amplitude.

Stimulation of the vagus is accompanied by a fall in the blood pressure.

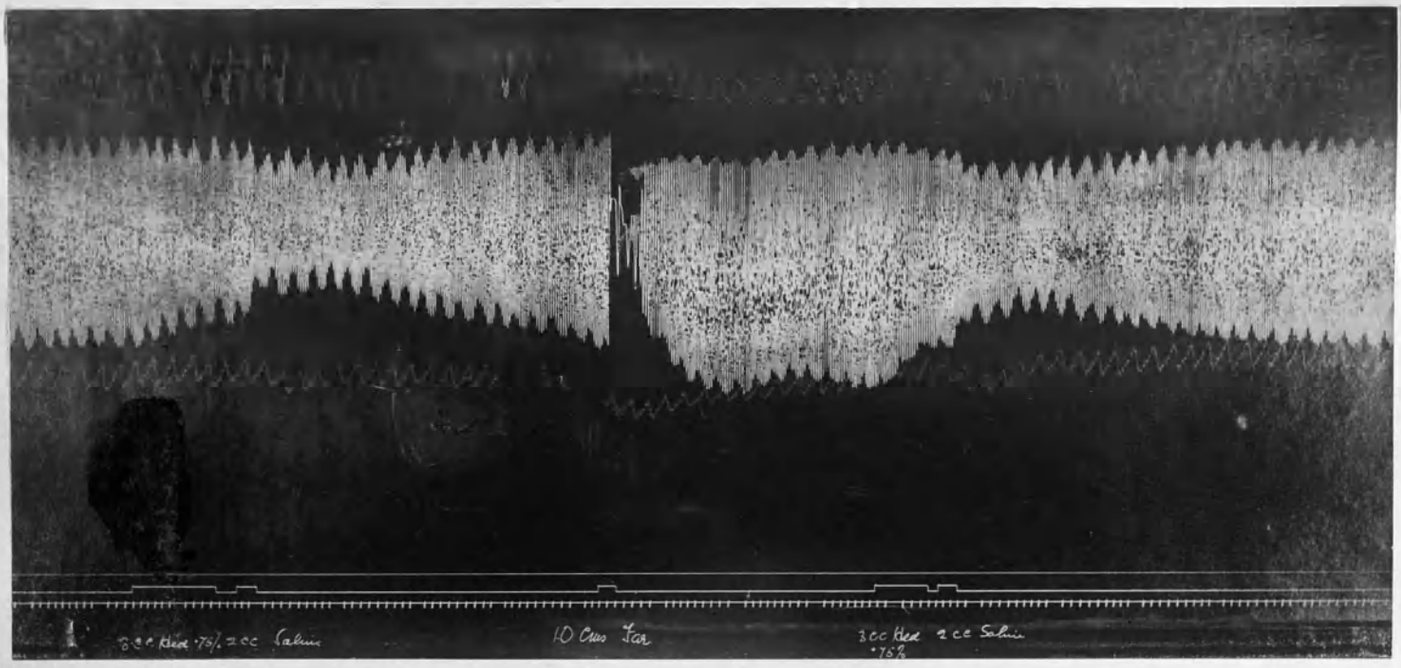
In the present experiments upon the vagus nerve the same steps were carried out in the preparation of the animal as in the experiments upon the auricle and ventricle of the heart, namely:-

1. Etherization.
2. Tracheotomy.
3. Insertion of venous cannula in left jugular vein and connection with double burette stand.
4. Insertion of arterial cannula in right carotid and McColl's electric connection to the manometer.
5. Opening the thorax and connecting the auricle and ventricle with the travelling smoked paper by means of threads.

In addition, the vagus nerve was dissected out and a loose ligature was passed round it, so that when wanted it could be gently pulled into view. This is conveniently done at the time the carotid is dissected out, as nerve and artery lie in the same sheath.

The two terminals from the secondary winding of a faradic coil were then placed under the vagus nerve, making quite sure of the contact.

Figure XXIX.



·51 Natural Size.

A centimeter measure was used with the coil to measure the current.

The strength of Hedonal solution used with the rabbit was .75%: in the dog it was 1%.

As the whole dissection in this series of experiments was extensive, the animal was placed on a warm water tank and the various steps were proceeded with as expeditiously as possible, to prevent shock.

FIGURE XXIX.

Figure xxix shows a tracing from a rabbit weighing 2800 grammes. There is an upper faint line from the auricle, a middle broad tracing from the ventricle and a lower blood pressure line. The Figure shows the effects of 3 c.c. of Hedonal solution, and while this effect was still present but passing off, the right divided vagus nerve was stimulated at the distal extremity, the secondary coil standing at 10 c.m.. The effect is seen very prominently in the ventricle line and blood pressure line, but also in a lesser degree in the tracing of the auricle.

Immediately before faradic stimulation, the following were the conditions:-

The heart was recovering from a moderate dose of 3 c.c. of Hedonal applied 60 seconds previously.

Amplitude of contraction of the ventricle was 65 m.m.

Blood pressure in the carotid was 60 m.m. of mercury.

Cardiac rate 17 in 4 seconds.

Conditions during stimulation.

Amplitude of contraction of the ventricle 22 m.m. - a loss of 66%.

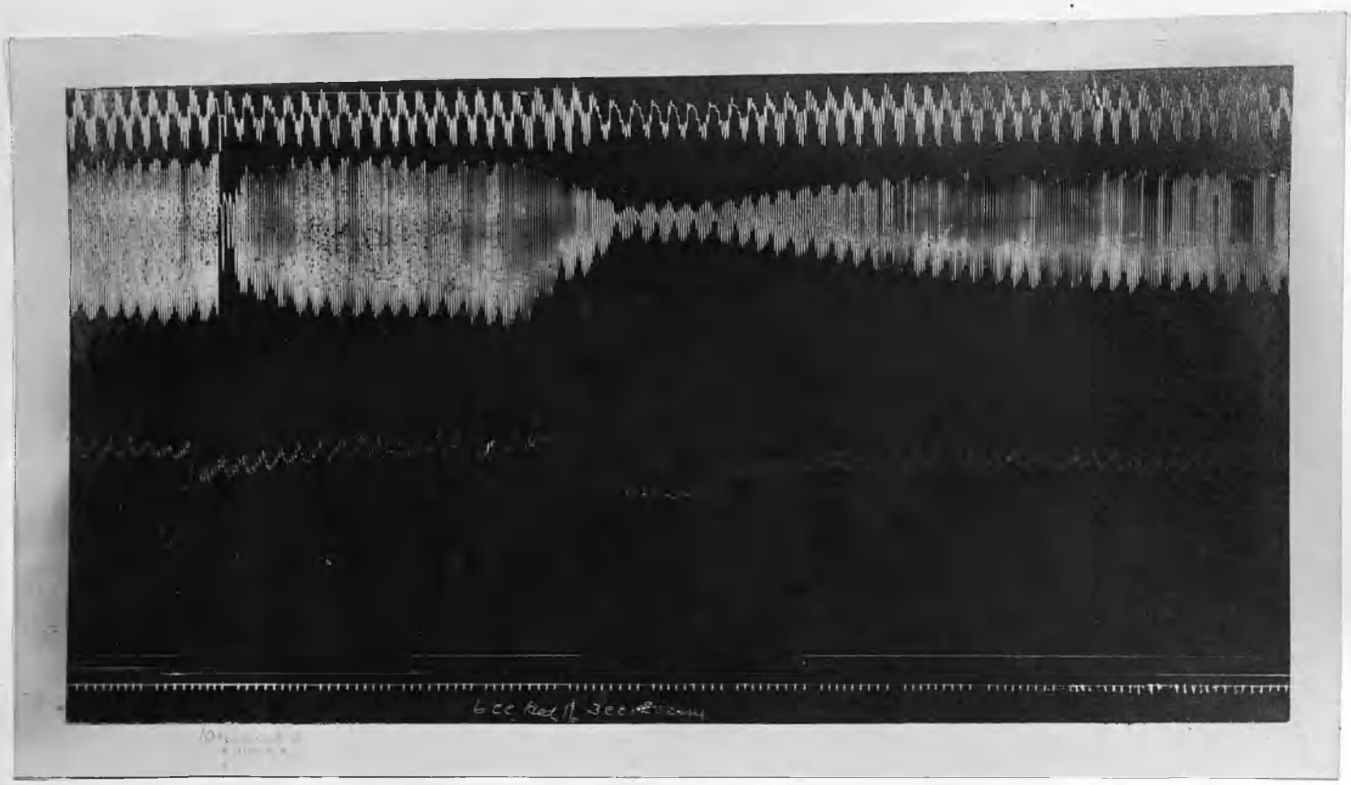
Blood pressure 45 m.m. - a reduction equal to 25%.

Cardiac rate 5 in 4 seconds - a reduction of 70%.

The action of the heart almost ceased.

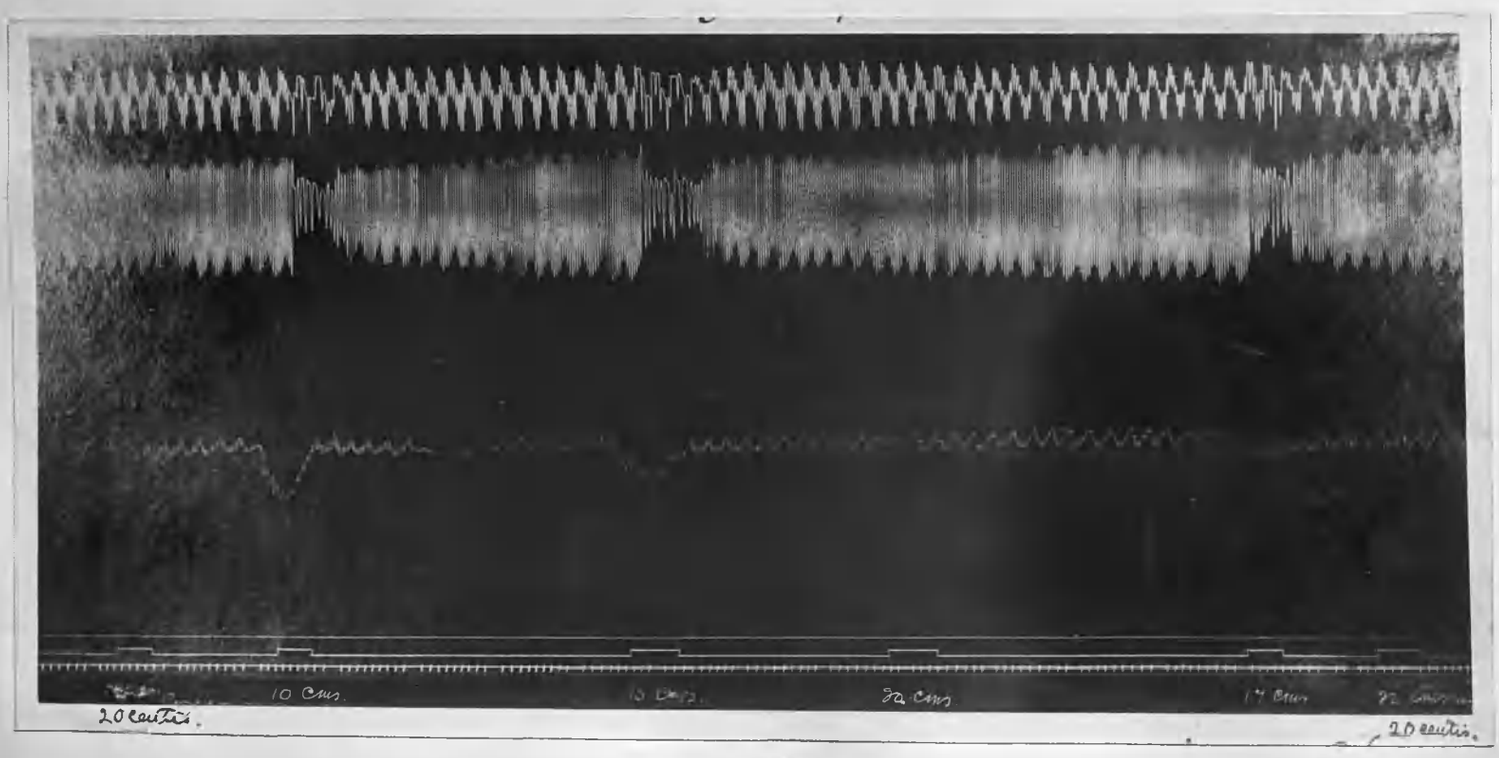
When stimulation ceased, the cardiac rate became normal. The amplitude of contraction was normal in 10 seconds. In the above experiment it should be noted that the rabbit was relatively heavy, that the dose of Hedonal was a moderate one, and that the faradic stimulation was given when the effect of Hedonal was almost recovered from.

Figure XCIII.



·47 Natural Size

Figure LXXXVII.



·47 Natural Size.

FIGURE XCIII.

The rabbit in Figure XCIII is the same one as in Figure XXIX. It weighed 2800 grammes. There is shown the result of faradic stimulation of the distal extremity of the cut right vagus. The animal was in an anaesthetic state due to Hedonal at the time of stimulation, but the immediate effect of any one dose had quite passed off when the stimulation was made. The secondary coil was standing at 10 c.m. The auricle line has been clearly traced. The effect is greater in the ventricle than in the auricle.

The results are similar to what was found in Figure XXIX.

The cardiac rate was reduced from 14 to 8 - a loss of 42%

The amplitude of contraction in the ventricle was reduced from 23 to 7 - a loss of 69%.

FIGURE LXXXVII.

Figure LXXXVII is also from the same rabbit, which weighed 2800 grammes.

The tracing of the auricle, ventricle and blood pressure is shown. The right vagus was cut and the distal extremity was stimulated by faradic current. This being a heavy rabbit and no dose of Hedonal having been recently given, there was not found any "stand-still" of the heart when the coil stood at 15 c.m., or even at 10 c.m.

The faradic stimulations seen in the tracing were as follows:-

(a)	Stimulation with coil at	20 c.m.
(b)	"	10 c.m.
(c)	"	15 c.m.
(d)	"	20 c.m.
(e)	"	17 c.m.
(f)	"	20 c.m.

Stimulation (a) caused slight retardation of the cardiac rate and slightly diminished the amplitude of contraction.

Stimulation (b) caused retardation of the cardiac rate equal to a loss of 44%, diminished amplitude of contraction in the ventricle equal to 71%, and reduction in blood pressure of 21%.

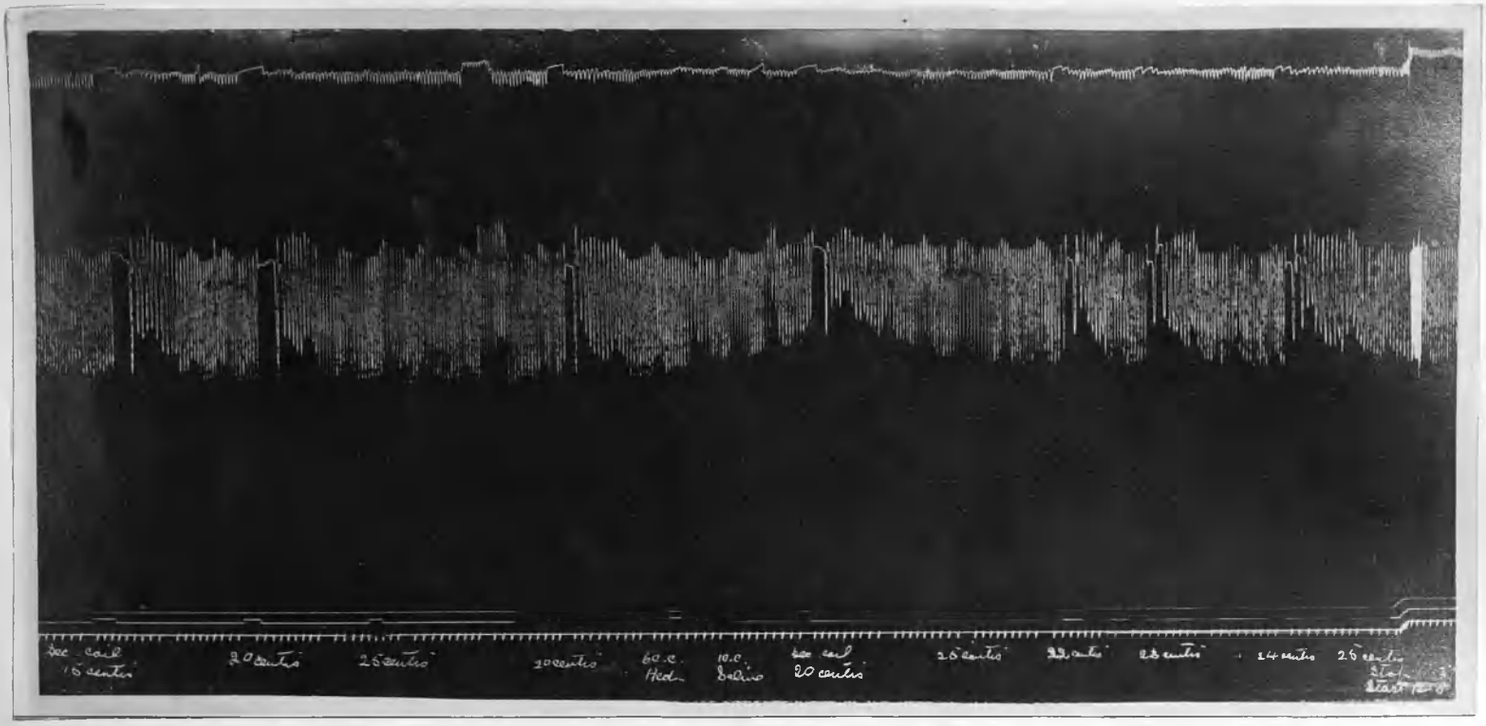
Stimulation (c) produced a similar effect but not so great.

Stimulation (d) caused no apparent result.

Stimulation (e) caused less effect than (c).

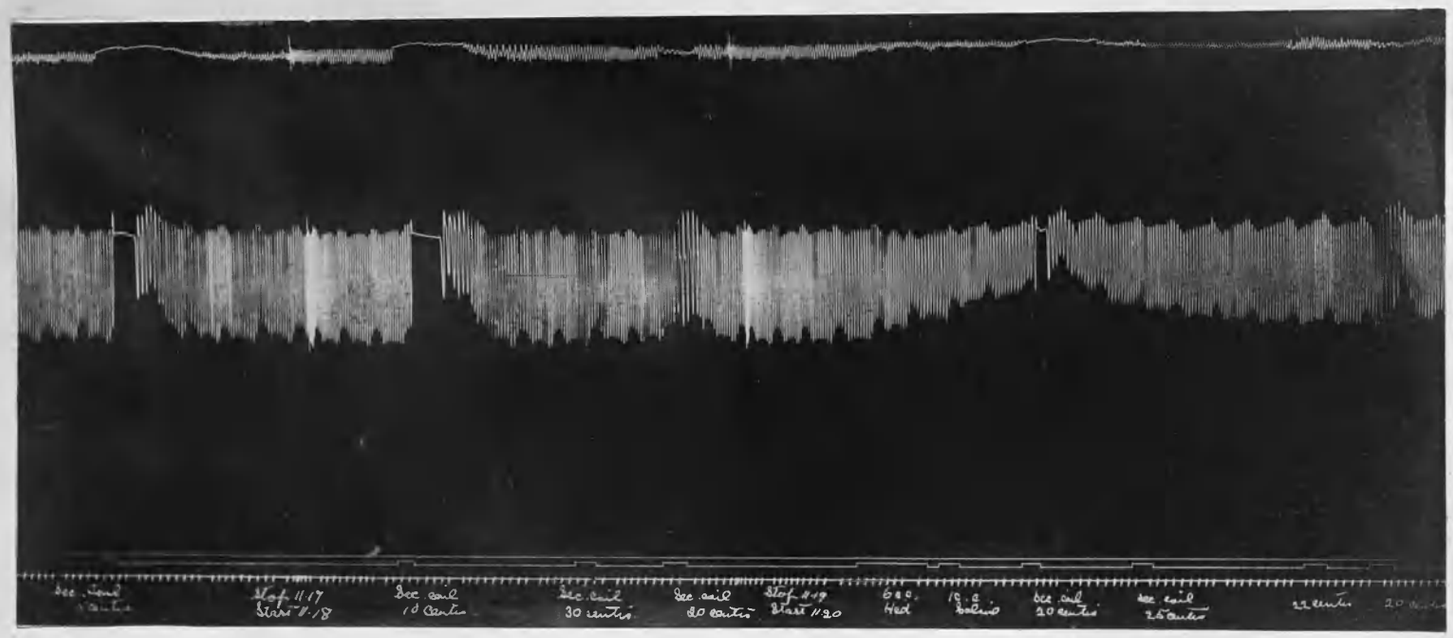
Stimulation (f) caused no effect.

Figure LXXXI.



·47 Natural Size.

Figure LXXXIX.



·44 Natural Size.

FIGURE LXXXI.

Figure LXXXI was taken from a rabbit weighing 2100 grammes. The tracing from the auricle and ventricle is shown. Several stimulations by faradic current were applied to the distal extremity of the severed right vagus, the left vagus having been already cut. One of the stimulations was applied when the full effect of a dose of 6 c.c. Hedonal solution was shown.

The tracing shows in order from left to right the following:-

1. Electric stimulation with secondary coil at 15 centimeters.
2. " 20 "
3. " 25 "
4. " 20 "
5. Application of 6 c.c. Hedonal (.75%).
6. Electric stimulation at 20 centimeters during maximum effect of Hedonal.
7. Electric stimulation with coil at 25 centimeters.
8. " 22 "
9. " 23 "
10. " 24 "
11. " 25 "

During the whole time of this experiment the animal was in the anaesthetic state due to Hedonal, the corneal reflex having been absent.

The results are stated below:-

1. When the secondary coil stood at 25 c.m. there was no result in either tracing.
2. When the coil stood at 22, 23, or 24 c.m. respectively, the cardiac rate was reduced from 8 to 2 pulsations in 3 seconds - the duration of the stimulation. This was a reduction equal to 75%.
3. When the coil stood at 15 or 20 c.m."stand-still" of the heart in diastole resulted, while the stimulation continued. This is seen in both the auricle line and ventricle line. The heart began to beat immediately the stimulation ceased. For 10 seconds,however, after the stimulation ceased, the rate was reduced. Twenty-two pulsations became 16, equal to 27% of a reduction. There was thereafter complete restoration of amplitude and cardiac rate.

In this experiment the result of vagus stimulation is seen to be greater than in Figure XXIX, XCIII, and LXXXVII, probably because the animal is of lesser weight.

FIGURE LXXXIX.

Figure LXXXIX shows that a certain intensity of current from the secondary coil when the vagus is stimulated and the heart not showing the effect of any recent dose of Hedonal, may cause only retardation of the cardiac rate; but if on the other hand the same stimulation be made at the height of a Hedonal effect, complete"stand-still" of the heart in diastole is the result. The rabbit weighed 2100 grammes. The left vagus was cut and the distal extremity was electrically stimulated, the position of the secondary coil varying from 5 to 30 centimeters. There was also given one dose of Hedonal of 6 c.c..

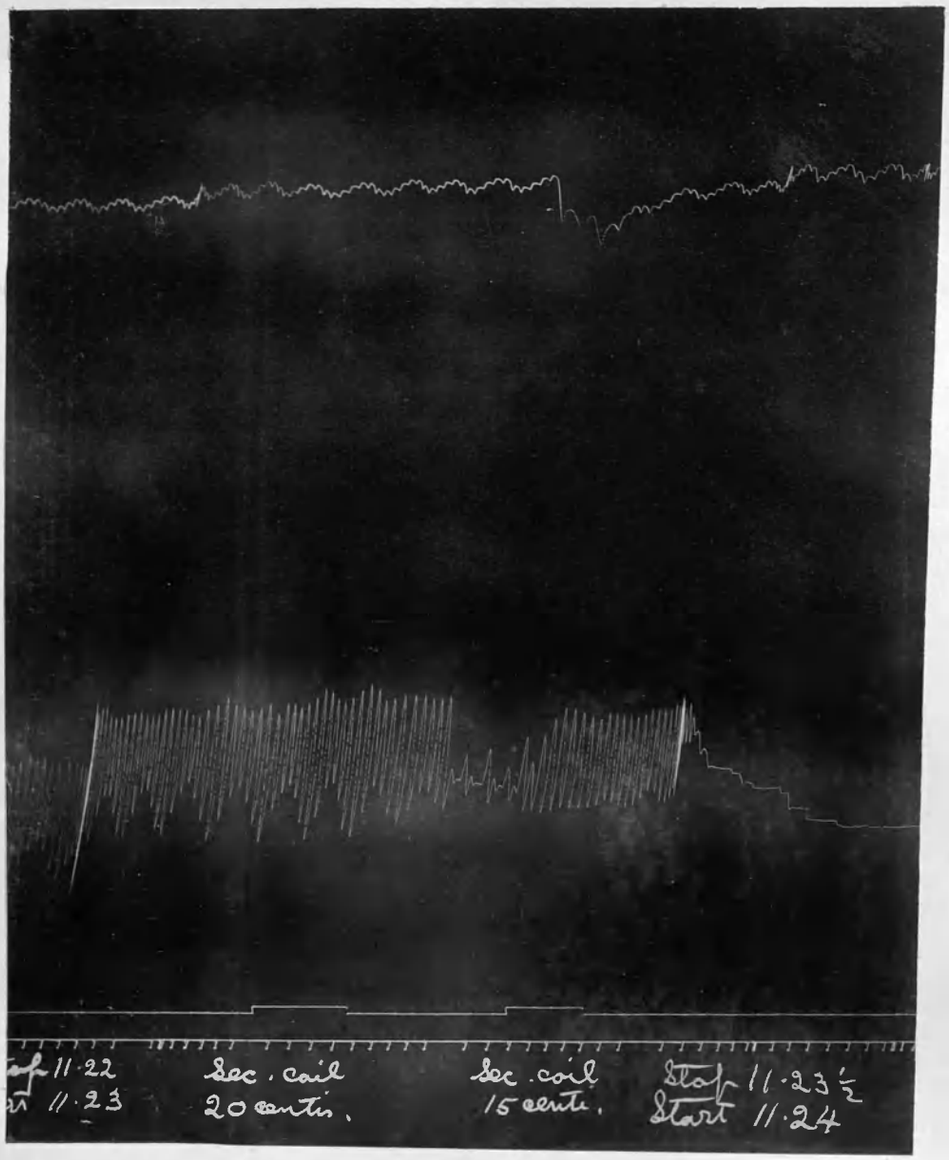
Electric stimulations at 5 and 10 centimeters showed marked effect, the heart stopping in diastole.

Stimulation at 22, 25, or 30 c.m. caused no appreciable effect.

Stimulation at 20 c.m. was carried out in this tracing 3 times. The first one is seen in the middle of the ventricle line. The result is an "organ-pipe" appearance in the tracing, indicating reduction in the cardiac rate. Amplitude of contraction was not appreciably affected. The second stimulation at 20 c.m. was given when the maximum effect was present, due to 6 c.c. of Hedonal solution. The result is different - more marked. There was "stand-still" of the heart in diastole. The third stimulation at 20 c.m. (seen at the end of the tracing) is similar to the first of these three, there having been no Hedonal effect present.

This means in my opinion that the heart of the rabbit is more sensitive to the physiological effect of a faradically stimulated vagus when it has been much affected by a recent dose of Hedonal, than when the heart has not been so affected.

Figure LXXXVIII.



·87 Natural Size.

FIGURE LXXXVIII.

The tracing in Figure LXXXVIII was taken from a dog weighing 6000 grammes. The animal was prepared for an experiment on the arterioles, the kidney having been withdrawn and placed in an oncometer. The upper thin line is the tracing from the oncometer; the lower broad one being the blood pressure.

The Hedonal solution perfused by the jugular vein in this experiment was 1% solution.

There were given at intervals the following doses:- 7 c.c., 8.c.c., 10 c.c., 10 c.c., and 10 c.c.,

With the faradic electrode against the distal extremity of the cut right vagus nerve, a stimulation was attempted. There was no response because one rheophore, was loose. Stimulation was then made at 15 c.m. when the following marked effect resulted:-

1. The pulse rate, which was 12 in 5 seconds, became 6, equal to a loss of 50%.
2. The amplitude of contraction of the carotid, which was 18 m.m. became 6 m.m. - a loss of 66%.

In the dog, therefore, according to this experiment, Hedonal does not affect the vagus nerve: the nerve still acts in a physiological way.

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SECTION VII.

EFFECT OF HEDONAL
ON
BLOOD PRESSURE
IN
RABBIT AND DOG.

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The effect of Hedonal on the Blood Pressure.

This has been investigated in the rabbit and the dog.

The results in the rabbit are seen in Figures XCII, LXXXIV, LXXX, XXI, XCIII, and LXXV. Every dose reduced the pressure. A dose of 2 c.c. Hedonal (.75%) containing .23 grain, caused a fall of 13 m.m. or 6 m.m. per kilogramme of body weight (See Figure LXXXV.). Even 1 c.c. (.11 grain) caused a reduction in the blood pressure of 16 m.m. per kilogramme.

The average fall of pressure per kilogramme from a dose of 6 c.c. (.69 grain) was 9 millimeters, as may be understood from the following table:-

Dose.	Figure.	Weight of rabbit.	Fall in pressure.	Fall per kilogramme.
6 c.c.	92	1800 grammes.	22 m.m.	12 m.m.
6 c.c.	92	1800 grammes.	15 m.m.	8 m.m.
6 c.c.	93	2800 grammes.	18 m.m.	6 m.m.
				Average 9 millimeters.

The figures in the table represent the total fall in pressure from one dose, apart from recovery, which again might be partial or complete.

It should also be observed in these experiments detailed that the ether had been withdrawn and there were no conditions existing such as would result from an artificial state of pressure due to adrenalin or nitrite of amyl. These latter have been considered separately.

The results from experiments in the dog are shown in Figures XVIII and XXII. These are similar to those found in the rabbit, but are very much less. There was an initial increase of blood pressure (also seen in the rabbit) during the introduction of the drug, and then a more marked fall.

The average loss of blood pressure in the dog was 1.7 m.m. per kilogramme of body weight from a dose of 6 c.c. (.69 grain). The rabbit is at least 4 times as sensitive as the dog regarding blood pressure.

The experience of other workers regarding blood pressure may here be recalled.

Krawkow states:- "Accordingly it appeared to me uncommonly interesting and significant that the blood pressure, thanks to the latent effect of the amino group on the heart, is little reduced." Ref. 1.

And again by the same author:- "The heart functions remain nevertheless so strong that despite the dilatation of the vessels, it keeps the pressure to almost normal, and works almost without exhaustion till the animal's death." Ref. 1.

Lampsakow says that the dog in heavy sleep shows a fall in blood pressure of 20 to 30 m.m. Ref. 1.

Karlowitsch found that the blood pressure remained steady in the deepest narcosis. Ref. 65.

Dreser reported that rabbits in deep sleep showed no change in the blood pressure - only a few m.m.. Ref 54. and 11.

Jeremitsch (in Krawkow's laboratory) found in the dog only 5 m.m. of a fall in blood pressure, or none at all. Ref. 2.

Regarding the human subject we have in his own words:- "The introduction of the liquid has no effect on the blood pressure worth mentioning." Ref. 3.

Sidorenko states that the blood pressure fell a little at the beginning, to return soon to normal. Ref. 2.

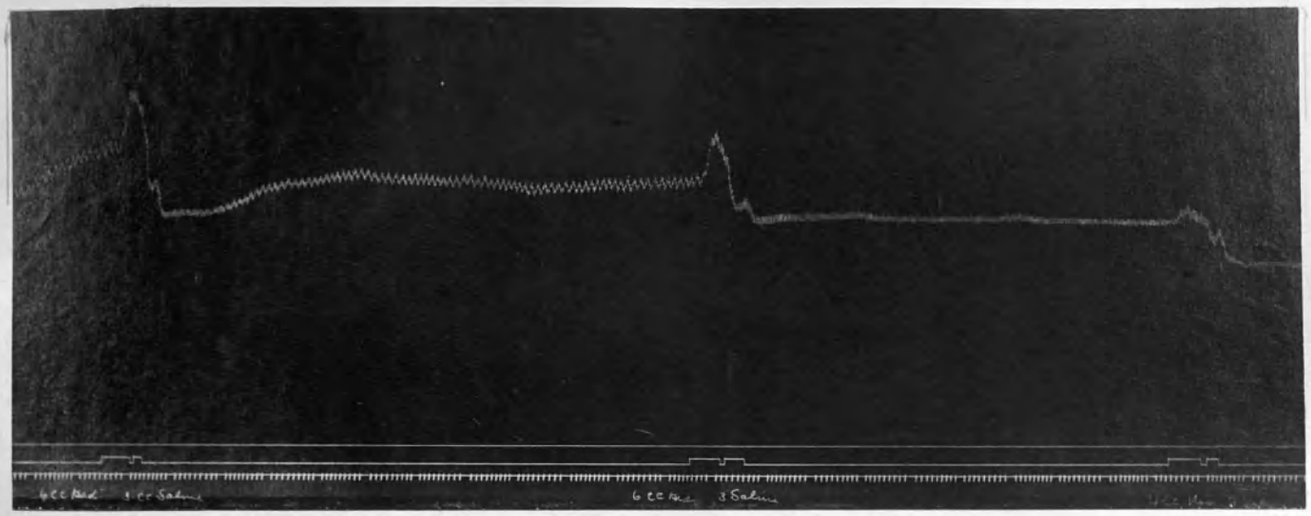
Burkhardt(of Nurnberg) said at the International Medical Congress, 1913, when speaking of Hedonal and Isopral, that he deprecated the use of the former "owing to the fall of blood pressure, the difficulty of regulating the dose, the prolonged sleep, and the danger of respiratory paralysis." Ref. 8.

W.F.Honan (of New York) states:-"Hedonal invariably lowered the blood pressure from 6 to 25 m.m. of mercury." Ref. 9.

This report of Honan refers to the human subject.

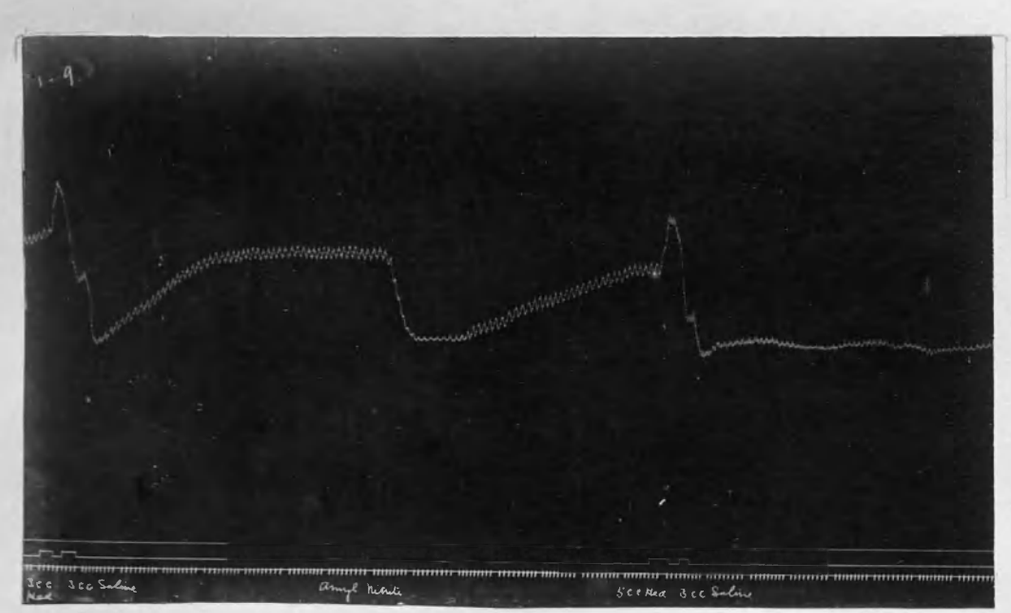
Unfortunately in the German translations (and also English) of the work of the above authors, we do not find any of the tracings produced.

Figure XCII.



·45 Natural Size.

Figure LXXXIV.



·42. Natural Size.

The opinion of the English surgeon, C.M.Page, of St.Thomas's is interesting. He records accurately in a table the pressure in several clinical cases, and tells us that the blood pressure drops slightly and then remains normal in the human subject, and adds the accurate facts regarding some 6 or so cases. Ref. 5.

On examining the chart, there seems to be a very substantial fall in the blood pressure, similar to what we should expect (see Introduction).

FIGURE XCII.

The tracing in Figure XCII was taken from a rabbit weighing 1800 grammes. The following were carried out:-

1. Etherization.
2. Tracheotomy.
3. Venous cannula inserted.
4. Arterial cannula inserted.
5. The kidney was withdrawn and placed in an oncometer to obtain a tracing.

The single line seen is the blood pressure tracing. The pressure at the beginning of the line is 70 m.m.. It is a pressure of recovery from previous treatment. It reached 90 m.m.. There was then administered through the venous cannula the following:-

6 c.c. Hedonal and
3 c.c. Saline.

Two peaks are well marked due to initial increase of pressure. The peak due to Hedonal represents a pressure of 105 m.m.. After the saline was introduced, the pressure became 68 m.m.. This took 10 secs. to show. There was thus a loss of 22 m.m.. Recovery took 45 seconds, the pressure however only registering 83 m.m.. This dose of 6 c.c. (.69 grain) caused a loss of blood pressure equal to 12 m.m. per kilogramme.

Then this dose was repeated about 100 secs. after the last one,- viz.,

6 c.c. Hedonal and
3 c.c. Saline.

Two peaks were again shown of increased pressure. Before perfusing this dose the pressure was 80 m.m.. It became 65 m.m. - a loss of 15 m.m.. Pressure kept/

kept very steady then for 90 secs. This dose of 6 c.c. caused a loss of 8 m.m. per kilogramme. A smaller dose was then given.

4 c.c. Hedonal and
3 c.c. Saline.

A pressure of 65 m.m. became 53 m.m.- a loss of 12 m.m.. The dose of 4 c.c. (.46 grain) caused a loss of 6 m.m. per kilogramme.

FIGURE LXXXIV.

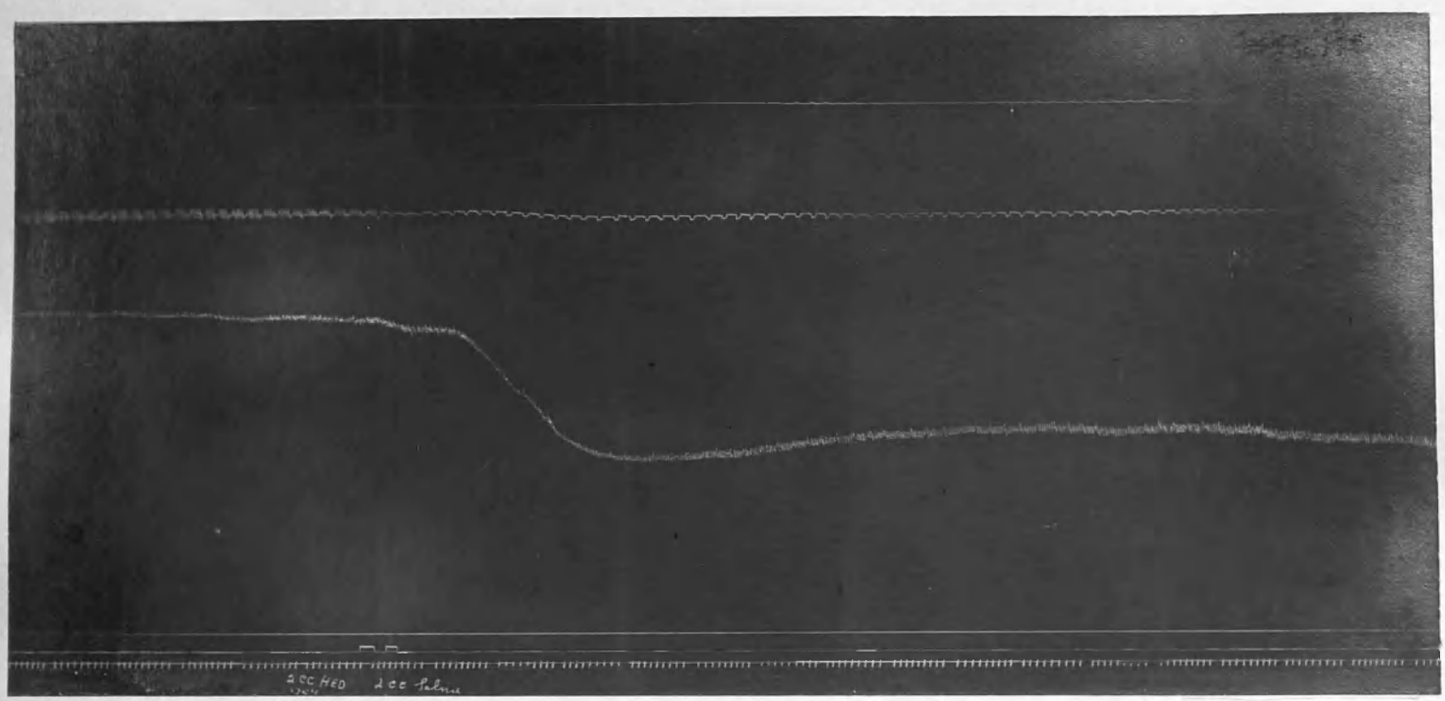
Figure LXXXIV shows the effect of Hedonal and of nitrite of amyl respectively upon the blood pressure of a rabbit weighing 1800 grammes. The following dose was administered:-

3 c.c. Hedonal and
3 c.c. Saline.

There are two initial peaks well marked due to increase of pressure. Then there was a fall in blood pressure produced during 12 secs.. In 30 secs. more recovery had taken place, but the pressure did not reach fully its former height. The pressure then remained steady for 40 secs., and a small vial of nitrite of amyl with the cork removed was brought near the opening of the tracheal tube for 2 secs.. There was immediately produced a profound and sharp fall of pressure differing from the former effect in that there was no initial peak from increase of pressure seen in the tracing. This effect is important and should be remembered by anaesthetists. Nitrite of amyl should never be administered to a patient suffering from chloroform collapse, because it reduces pressure, an effect which chloroform also tends to do. Nitrite of amyl certainly relaxes vessels as is seen in the arterioles of the face in the human being; but this may be a perilous thing to do, if this relaxation of vessels is going to deplete the heart and cause its cessation. In 60 secs. there was again recovery of the blood pressure to nearly its former height. Then there was given:-

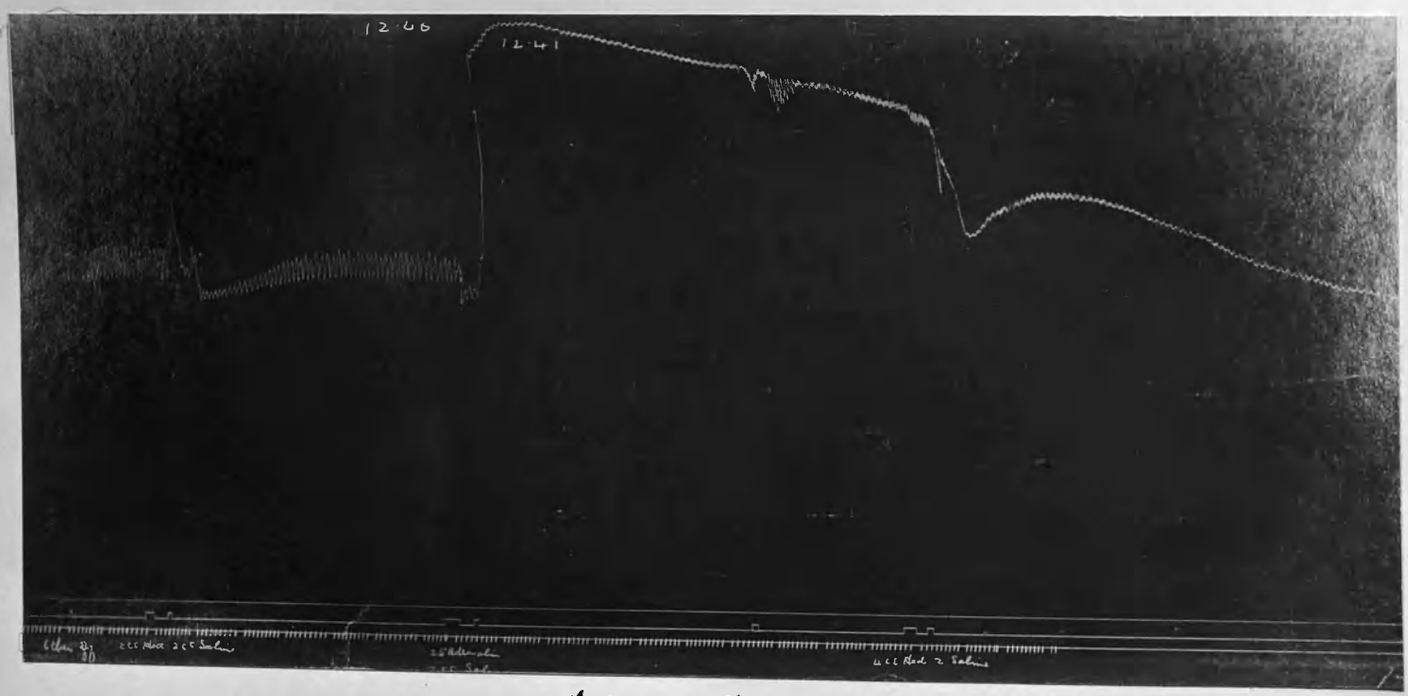
5 c.c. Hedonal and
3 c.c. Saline.

Figure LXXX.



·47 Natural Size.

Figure LXXXV.



·47 Natural Size.

The same result was seen as with a former dose of Hedonal. There was a fall of pressure equal to 18 m.m. per kilogramme. The details of the experiment are shown diagrammatically below. The numbers indicate the blood pressure in millimeters:-

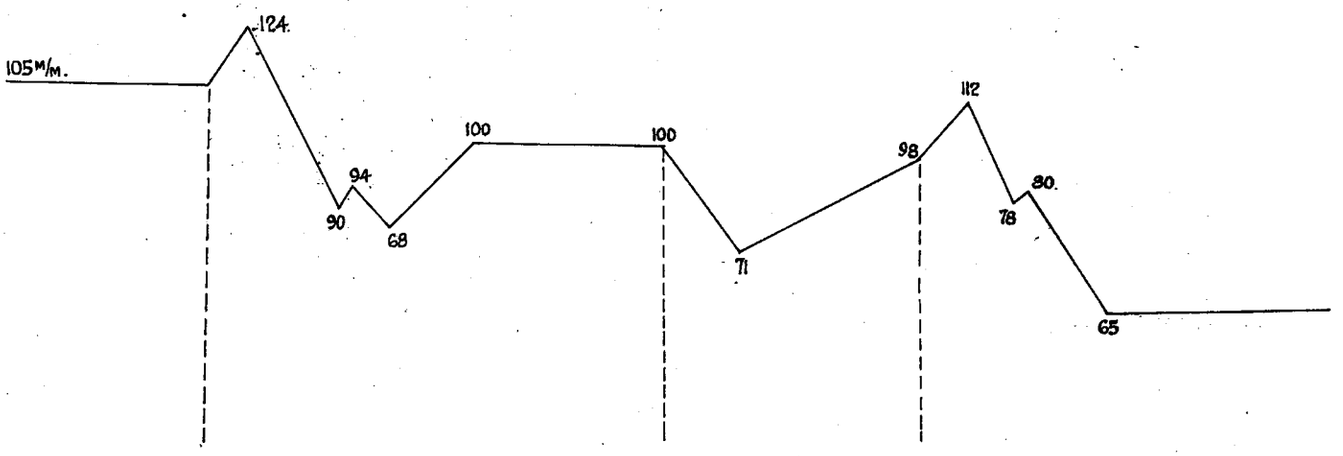


Figure LXXX.

Figure LXXX is taken from a rabbit weighing 1300 grammes. The lowest of the three lines represents the blood pressure. The beginning of the tracing shows a high blood pressure due to adrenalin having been introduced. The blood pressure was 95 m.m.. The following dose was then given:-

2 c.c. Hedonal and
2 c.c. Saline.

The pressure was reduced to 52 m.m. in 40 secs.. In 30 secs. more the pressure was 60 m.m.. This experiment was carried out after several former doses. It explains the great fall with a moderately small quantity of Hedonal perfused. There was no attempt to reach the high pressure with which the experiment started as it was an artificially produced pressure.

FIGURE LXXXV.

Figure LXXXV is a tracing which is of interest to show the effect of Hedonal upon the blood pressure when the latter was high. The first dose of Hedonal was given when the anaesthetic ether had just been withheld, the circulation being good at the time. The second dose of Hedonal was given after a still higher blood pressure had been obtained, due to adrenalin. The experiment was made upon a rabbit weighing 1950 grammes. The tracing at first represents a pressure of 105 m.m.. The pulse waves are clearly marked, their amplitude of movement being 10 m.m.. There was administered a dose of

2 c.c. Hedonal and
2 c.c. Saline.

Effect:-

(a) Two prominent peaks were seen from initial increase of blood pressure.

(b) The amplitude of movement of the vessel was reduced from 10 m.m. to 3 m.m. - only a third of what it had been.

(c) The total fall of blood pressure from 105 m.m. to 92 m.m. took place in 10 secs.. The dose of 2 c.c. (.23 grain) has caused a loss of 6 m.m. per kilogramme.

(d) Complete recovery of the pressure to 105 m.m. took 30 secs. from the time of the complete reduction.

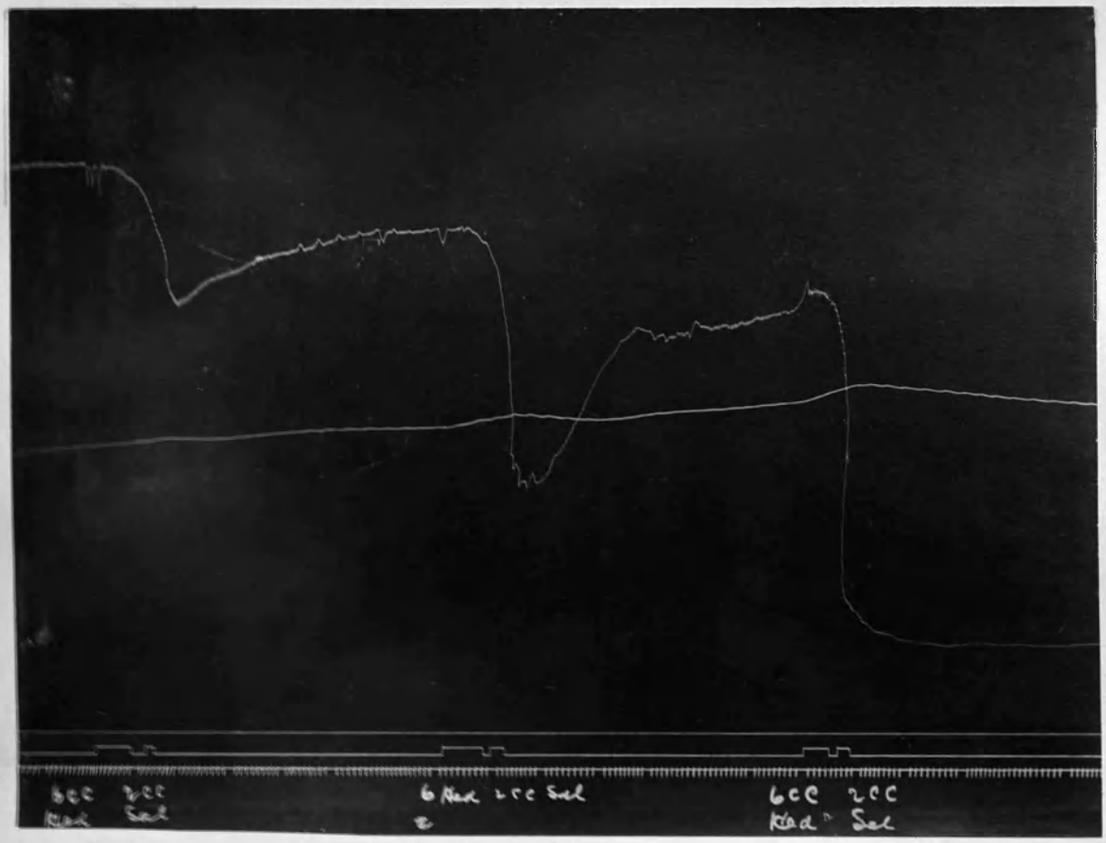
The pressure in this case returned to that with which it started, probably because the animal was in good condition when the first dose was given.

(e) The amplitude of movement of the vessel wall began to return to its former measurement of 10 m.m..

The tracing was not recorded after this for 1 minute. The blood pressure had fallen to 92 m.m. when a dose was given by hypodermic injection through the rubber tube of the venous cannula consisting of:-

.25 c.c. Adrenalin followed by
2 c.c. Saline

Figure XXI.



·62 Natural Size.

Within 10 secs. the pressure rose from 92 m.m. to 175 m.m. - an increase of 83 m.m.. In 90 secs. this high pressure fell to 150 m.m., when there was administered another dose consisting of :-

4 c.c. Hedonal and
2 c.c. Saline.

The result of this dose was a more abrupt fall of pressure than with the previous dose as it was twice the quantity. The lowest pressure recorded at this time was 114 m.m. equal to a loss of 36 m.m. in 12 secs.. This dose of 4 c.c. (.46 grain) has caused a loss of 18 m.m. per kilggramme. The effects passed off in 20 secs. more,but the pressure was then only 124 m.m..

FIGURE XXI.

Figure XXI was taken from a rabbit weighing 1700 grammes. The deeply indented line which at the beginning is placed higher represents the blood pressure, the other line being an oncometer line. Three large doses of Hedonal were introduced, and the effect on blood pressure was very marked. The blood pressure at first was 130 m.m.. There was given a dose of:-

6 c.c. Hedonal and
2 c.c. Saline.

In 20 secs. the pressure had fallen to 98 m.m.. In 40 secs. it recovered but only reached 115 m.m.. The same dose exactly was repeated:-

6 c.c. Hedonal and
2 c.c. Saline.

The pressure fell in 10 secs. to 56 m.m.. This was a very profound fall. In recovering, it reached 92 m.m.. Then a third dose of the same quantity was given:-

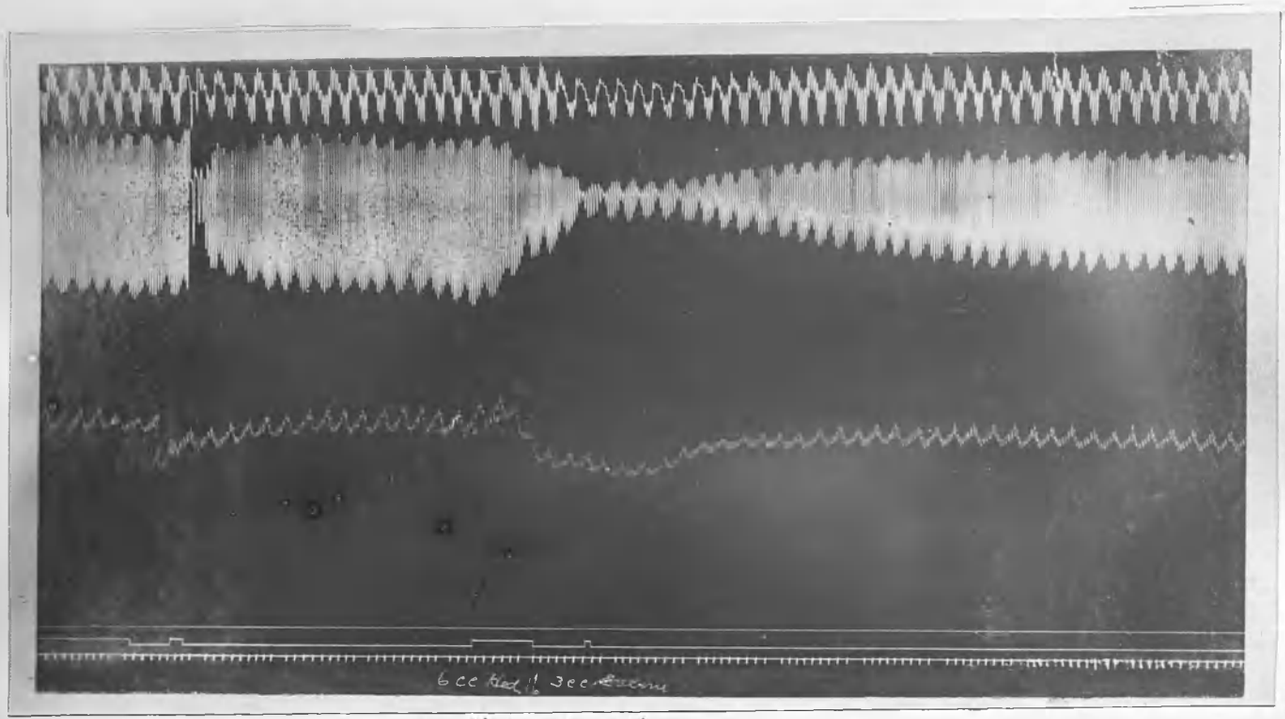
6 c.c. Hedonal and
2 c.c. Saline.

The pressure fell to 22 m.m. from which there was no recovery.

The reason that in this case the fall in blood pressure was so very marked was that this effect was obtained after many other doses had already been given.

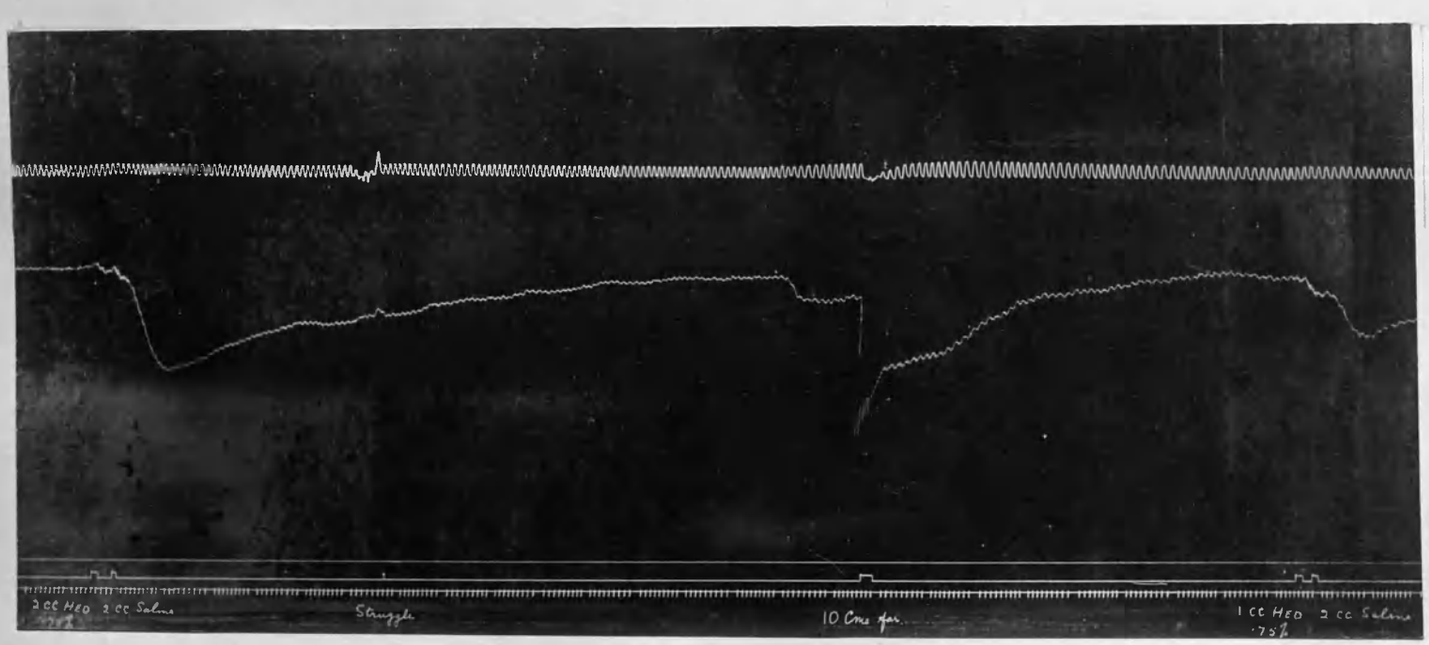
The effect of the first dose of 6 c.c. (.69 grain) was = loss of 18m.m.per kilo.
The effect of the 2nd dose of 6 c.c. was = loss of 34 m.m. per kilo.
The effect of the 3rd dose of 6 c.c. was = loss of 41 m.m. per kilo.

Figure XCIII.



·47 Natural Size.

Figure LXXV.



·47 Natural Size.

FIGURE XCIII.

Figure XCIII was taken from a large rabbit weighing 2800 grammes. The lowest tracing is a record of the blood pressure. A dose of 6 c.c. of Hedonal followed by 3 c.c. Saline was given, and is indicated at the middle of the line. The pressure before perfusion was 66 m.m.. The initial peak indicated 70 m.m.. The following pressure then reached 48 m.m.. It no sooner reached this minimum than it began to rise again, reaching a maximum of 62 m.m. in 30 secs.. The loss per kilogramme resulting from the dose of 6 c.c. (.69 grain Hedonal) was 6 m.m..

FIGURE LXXV.

Figure LXXV is a tracing from a small rabbit of 1300 grammes. The following steps were carried out:-

1. Etherization.
2. Tracheotomy.
3. Venous cannula inserted into the left jugular vein.
4. Arterial cannula inserted into the left carotid artery.
5. Left Vagus nerve isolated.
6. A balloon was applied to the abdomen, so that a tracing of the respiration might be taken.

At the time the above tracing was taken, the animal was breathing through the tracheotomy tube, no artificial means being used. The lower tracing in the Figure represents the blood pressure. The pressure was 88 m.m.. There was given a dose consisting of:-

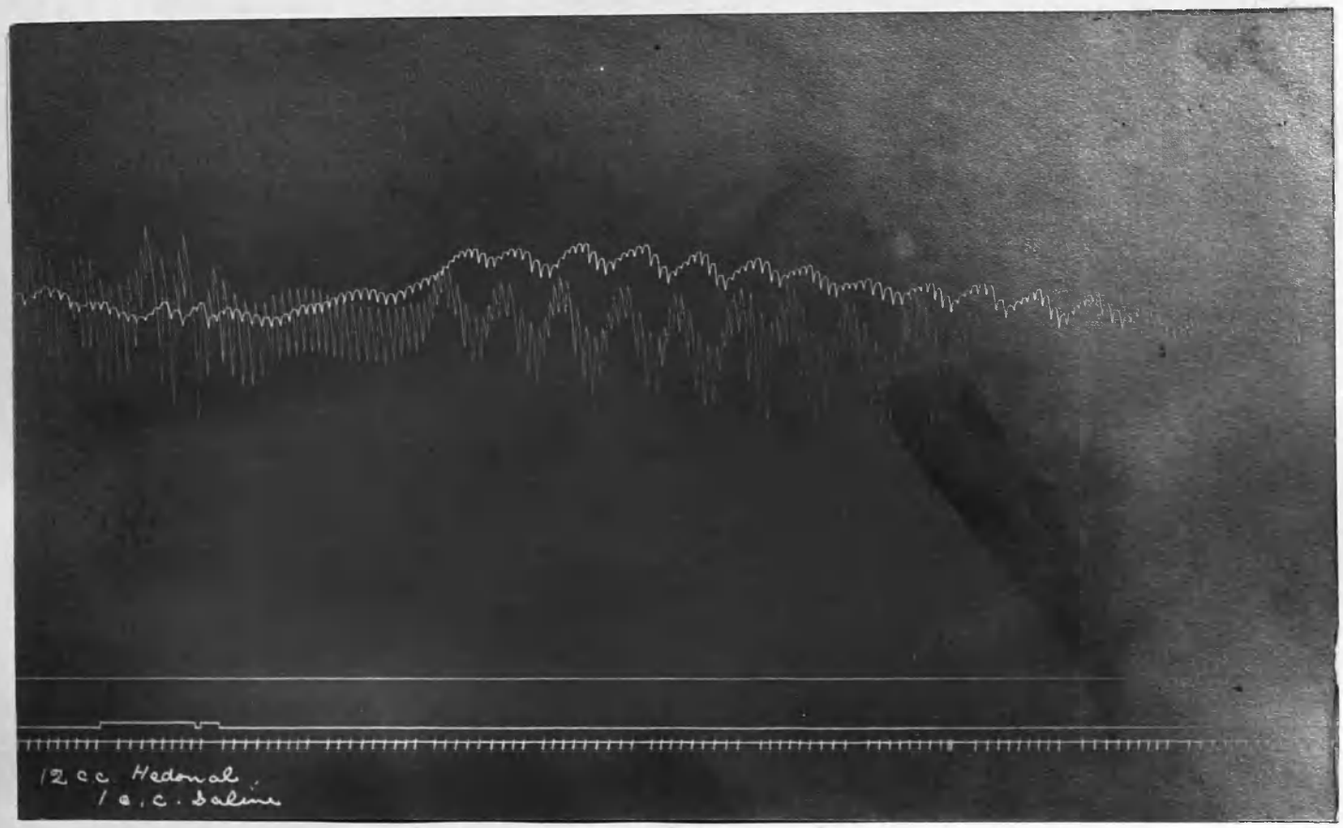
2 c.c. Hedonal and
2 c.c. Saline.

The blood pressure line immediately showed two small peaks. Then it fell to a minimum of 57 m.m. - a fall of 31 m.m. in 14 secs.. The loss from a dose of 2 c.c. (.23 grain) was equal to 23 m.m. per kilogramme. Recovery took place in 120 secs., the pressure then being 85 m.m.. A stimulation of the vagus was then made by faradic current. Afterwards there was perfused a dose of

1 c.c. Hedonal (.11 grain) and
2 c.c. Saline.

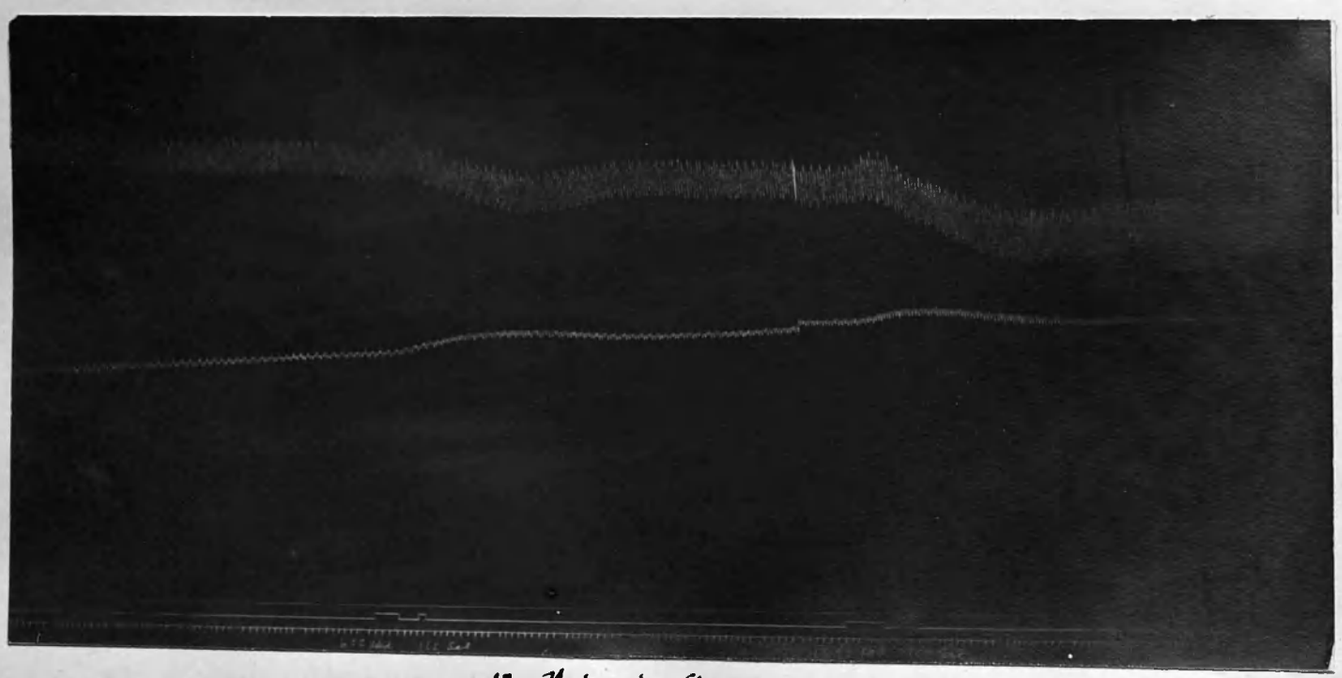
The effect showed two small peaks at the introduction of the drug. There was then a loss of 20 m.m. in 14 secs.. This dose has caused a loss of pressure equal to 15 m.m. per kilogramme.

Figure XVIII.



·65 Natural Size.

Figure XXII.



·45 Natural Size.

Effect of Hedonal on the blood pressure of the Dog.

The results from experiments on the dog are shown in Figures XVIII and XXII. These are similar to those found in the rabbit. There was an initial increase of blood pressure during introduction of the drug and then a more marked fall. In this respect the dog was found to be much less sensitive than the rabbit for equal weight and dose.

Dose.	Weight of dog.	Number of figure.	Loss per kilogramme.	Equivalent fall for dose of 6 c.c.
12 c.c.	6000 grammes.	Figure 18	3.3 m.m.	1.6 m.m.
6 c.c.	4400 grammes.	Figure 22.	1.5 m.m.	1.5 m.m.
10 c.c.	4400 grammes.	Figure 22	3.4 m.m.	2.0 m.m.

It has been shown in the present experiment. that in the dog the average loss of blood pressure was 1.7 m.m. per kilogramme for a dose of 6 c.c. (.69 grain Hedonal). In the rabbit the same dose caused an average reduction in blood pressure equal to 9 m.m. per kilogramme. The rabbit therefore is about 5 times as sensitive as the dog regarding the effect of Hedonal on the blood pressure.

FIGURE XVIII.

A dog weighing 6000 grammes was chosen in Figure XVIII. The animal was anaesthetized with morphia, then chloroform-ether. Tracheotomy was performed. A cannula was inserted into the external jugular vein and connected with a double burette, one tube containing Hedonal .75 % and the other tube normal Saline. The arterial pressure was taken from the carotid, using McColl's electric connection to the manometer. Figure XVIII shows the kind of result obtained.

There are two lines seen. The narrow heavy line ia an oncometer tracing (described elsewhere) drawn by a pointer made of straw. At the beginning this tracing passes through the middle of the blood pressure line, which is a broader line and more faintly traced because drawn by a hair wire. At the beginning of the tracing the mean maximum blood pressure was 82 m.m. of mercury. A dose of 12 c.c. of Hedonal was then perfused. The blood pressure fell to a mean minimum of 62 m.m. in 70 secs.. The pressure had returned to the previous height in 100 secs. after beginning to perfuse the drug. The dose of 12 c.c. caused therefore a fall in pressure of 20 m.m. equal to 24% but with complete recovery. There was therefore a loss of 3.3. m.m. of pressure per kilogramme with a dose of 12 c.c..

FIGURE XXII.

The tracing in Figure XXII was taken from a dog weighing 4.4 kilogrammes. The following preparations were carried out in the experiment:-

(1) A venous cannula was introduced into the left jugular vein for perfusion of the drug. This was connected with a burette for Hedonal and Saline.

(2) An arterial cannula was inserted to record pressure from the right carotid artery.

(3) The left kidney was placed in an oncometer and connected with a Schäfer's metallic tambour to record changes in the size of the walls of the arterioles.

There are two lines in the tracing. The broad upper one is the blood pressure line, and the lower is the oncograph line described elsewhere. Two doses of Hedonal were given. The result showed an initial small rise of blood pressure in each case at the moment of introduction, similar to that found in the rabbit, and then a more profound fall.

The first dose was given when the blood pressure was 145 m.m.. It consisted of:-

6 c.c. Hedonal and
1 c.c. Saline.

In 4 secs. the initial increase became 150 m.m. - a rise of 5 m.m., and then fell to 138 m.m., being a loss of 7 m.m.. This loss of pressure occurred in 25 secs. after beginning to perfuse the drug. In 20 secs. more recovery had taken place to 142 m.m.

The loss of pressure from 6 c.c. was equal to 1.5 m.m. per kilogramme.

Another dose was given when the pressure was 140 m.m. consisting of:-

10 c.c. Hedonal and
1 c.c. Saline.

The same kind of result followed, but more profound. The pressure fell to 125 m.m., equal to 15 m.m. or a loss of pressure of 3.4 m.m. per kilogramme.

METHYLPROPYLCARBINOL URETHANE

PHYSIOLOGICAL ACTION

IN

ANIMALS,

By

John Donald, M.D.

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Vol.II.

SECTION VIII.

Effect on the Arterioles of the rabbit and dog as seen in the kidney and intestine.

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Effect of Hedonal on the Arterioles.

This has been investigated in the rabbit and dog, the kidney and intestine having been used for the purpose.

All the results of experiments show a relaxation of the walls of the arterioles; Hedonal is a vaso-dilator. There is probably a paralysing effect on the vaso-constrictor centre in the medulla.

When experimenting with rabbits, the animal was anaesthetised with ether; in the case of the dog there was given morphia and chloroform followed by ether.

Tracheotomy was then performed and one of McColl's brass tracheal tubes was inserted. These tubes make it possible to regulate the quantity of air entering.

The left common jugular vein was dissected out and connected with a double burette stand to hold Hedonal solution (.75%) and normal saline. The burettes were graduated to 33 c.c.

The right common carotid was then separated and the glass cannula inserted, using McColl's electric connection to the manometer.

When the kidney was used, the organ was placed in an oncometer, of suitable size, made of gutta percha. When the intestine was used, a loop of the bowel with mesentery 12" long was placed in a cell measuring 5 x 3 inches, and made of celluloid to directions. The flanges of the two halves of this oncometer were bound tightly together by butterfly screws, and anhydrous lanoline was applied to prevent the passage of air without unduly constricting the vessels. The marking pointer of the oncograph was a sharpened piece of straw which made a heavy line. The pointer for the blood pressure was a fine hair wire, the line being very lightly drawn.

The results were more apparent in the dog than in the rabbit, and when using a loop of bowel than when using the kidney, doubtless on account of there being more vessels affected in the former case. Figure XVIII shows the kind of result obtained,- a fall of arterial pressure with an increase in volume of the gut,- a dilatation of all the arterioles. When the kidney was used only a slight dilatation was able to be recorded, with a slight fall in the pressure (Figure XXII).

In some cases a small dose of adrenalin was administered when the animal was moribund, after several large doses of Hedonal. The effect may be seen in Figures XXIII, LXXXIII, and LXXXV.

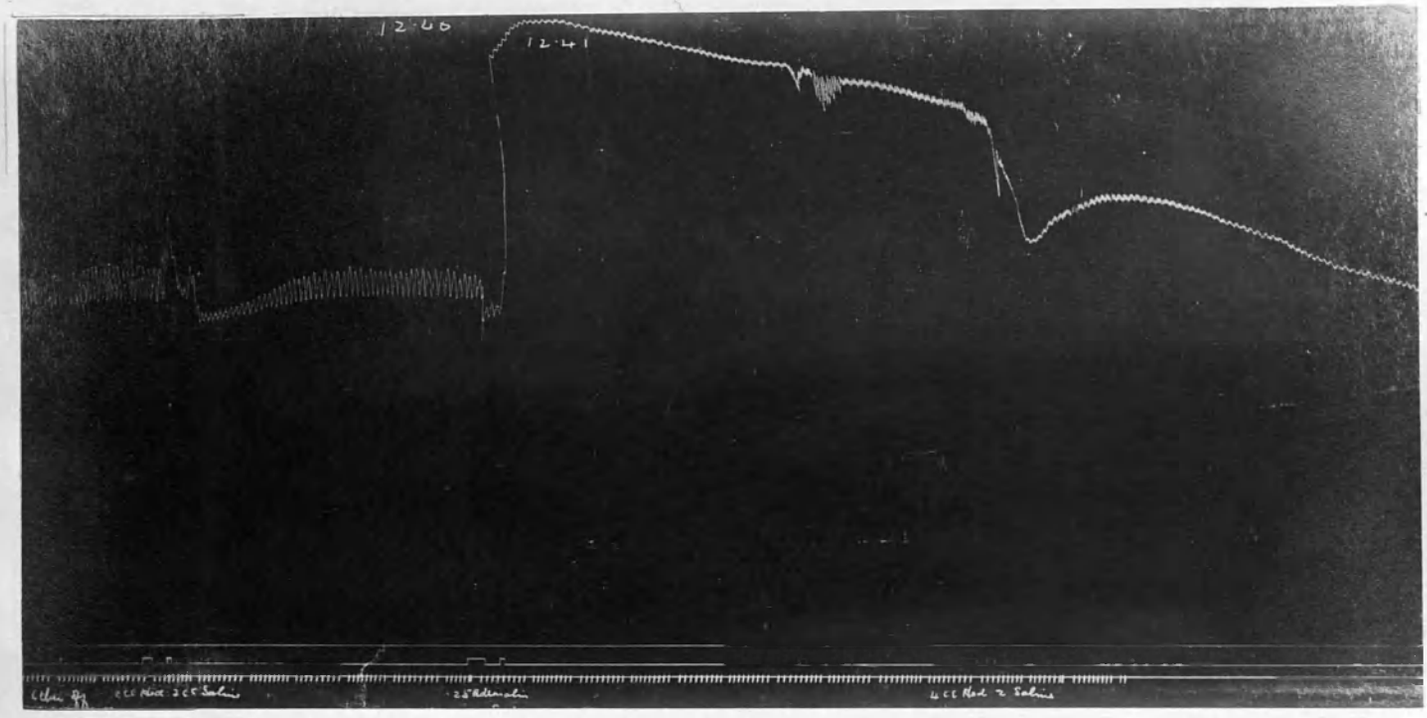
A chart is shown below giving a short list of experiments which have been selected from a number of others.

Animal used.	Weight.	Figure.	Kidney.	Intestine.
Rabbit	1950 grammes.	85	+	
	1700 grammes.	21		+
	5600 grammes.	25	+	
	6000 grammes.	18		+
	6000 grammes.	19		+
	6000 grammes.	82		+
Dog.	4400 grammes.	22	+	
	4400 grammes.	23	+	
	4400 grammes.	24	+	
	4400 grammes.	83	+	

The first experiment was a simpler one than the others in that no graphic representation was recorded from the oncometer. The rabbit weighed 1950 grammes. The treatment of the animal was as already detailed. In this case the kidney was chosen and placed in a small oncometer made as follows:- A walnut was taken and two sheets of white gutta percha 1 m.m. thick were placed in hot water and then moulded on the upper and lower halves of the walnut shell. A flange was made at the junction. It was then placed in cold water to harden. A hole was bored in the upper half of this bi-valve and a glass tube

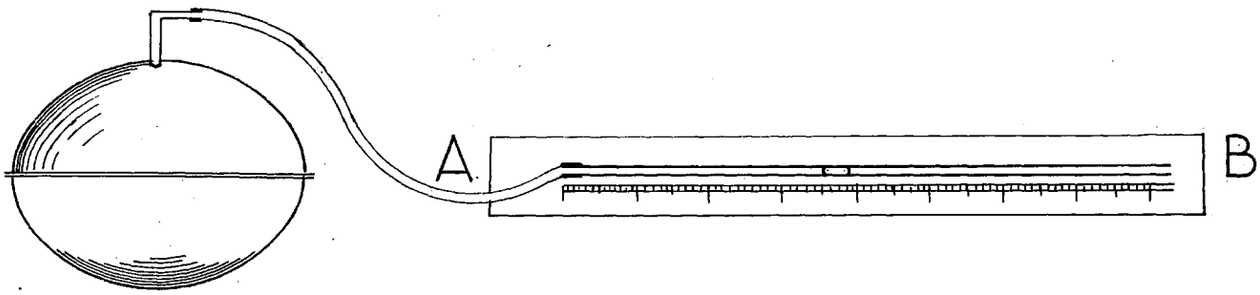
was/

Figure LXXXV.



·47 Natural Size.

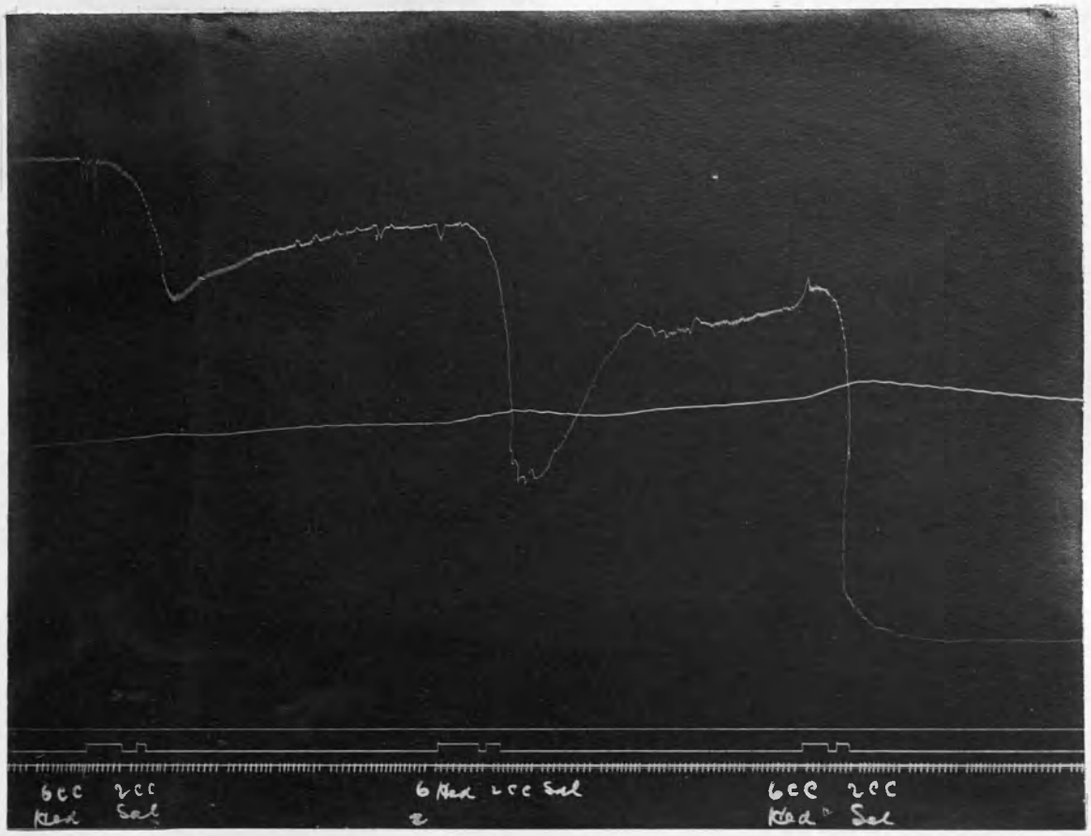
was introduced from within, so that it fitted tightly. A drawing is shown below.



Rubber tubing was led to a long glass tube 3 m.m. in diameter which was placed on a paper measure marked in centimeters, and fixed steadily on the table. A bead of water was introduced into the centre of this glass tube. Several doses of from 2 c.c. to 6 c.c. of Hedonal Solution were perfused into the jugular vein. The bead of water moved in the direction of B to the extent of 2 to 4 centimeters - in one case 12 centimeters. This proved that Hedonal was a vaso-dilator in the rabbit. The kidney became larger and sent air out of the oncometer pushing before it the bead of water. Then adrenalin (1 in 1000) was introduced in 2 doses of .1 c.c. and .25 c.c., respectively, when the opposite effect was obtained - the bead of water actually travelling in the opposite direction toward A.

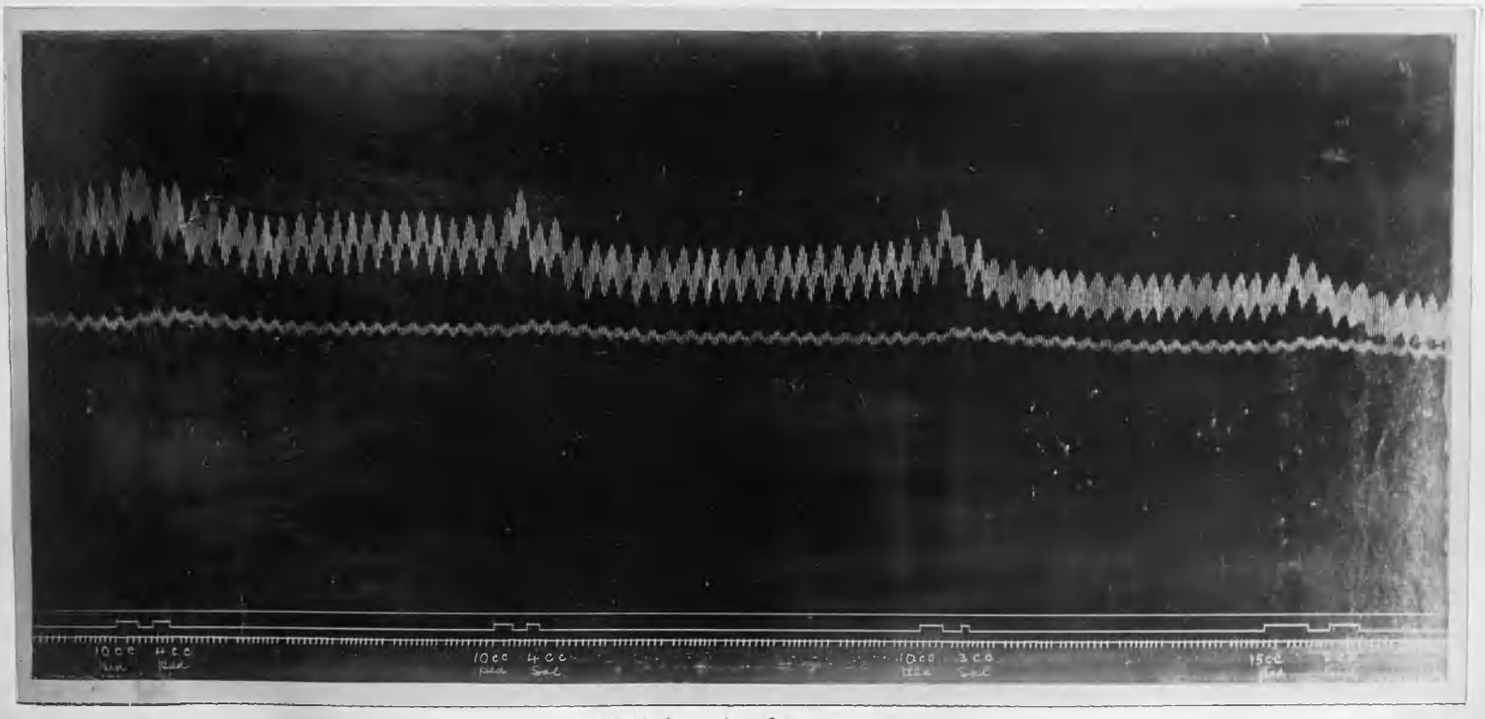
This method has been described by D. Noël Paton. Figure LXXXV is produced to show the effect of adrenalin (.25 c.c.) in increasing the pressure and 4 c.c. Hedonal in reducing the pressure in the above experiment although there was no oncograph tracing made. Ref. 31.

Figure XXI.



·62 Natural Size

Figure XXV.



·47 Natural Size.

FIGURE XXI.

Figure XXI was taken from a rabbit weighing 1700 grammes. The kidney in this experiment was first of all placed in the oncometer; but the result was so indefinite that it was replaced in the abdomen and a loop of bowel was chosen and placed in a larger receiver made of celluloid. There are two lines seen in the tracing. The upper deeply indented one is the blood pressure. The lower one is the oncograph tracing from the intestine. There is seen the effect of 3 doses of Hedonal of 6 c.c. followed by saline.

The first dose shows hardly any change in the oncograph line; but the next two show a distinct rising of the line which corresponds in time with an extreme falling of the blood pressure. This change began to show while the drug was being perfused. The effect on the blood pressure is extremely well marked.

FIGURE XXV.

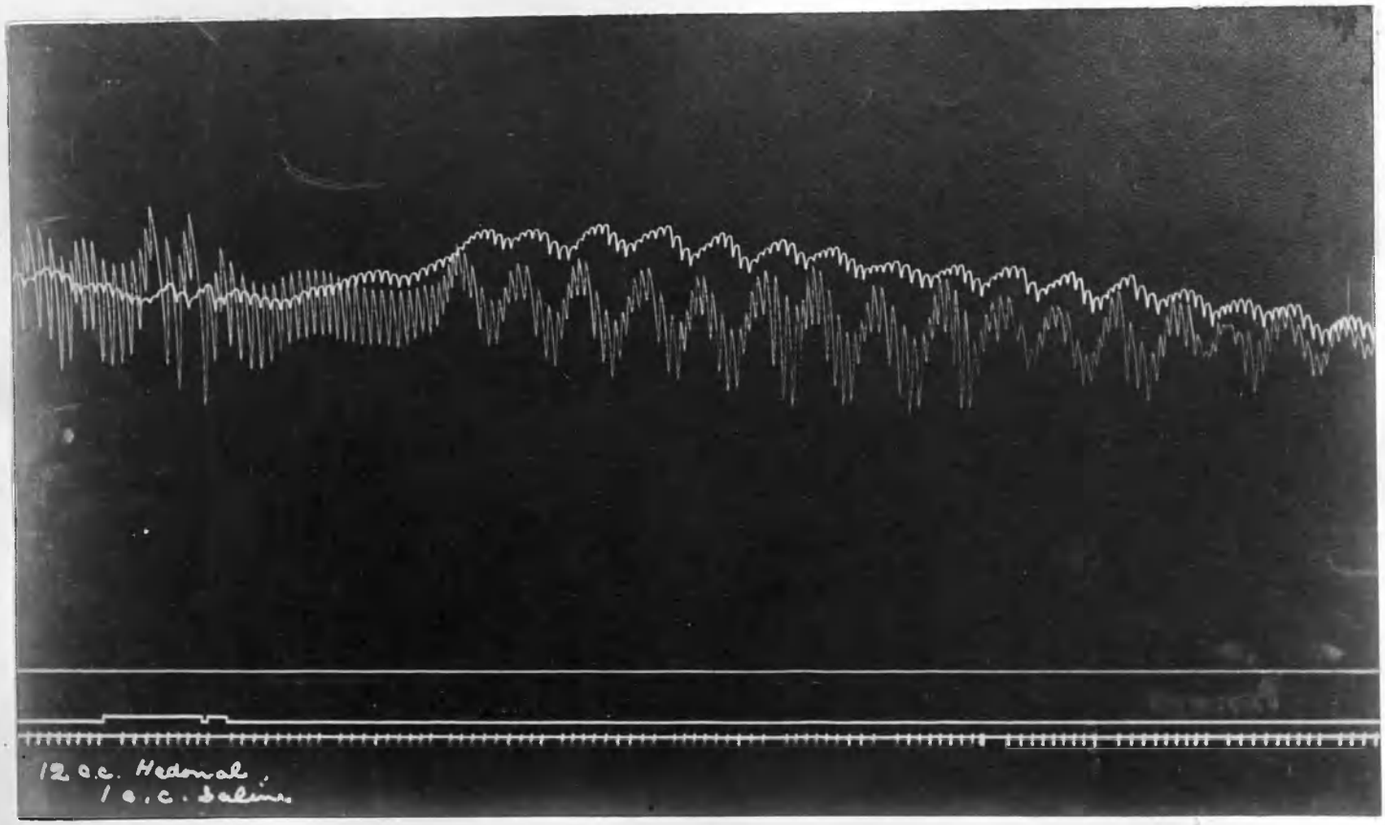
Figure XXV has been taken from a dog weighing 5600 grammes. The upper broad line represents the blood pressure, the lower being the oncograph from the kidney.

There were in all nine doses of Hedonal administered, each being followed by a small dose of saline.

The doses were 2 c.c., 5 c.c., 10 c.c., 10 c.c., 10 c.c., 15 c.c., 15 c.c., 15 c.c., 10 c.c., The figure shows that doses of 10 c.c. and 15 c.c. gave an initial increase of blood pressure, immediately followed by a fall. The oncograph line rose to meet the falling blood pressure line as each quantity was perfused. These relatively large doses were introduced rapidly in from .3 to 6 seconds, due to the liquid in the burette standing at a higher level than some other doses which took longer to perfuse.

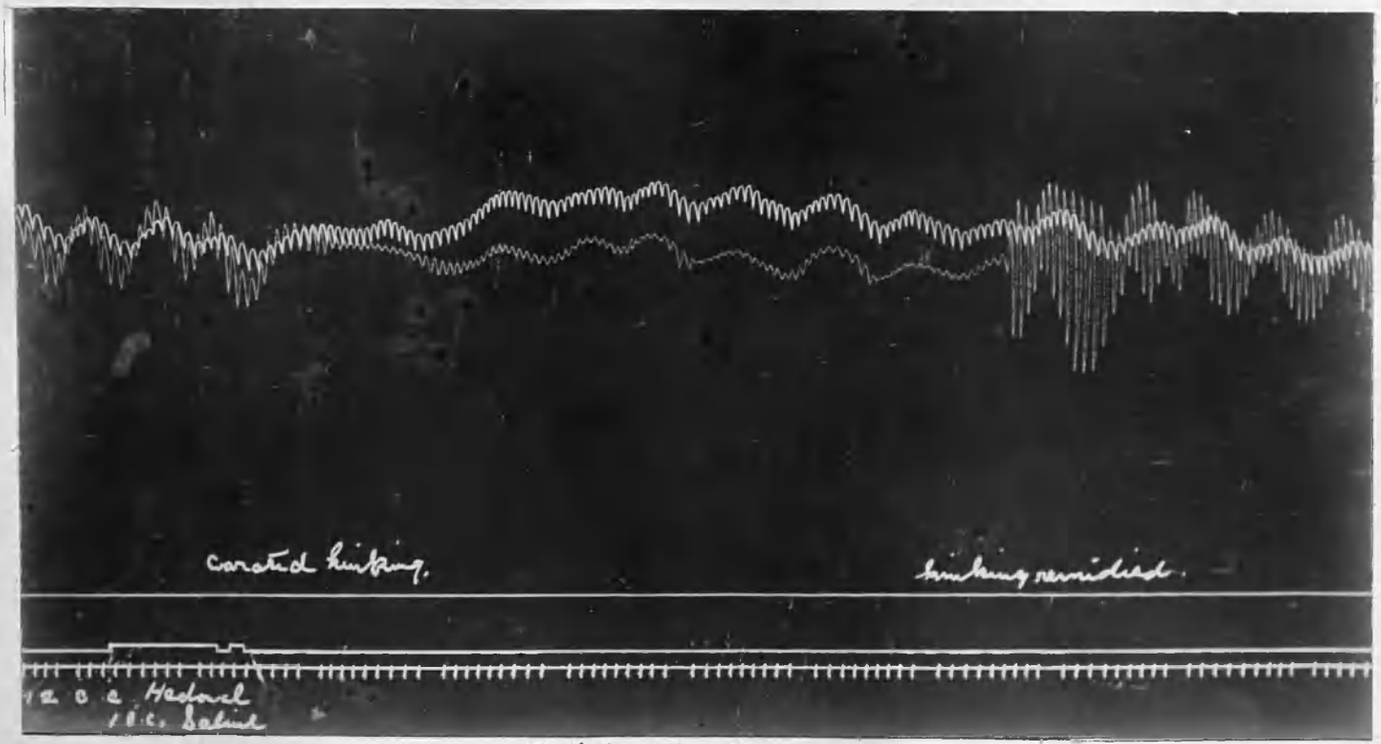
The conclusion from the above experiment is that Hedonal reduces blood pressure in the dog, and that it acts on the arterioles of the kidney as a vaso-dilator. This latter result is not so prominently seen as when a loop of bowel has been enclosed in the oncometer.

Figure XVIII.



·65 Natural Size.

Figure XIX.



·7 Natural Size.

FIGURE XVIII.

Figure XVIII is a tracing taken from a dog weighing 6000 grammes. The abdomen was opened and a loop of bowel with the mesentery 12" long was placed in the celluloid oncometer. The heavy but narrow line is the oncograph line. The fine but deep line is the blood pressure taken from the carotid. The time is marked in seconds. The dose administered was 12 c.c. of Hedonal solution followed by 1 c.c. of saline. The upper heavy line shows relaxation of the walls of the arterioles, the lower showing a reduction of blood pressure. The change in the oncograph line and the blood pressure began to show at the same moment - 20 seconds after beginning to perfuse the drug. The former rose due to relaxation of the arterioles in the loop of bowel. The effect lingered 100 seconds.

At the beginning of the tracing the mean maximum blood pressure was 82 m.m.. It then fell. The dose administered reduced this pressure to a mean minimum of 62 m.m. in 80 seconds. The two lines then merged towards each other, so that in 100 seconds from the start they had returned to their normal position.

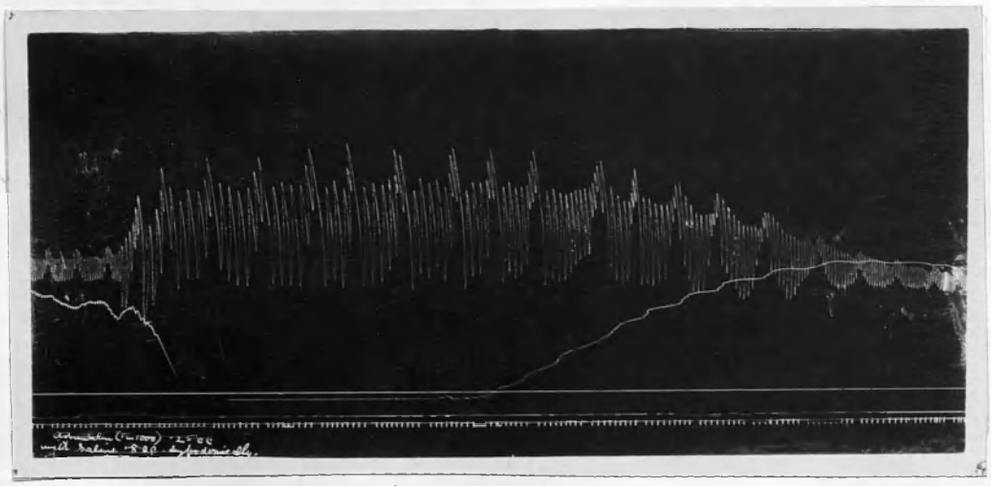
FIGURE XIX.

Figure XIX is from the same experiment as Figure XVIII. It shows a similar effect of a further dose of 12 c.c. of Hedonal solution. The effect in both lines passed off in 100 seconds. The heavy tracing is the oncograph line and the other the blood pressure. The blood pressure became very narrow during 60 seconds. This was found to be due to kinking of the carotid tube. This was remedied and immediately the pulsations increased greatly in amplitude.

In Figures XVIII and XIX after perfusing the Hedonal, relaxation of the arterioles took place in the portion of bowel in the oncometer.

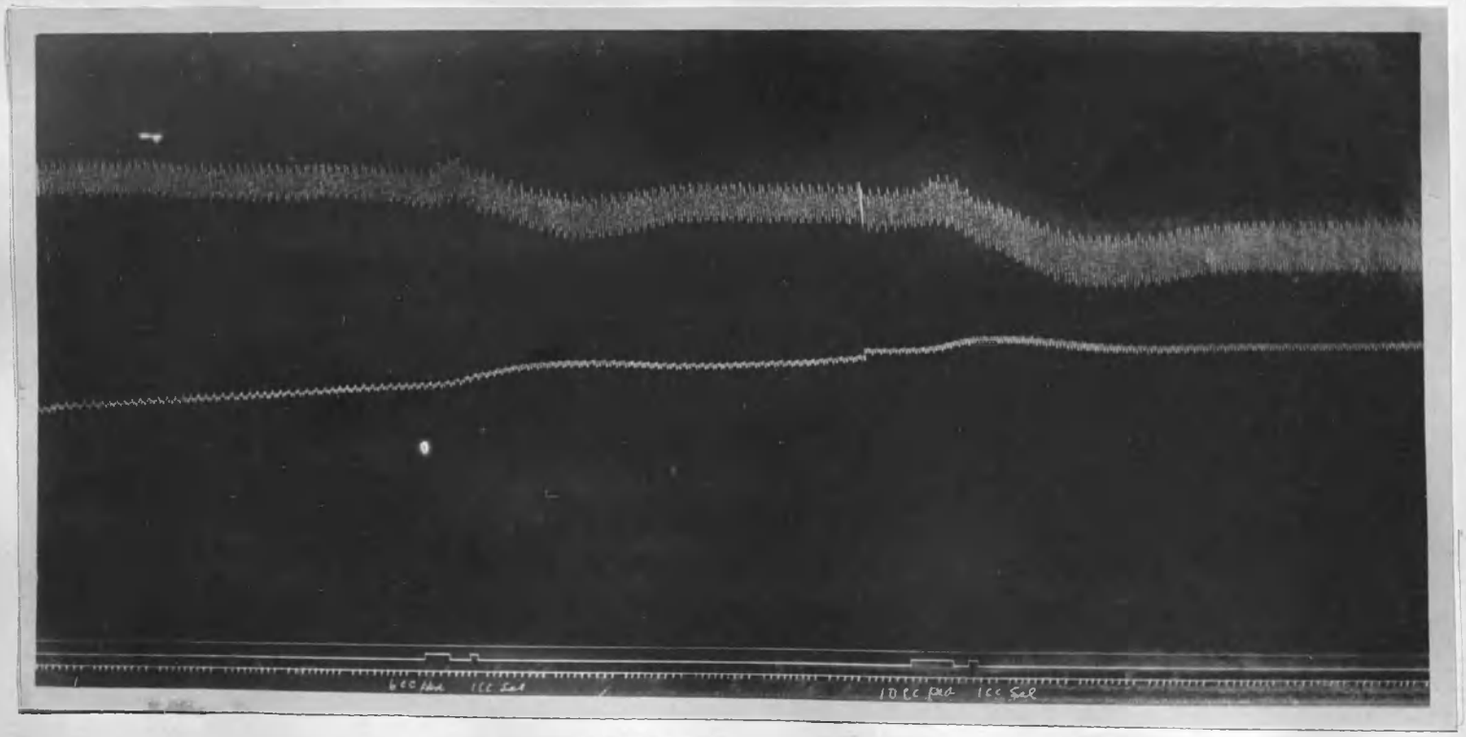
The/

Figure LXXXII.



·3 Natural Size.

Figure XXII.



·45 Natural Size.

The loop of bowel therefore occupied more space. Air was driven out of the oncometer and sent along the tube at the top of the box. This air pressed up the wooden float in Schäfer's oncograph and raised the lever with the aid of the counterpoise at the other end and thus the tracing took a more elevated position.

FIGURE LXXXII.

The tracing in Figure LXXXII is from the same experiment as Figures XVIII and XIX, the weight of the dog being 6000 grammes.

It is an adrenalin effect. There has been given in all of Hedonal 6 doses - 5 c.c., 12 c.c., 12.c.c., 14 c.c., 15 c.c., 14 c.c.,each being followed by saline. In both lines the result is the opposite of the Hedonal effect, At the beginning of the tracing the lower line is the oncograph, the upper being the blood pressure.

After the above doses had shown their effect as has been detailed, the conditions were at the start of the tracing:-

(a) Blood pressure maximum 68 m.m.

(b) Amplitude of the pulse beats in the blood pressure line 12 m.m.

(c) The oncograph line which stood at a height of 48 m.m. from the abscissa was slightly falling.

There was then introduced by hypodermic needle into the rubber tubing of the venous cannula

.25 c.c. adrenalin,
.8 c.c. saline.

The effect was as follows:-

(a) Blood pressure increased to 100 m.m. in 20 seconds.

(b) Amplitude of the pulse in the right carotid artery seen in the blood pressure line increased to 60 m.m. in the same time - 20 seconds.

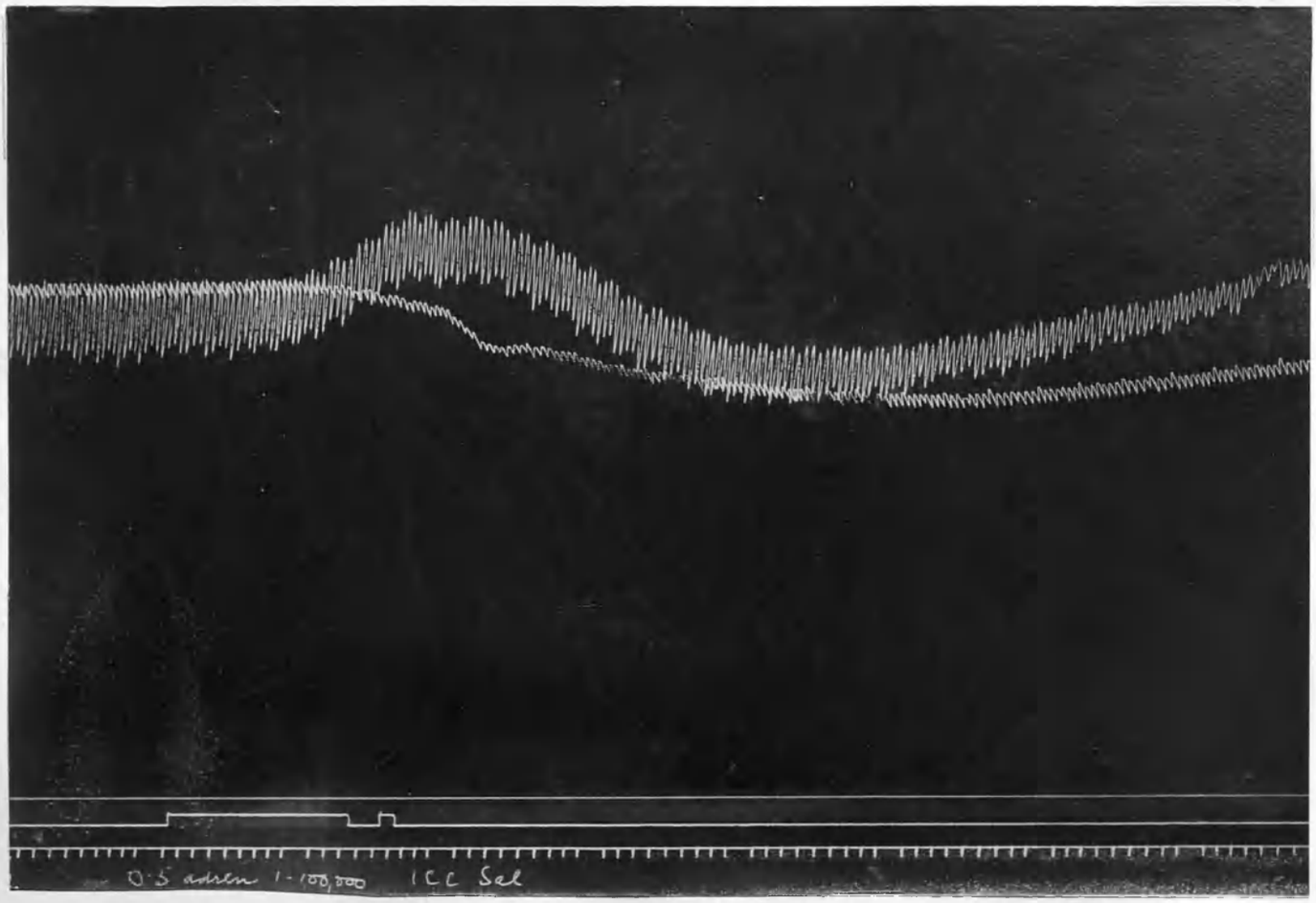
(c) The oncograph line began to fall in about 10 seconds after the Hedonal was begun to be perfused. At 20 seconds from the start, it had fallen/

fallen to its lowest point - 4 m.m. below the level of the abscissa line - a fall of 50 m.m.. It would have fallen further but the lever hit against a portion of the stand. In 60 seconds more the line rose above the abscissa. In 110 seconds it reached its former height and the two lines then began to cross each other. The adrenalin therefore caused an effect which lasted 140 seconds. There was a constriction in the walls of the arterioles in the loop of bowel enclosed in the oncometer. The volume of the gut was diminished, more air entering the oncometer. The float in Schäfer's oncograph therefore fell. The line traced is very low. The blood pressure in the carotid has been increased.

FIGURE XXII.

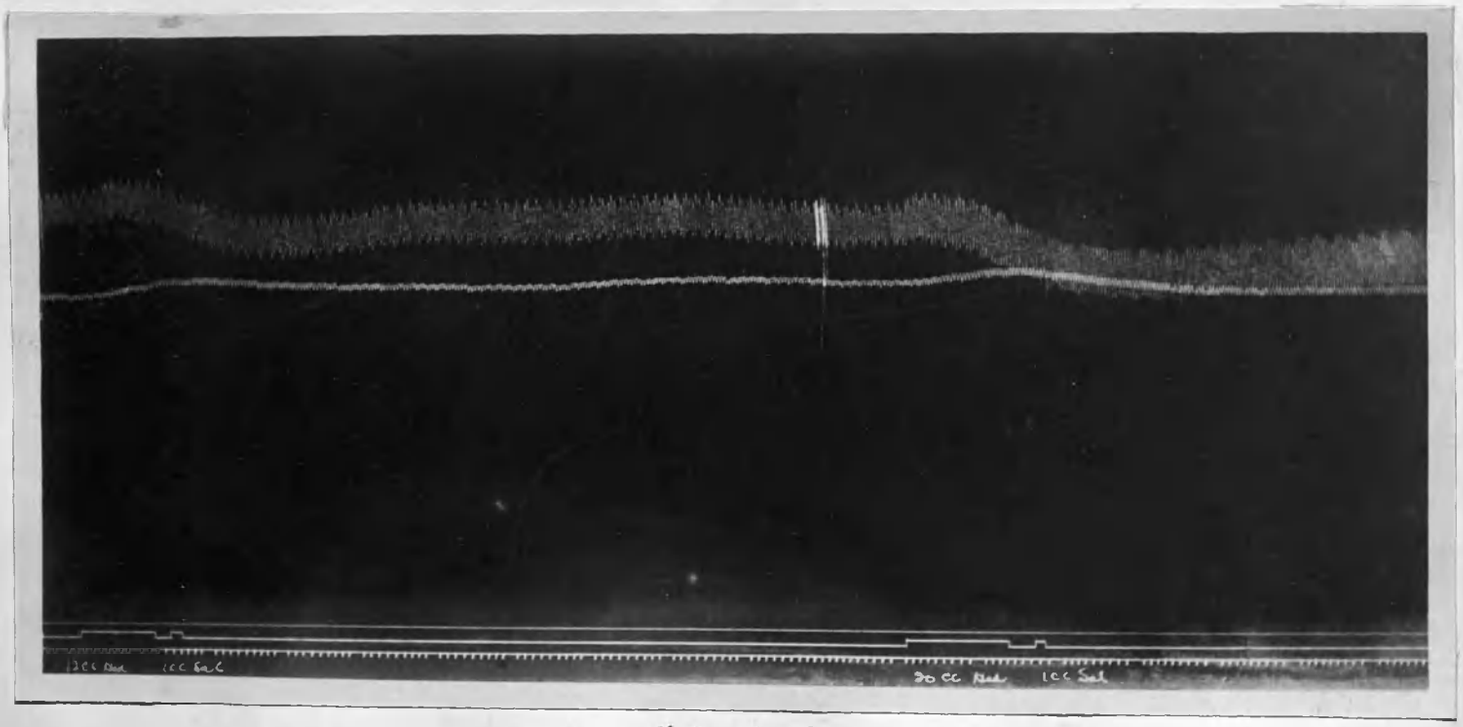
Figure XXII is taken from a dog weighing 4400 grammes. The venous and arterial cannulae were inserted in the usual way and the left kidney was placed in an oncometer, being connected with a Schäfer's metallic tambour to record the changes in the vessel walls. There are two lines in the tracing. The broad upper one is the blood pressure and the lower is the oncograph line. The experiment proves that Hedonal relaxes the walls of the arterioles in the kidney of the dog, and also reduces blood pressure. These two lines therefore, when a dose of Hedonal has been perfused, approached each other. This was seen to occur with two doses, viz., 6 c.c., and 10 c.c., respectively.

Figure XXIII.



·9 Natural Size.

Figure XXIV.



·44 Natural Size

FIGURE XXIII.

Figure XXIII was taken from the same experiment as Figure XXII. It shows the effect of adrenalin upon the blood pressure and the walls of the arterioles in a dog's kidney. The weight was 4400 grammes. A dose of .5 c.c. adrenalin (1 in 100,000) followed by saline was introduced. The two lines are seen receding from each other. The oncograph line has fallen and the blood pressure line has risen. The vessels in the kidney have contracted and the organ has occupied less space. Air has returned to the oncometer lowering the pointer and the tracing.

It took 12 seconds to perfuse the Hedonal and at the 8th second the changes began to be apparent.

FIGURE XXIV.

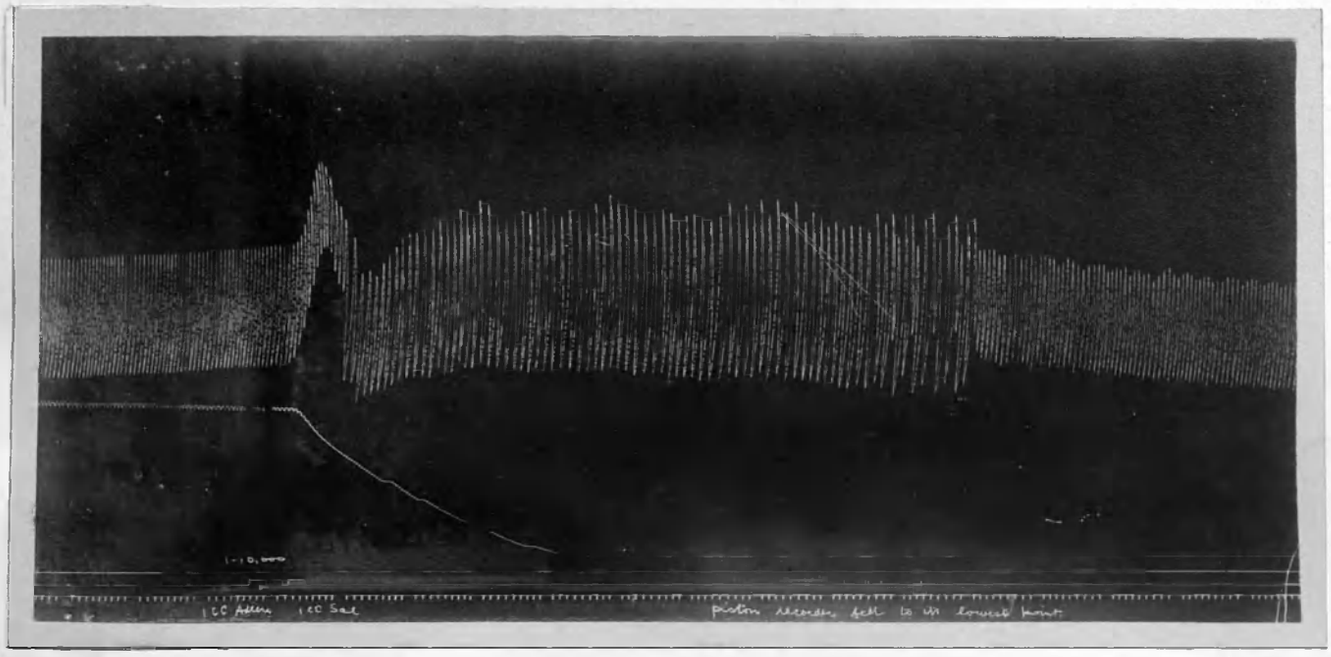
Figure XXIV is from the same experiment as Figures XXII and XXIII, the dog weighing 4400 grammes. The upper broad line is the blood pressure. The lower narrow line is the oncograph line from the kidney. Two doses of Hedonal -12 c.c. and 20 c.c. respectively - were administered. A similar result to that of Figure XXII has been obtained.

The first dose took 10 seconds to perfuse. At the third second there can be seen an initial increase in the blood pressure followed by a reduction.

The blood pressure fell from 135 m.m. (an artificial pressure due to adrenalin) to 129 m.m., a loss of 6 m.m. in 30 seconds from the moment of perfusion.

In the same time the oncograph line rose continuously until both lines approached each other. The figure shows a pause in the tracing which was made 100 seconds after starting the dose. Then the dose of 20 c.c. was administered. The same kind of result followed; the two lines approached each other and finally the lower ran through the upper one.

Figure LXXXIII.



·42 Natural Size.

FIGURE LXXXIII.

Figure LXXXIII was taken from the same experiment as Figure XXIV. It is an adrenalin effect after several doses of Hedonal had been perfused. In the whole experiment the doses administered were as follow:-

(1) 6 c.c. Hedonal
1 c.c. Saline.
(2) 10 c.c. Hedonal.
1 c.c. Saline.
(3) 12 c.c. Hedonal.
1 c.c. Saline.
(4) 20 c.c. Hedonal.
1 c.c. Saline.

A larger oncometer was then introduced to hold the kidney.

(5) .5 c.c. Adrenalin (1 in 100,000).
1 c.c. Saline.
(6) 1 c.c. Adrenalin (1 in 100.000)
1 c.c. Saline.
(7) 1 c.c. Adrenalin (1 in 100,000)
1 c.c. Saline.
(8) 1 c.c. Adrenalin (1 in 10,000) - marked in the tracing.
1 c.c. Saline.

The upper broad tracing is the blood pressure, the lower being the oncograph line taken from the kidney.

The figure shows the effect of the last dose administered.

Conditions before this dose:-

(a) Maximum pressure 105 m.m.

(b) Oncograph line standing at the level of 53 m.m. above the abscissa.

(c) Rate of the pulse 52 in 30 seconds.

It took 5 seconds to inject the Adrenalin. At the sixth second when saline was being perfused, there was a marked effect noted as follows:-

(a) The pressure rose to a maximum of 133 m.m. in 10 seconds - an increase of 26%.

(b) The oncograph descended at once and reached the abscissa in 40 seconds.

(c) Rate of the pulse 26 in 30 seconds, a reduction of 50%.

SECTION IX.

EFFECT OF HEDONAL ON ARTERIOLES OF FROG.

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The effect of Hedonal on the arterioles has been shown to be that of vaso-constriction, when the drug solvent and restorative were identical. This effect has been obtained under several different conditions of the experiment, and it is to be noted that the results in the frog are quite different from those in the mammal.

I. When the drug was dissolved in Saline .75% and the restorative used was Saline .75%:-

(a) When the Hedonal solution was strong - .4%.

(b) When the solution was weak - .075%.

(c) When the frog was pithed, and

(d) When the frog was not pithed.

II. When the drug was dissolved in Sherrington's solution and the restorative was Sherrington's solution.

Its composition was:-

Sodium Chloride	6 grammes.
Potassium Chloride	.0075 gramme.
Calcium Chloride	.01 gramme.
Bicarbonate of Soda	.01 gramme.
Distilled water to	100 c.c.

(a) When the Hedonal solution was strong - .4%.

(b) When it was weak - 1 in 2000.

(c) When unpithed.

III. When Frog's "Ringer" was the drug solvent and restorative.

The frog's "Ringer" had the following composition:-

Sodium Chloride	6 grammes.
Potassium Chloride	.05 gramme.
Bicarbonate of Soda	.1 gramme.
Distilled water to	1000 c.c. (without oxygen).

Again this result was obtained

(a) With strong Hedonal - .4%.

(b) With weak Hedonal - .075%.

(c) When the frog was pithed.

(d) When unpithed.

The effect is independent of the brain and spinal cord. It is

therefore/

therefore not a reflex action. The action may be upon the intrinsic nervous ganglia situated in the walls of the arterioles. In this case in the present experiments, the drug is either an excitant of the vaso-comstrictor fibres, or an inhibitor of the vaso-dilators.

On the other hand, the action may be a direct one on the muscular wall itself. In this case it would be the circular muscular fibres which would be acted upon, as it is inconceivable that any such effect could result from an action on the longitudinal muscular coat.

The vaso-constrictor effect was shown in 17 tracings which have been chosen; but many others constantly gave the same result, when the drug solvent and the control were similar.

Besides the tracings mentioned and here produced, in one experiment no effect was obtained. The drug was dissolved in frog's "Ringer" and the restorative was "Ringer". No change occurred in this experiment, using a strong solution of Hedonal (.4%) nor when it was weak, (.075%). The frog had been pithed. (See Figs. 18 and 19 from the same frog.)

In opposition to the above findings, in two cases a vaso-dilator effect was obtained. The tracings are shown. In one of these (Fig.20) the Hedonal was dissolved in distilled water (.4%) the restorative being Saline (.75%). It was a pithed frog. The drug solution was not isotonic with the blood, and the control solution differed from the solvent of the drug. In the other tracing (Fig.21) showing vaso-dilatation, the Hedonal, (.75%) was dissolved in normal Saline and the restorative was frog's "Ringer". The animal was pithed. In this experiment also the solvent and restorative were not similar.

There are three experiments in which the drug-solvent and the restorative were normal saline (.75%). In each of these the Hedonal solution was .4%.

The loss in outflow from the ductus venosus was

Figure 1 = 16%.
" 2 = 13%.
" 3 = 15%.

There has been an average loss in outflow of 14.6% due to Hedonal acting as a vaso-constrictor.

Eight experiments have been shown where the drug-solvent and the restorative were "Sherrington".

Figure.	Hedonal solution used.	Loss in output* from arterioles.
6	.05 % or 1 in 2000	39%.
10	.05% "	8.6%.
5	.1% or 1 in 1000	79%.
9	.1% "	14%.
7	.1% "	15%.
4	.4% or 1 in 250	29%.
8	.4% "	21%.
11	.4% "	12%.

* The loss in output was calculated upon the number of drops which fell in a given time.

The output from the arterioles by the action of Hedonal of three different strengths, when perfused through the intact heart in the above 8 experiments, has always been diminished. Hedonal is therefore a vaso-constrictor in the frog. The loss of output due to Hedonal has varied from 8.6 to 79%.

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Apparatus used in experiments
on Arterioles of frog.

In the following six experiments the drug-solvent and restorative were "Ringer."*

Figure.	Strength of solution.	Loss in output from arterioles.
13	.075%	7%
14	.075%	10%
15	.075%	16%
16	.075%	28%
17	.4%	9%
18	.4%	32%

The loss due to Hedonal has varied from 7% to 32% in the above experiments.

Method adopted in the present experiments:-

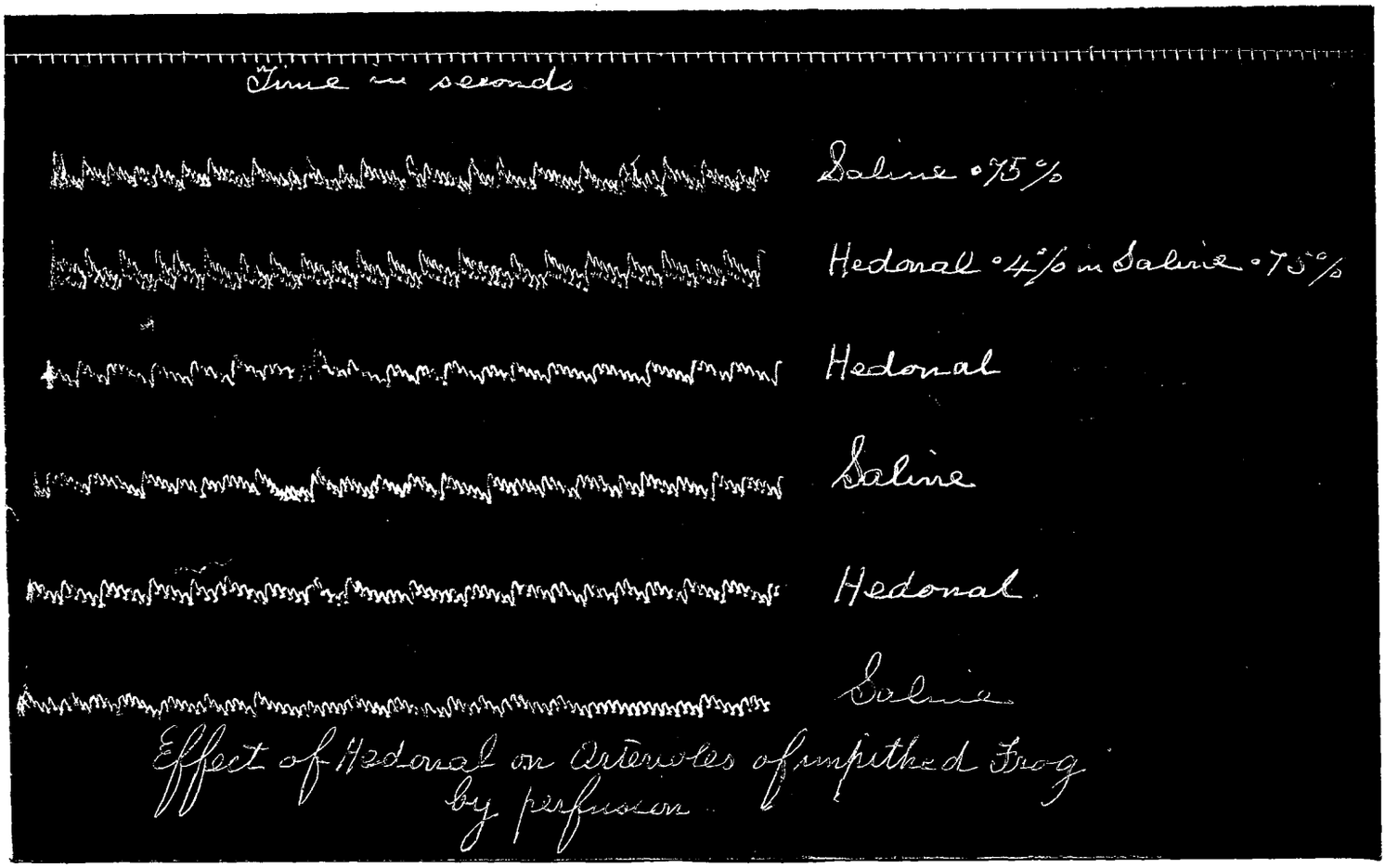
In some of the experiments, the frog was stunned and completely pithed. Some were stunned and the brain only destroyed. The heart was then exposed and pericardium removed. A glass cannula was inserted into the left aorta, and the right aorta ligatured. The ductus venosus or the ventricle was snipped with scizzors. Two glass vessels at a height of 10 inches above the frog contained the restorative and the Hedonal solution respectively. By rubber tubing and a Y-shaped glass tube, they were connected with the glass cannula in the aorta. A run-out pinch cock was introduced, so that the rubber tube could be emptied of the previous liquid when a change was being made as to the perfused liquid.

The frog was placed on a slanting board covered with zinc and having a gutter, so that any drops from the vascular system would be conducted to a convenient point. The drops fell on an obliquely placed disc fixed to the long lever, which recorded each movement on the revolving drum. A time line in seconds or tenths of a second

was/

* For composition see p. 18, Vol. II.

Figure I.



Natural Size.

was made on the smoked paper by the electro-magnetic time recorder.

The real experiment consisted in sending the restorative solution into the aorta first to get the normal condition of output, and then perfusing the Hedonal solution. This was done several times in each experiment. The markings on the tracings made by the falling drops were counted in a certain period of time and compared - the normal with the Hedonal effect - so that the percentage was obtainable.

The following are the actual experiments:-

Figures 1, 2 and 3 show the effect of Hedonal on the walls of the arterioles of the frog, the strength of the solution in each case being .4%. Two of the experiments were with the pithed animal and one unpithed. In all three, there is an appearance like pulsations or respiration waves which has been caused by the position of the disc mentioned. The drops did not fall off at once separately but accumulated until several fell together. In each case a vaso-constrictor effect is seen from the Hedonal.

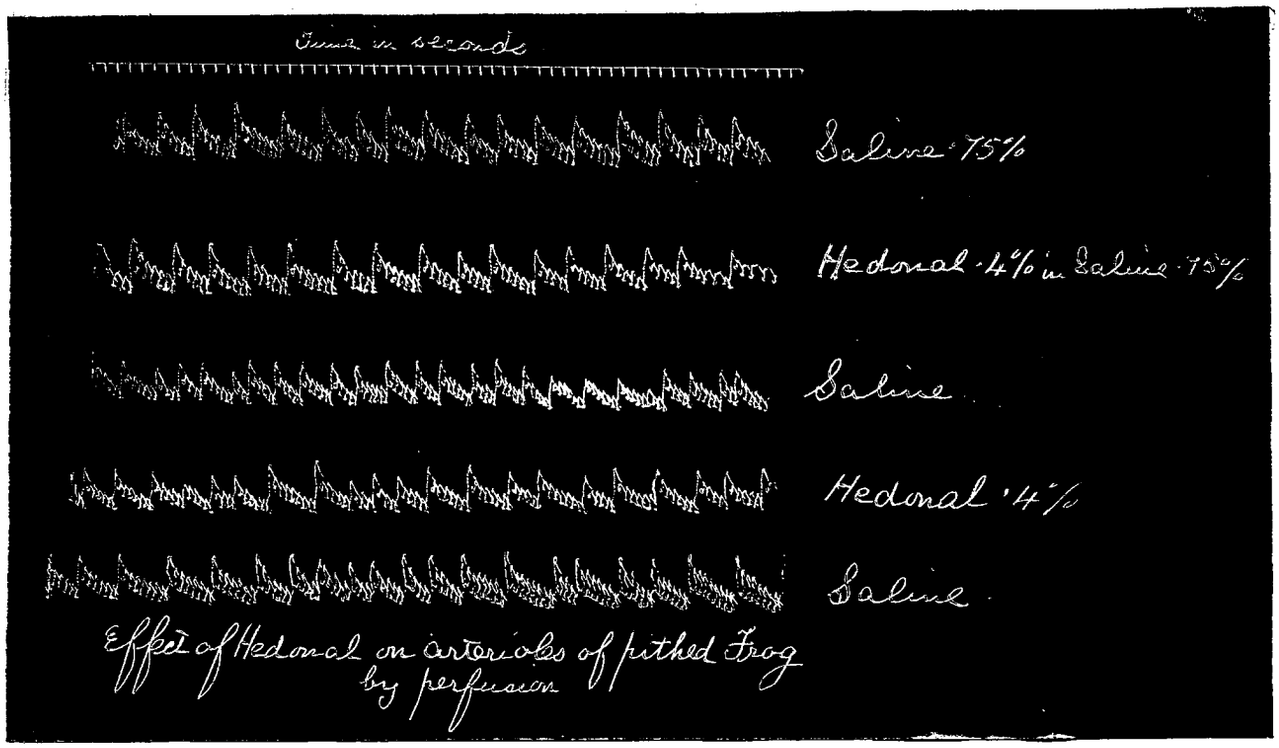
FIGURE I.

In Fig.1. the drops have been counted and the percentage estimated. As line 2 and line 3 were both Hedonal, the calculation has been made on the last four lines, which are alternately Saline and Hedonal.

Line	Solution perfused.	Number of drops.
1	Saline	62
2	Hedonal	62
3	Hedonal	46
4	Saline	57
5	Hedonal	44
6	Saline	50

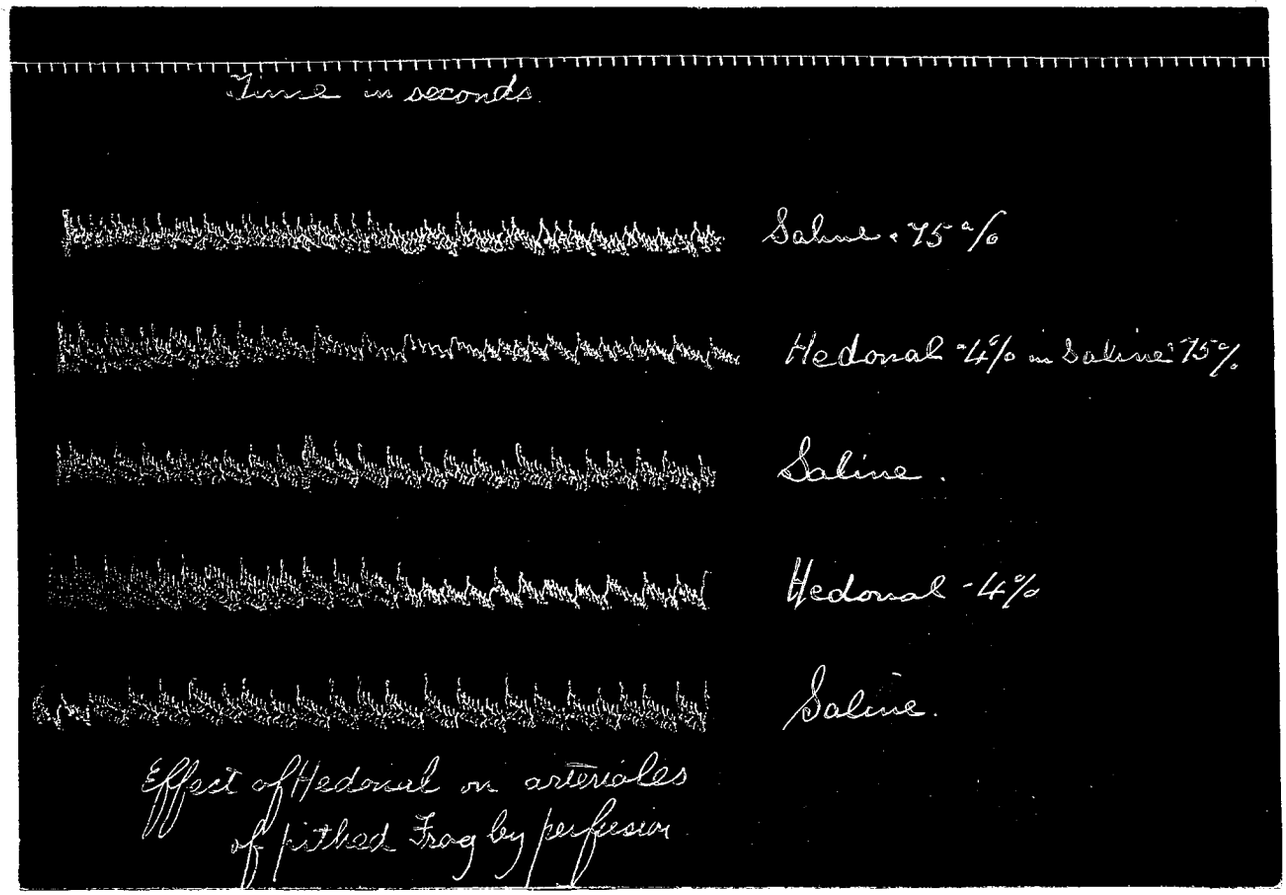
The drops were counted in periods of 30 seconds. Hedonal has caused a loss in output of 15% and is thus a vaso-constrictor.

Figure II.



Natural Size.

Figure III.



Natural Size.

FIGURE II.

In Figure 2 the vaso-constrictor effect of Hedonal is equal to a diminished output from the arterioles of 13%. The calculation was made on the first four lines and upon periods of 30 seconds. The details are tabulated:-

Line.	Solution perfused.	Number of drops.
1	Saline	62
2	Hedonal	55
3	Saline	73
4	Hedonal	62
5	Saline	65

FIGURE III.

The output from the arterioles in this case has been diminished by 16% due to Hedonal.

The interval chosen for the estimation was 23 seconds.

Line.	Solution perfused.	Number of drops.
1	Saline	83
2	Hedonal	65
3	Saline	92
4	Hedonal	82

Figure IV.

Scale:- 2/3rds Natural Size.

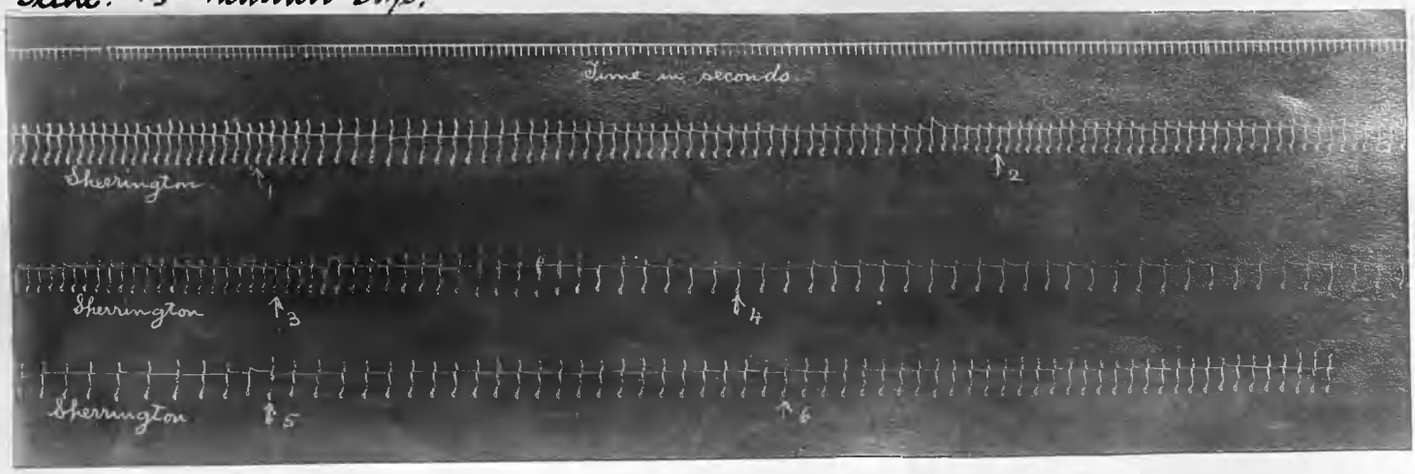


Figure V.

6/7ths Natural Size

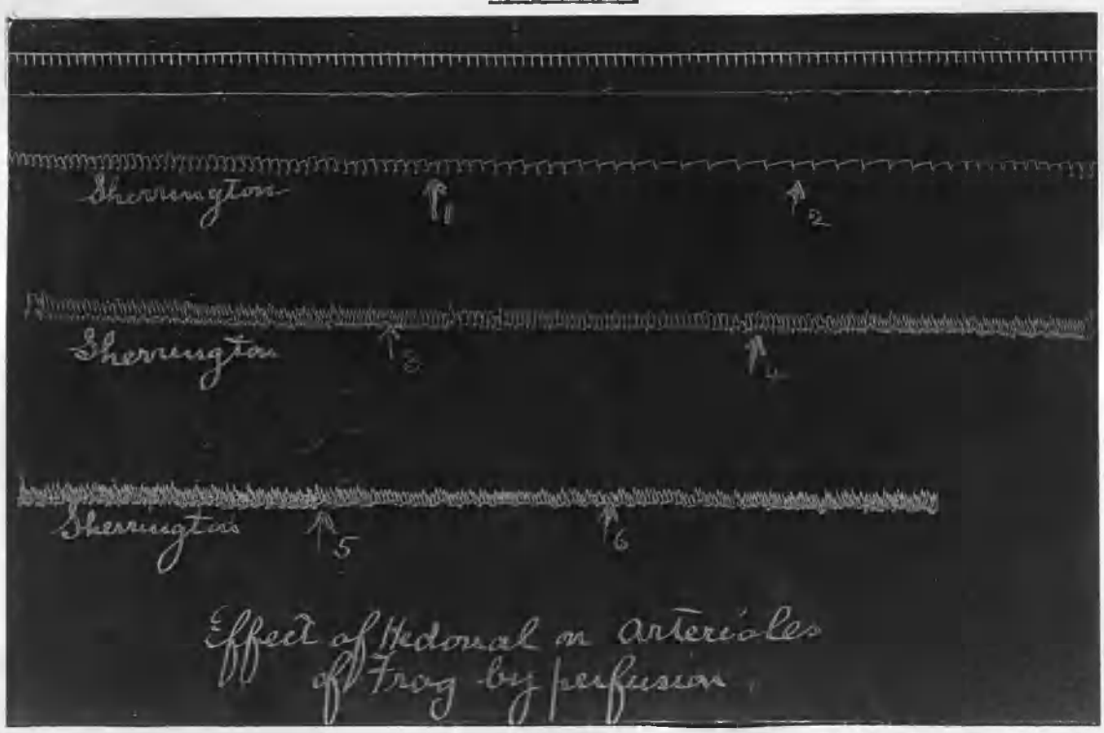
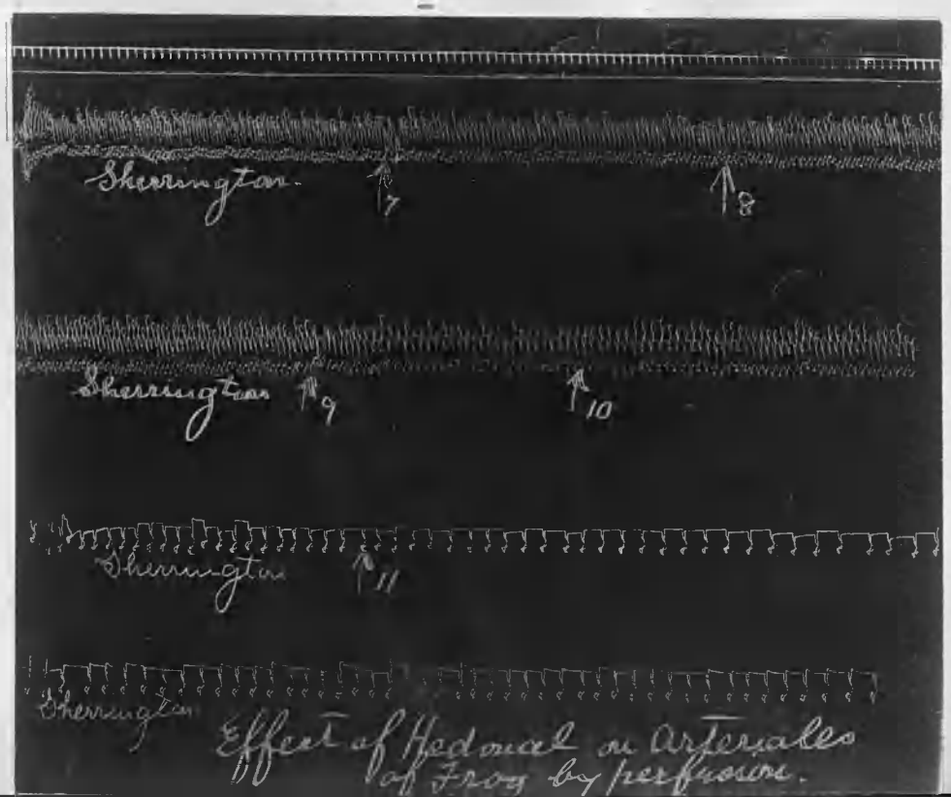


Figure VI.

6/7ths Natural Size



The following eight experiments were carried out with"Sherrington" solution for the restorative and also for the drug-solvent. Vaso-constriction is the result in each.

FIGURE IV.

In this experiment the frog was not pithed: it was stunned and the head removed behind the eyes. There are seen three lines and a time line in the tracing. The tracings all read from left to right. "Sherrington" solution has been running at the beginning of each line. The further details are as follows:-

1. Hedonal. .4% in "Sherrington".
2. "Sherrington".
3. Hedonal .4%.
4. "Sherrington".
5. Hedonal .4%.
6. "Sherrington.

The calculation of the percentage of loss in output has been made upon periods of 32 seconds.

Line.	Solution perfused.	Drops in 32 seconds.
1	"Sherrington"	22
	Hedonal	16
	"Sherrington"	22
2	Hedonal	12
	"Sherrington"	11
3	Hedonal	11
	"Sherrington"	17

The loss in output due to vaso-constriction by Hedonal was in this experiment 29%. (calculated on the first three couples).

FIGURE V.

Here there is shown in Figure V a pronounced vaso-constriction effect, when using a weak solution of Hedonal.

The time line is in seconds. Each of the other three lines begins with "Sherrington" being perfused. The frog was unpithed.

1. Hedonal - 1 in 1000 of "Sherrington".
2. "Sherrington".
3. Hedonal - 1 in 1000.
4. "Sherrington".
5. Hedonal, 1 in 1000.
6. "Sherrington".

Line.	Solution perfused.	Number of drops in 34 seconds.
1	"Sherrington"	33
"	Hedonal	16
"	"Sherrington"	70
2	Hedonal	49
"	"Sherrington"	102
3	Hedonal	77
"	"Sherrington"	96

The calculation has been made on the first six estimations of the drops. The loss due to vaso-constriction by Hedonal is 30%.

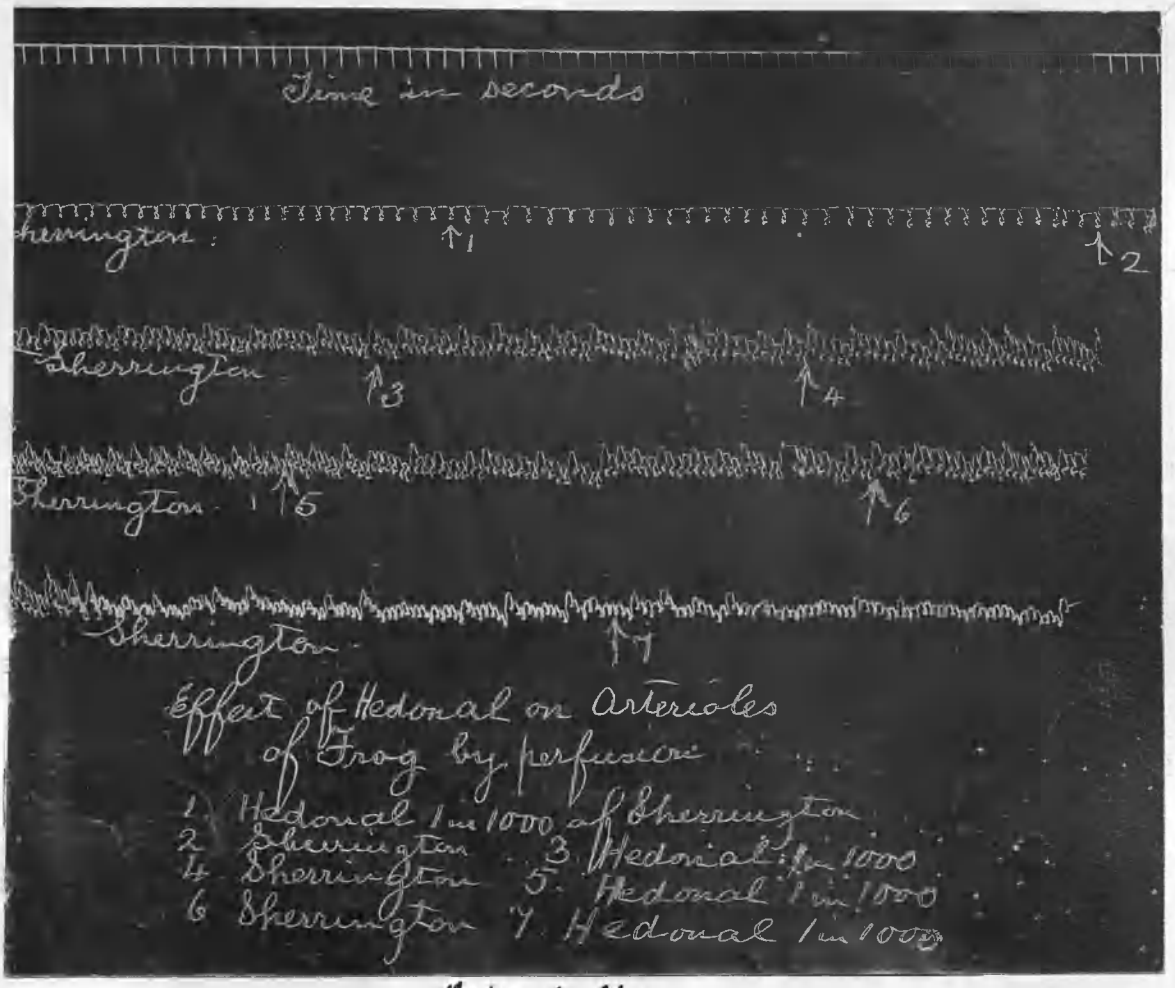
FIGURE VI.

The tracing in Figure 6 was taken from the same frog as Figure 5. A weaker solution is used in this case (1 in 2000). The perfusions have been numbered 7 to 11, as being continuous with Figure V. The frog was unpithed, the time line being in seconds. The numbers are explained below.

7. Hedonal-1 in 2000 of "Sherrington".
8. "Sherrington".
9. Hedonal, 1 in 2000.
10. "Sherrington".
11. Hedonal.

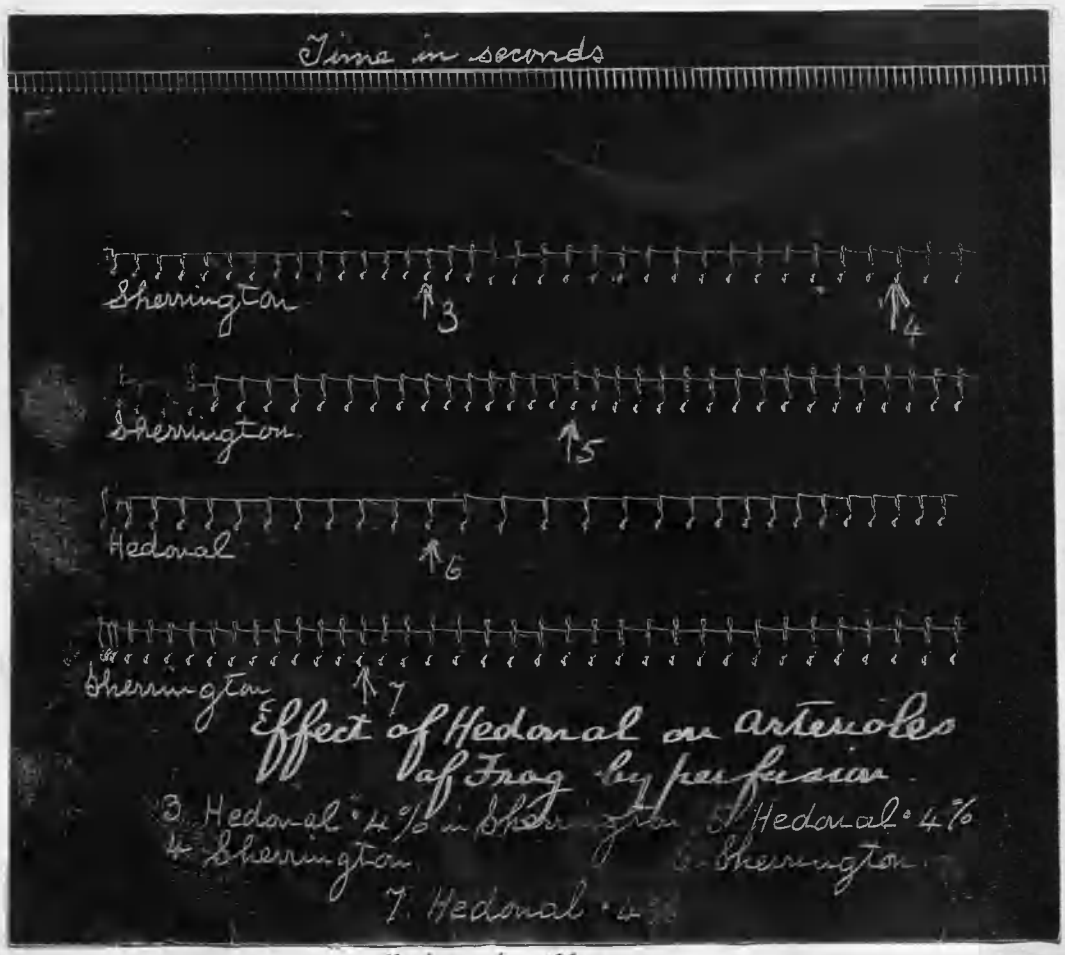
Line.	Solution perfused.	Number of drops in 28 seconds.
1	"Sherrington"	65
"	Hedonal - 1 in 2000	45
2	"Sherrington"	48
"	Hedonal.	32
"	"Sherrington"	33
3	Hedonal.	11
4	"Sherrington"	14

Figure VII.



Natural Size

Figure VIII.



Natural Size.

The calculation in foregoing Table has been made upon the first six estimations. The loss due to Hedonal is 39%.

FIGURE VII.

In this experiment the frog was unpithed, the cerebrum only being destroyed. There are four lines and a time line. The details are written in the tracing. The solution of Hedonal was 1 in 1000.

Line.	Solution perfused.	Drops in periods of 18 seconds.
1	"Sherrington"	18
"	Hedonal	17
2	"Sherrington"	39
"	Hedonal	35
3	"Sherrington	50
"	Hedonal	35
4	"Sherrington"	48
"	Hedonal	45

The loss in output due to Hedonal is 14%.

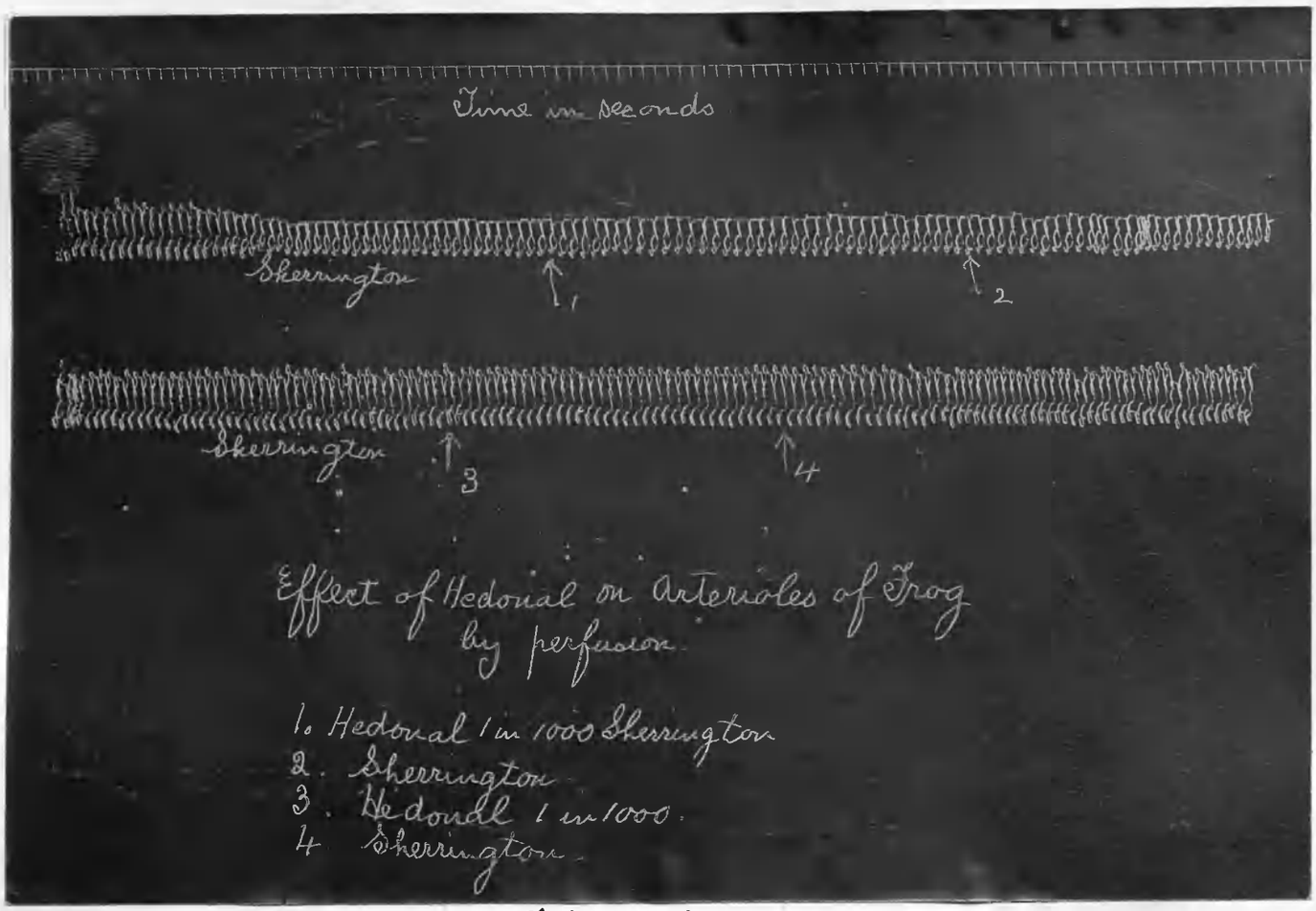
FIGURE VIII.

Figure VIII shows the vaso-constriction effect with a strong solution of Hedonal - .4%. Four lines and a time line are seen.

Line.	Solution perfused.	Drops in periods of 30 seconds.
1	"Sherrington"	12
"	Hedonal	10
2	"Sherrington"	12
3	Hedonal	10
4	"Sherrington"	13
"	Hedonal	10

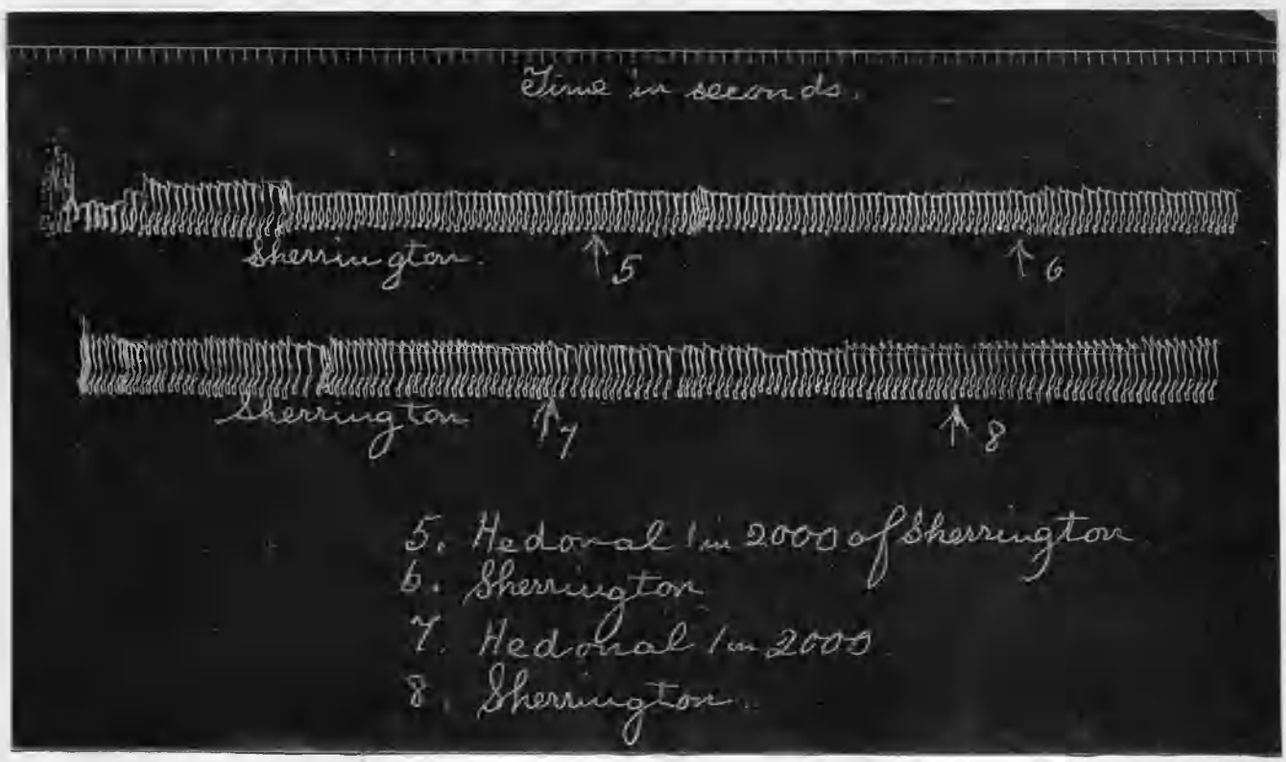
The loss in output in Figure VIII is 18%.

Figure IX.



Natural Size.

Figure X.



Natural Size.

The next three figures are taken from an experiment with the same frog and are consecutive. The Hedonal used is in different strengths.

FIGURE IX.

The Hedonal solution in Figure IX was 1 in 1000 of "Sherrington". There are two lines and a time line.

Line.	Solution perfused.	Drops in periods of 27 seconds.
1.	"Sherrington"	34
"	Hedonal	28
2	"Sherrington"	38
"	Hedonal	34
3	"Sherrington"	40

The loss due to Hedonal calculated from the first two couples is 13%.

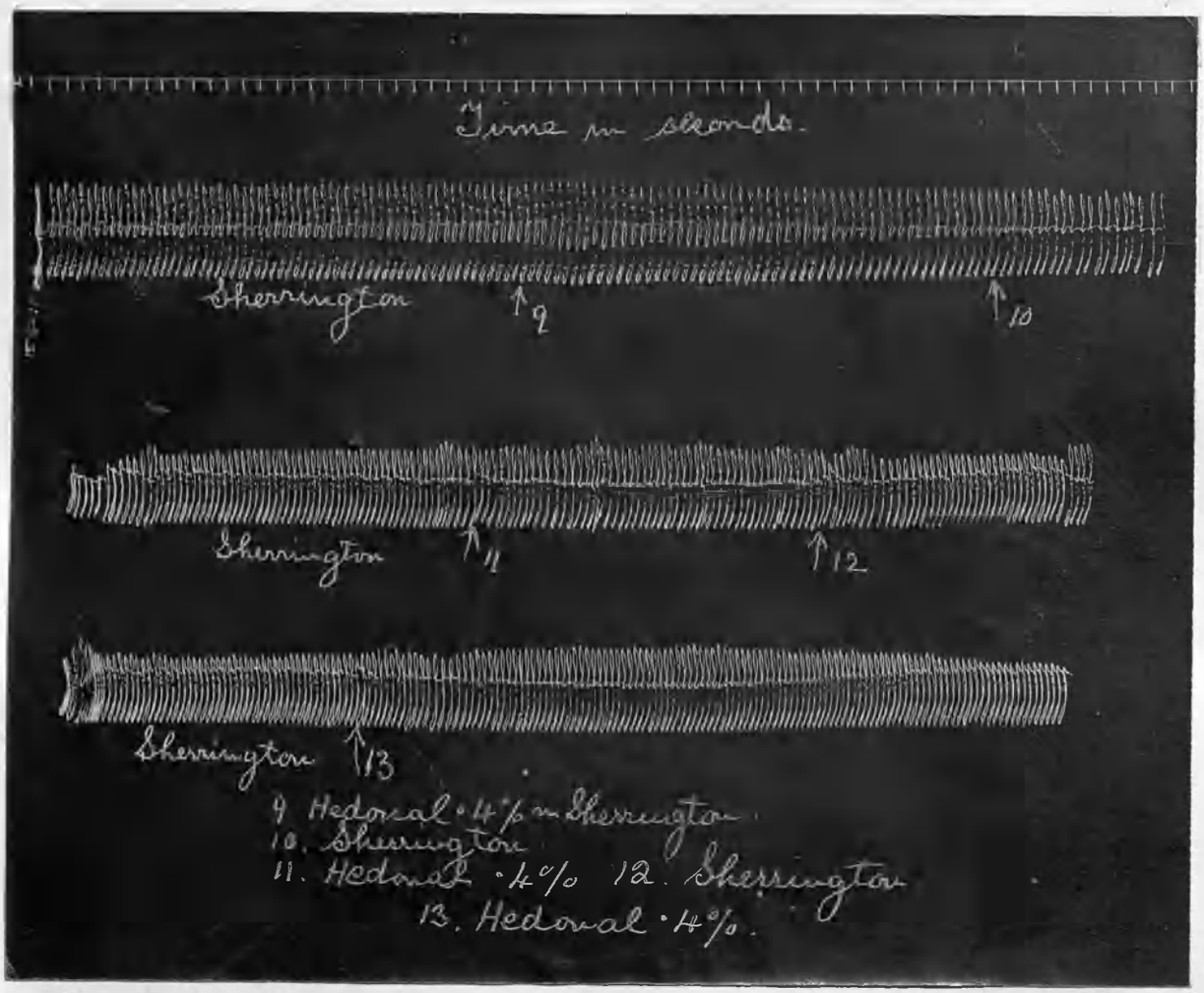
FIGURE X.

The Hedonal solution in Figure X was one in 2000. There are two lines and a time line.

Line.	Solution perfused.	Drops in periods of 17 seconds.
1	"Sherrington"	46
"	Hedonal	44
2	"Sherrington"	46
"	Hedonal	40

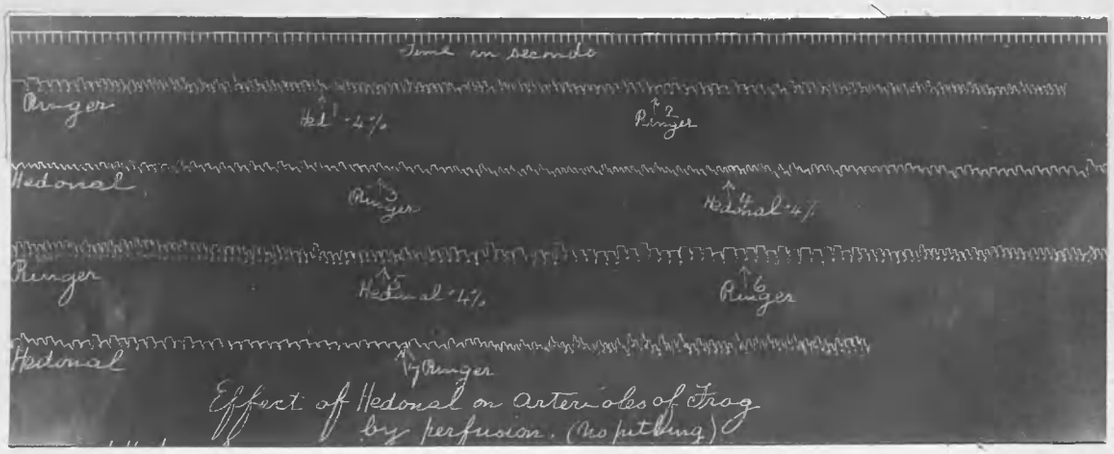
Hedonal has diminished the output by 8.6%.

Figure XI.



Natural Size.

Figure XII.



2/3rds Natural Size.

FIGURE XI.

In Figure XI the Hedonal solution used was dissolved in "Sherrington" as before. The strength in this case was 1 in 250 (.4%). There are three lines and a time line.

Line.	Solution perfused.	Drops in periods of 16 seconds.
1	"Sherrington"	34
"	Hedonal	30
2	"Sherrington"	44
"	Hedonal	40
3	"Sherrington"	50
"	Hedonal	42

The loss in output is 12%.

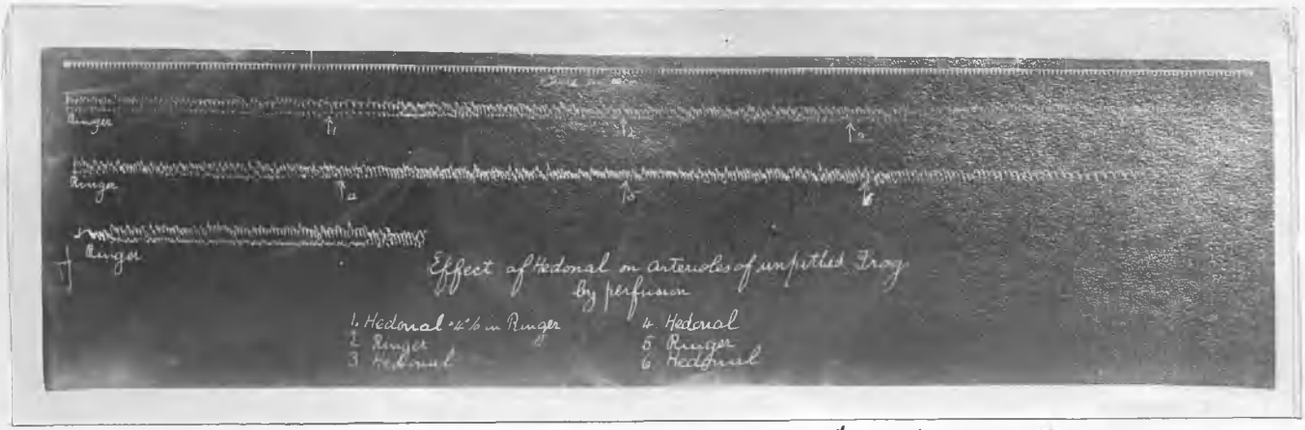
The next six tracings showing vaso-constriction have been chosen from experiments where "Ringer" solution was the drug-solvent and also the restorative. Two were obtained when a strong solution (.4%) was used, and four when a weak solution (.075%) was used.

FIGURE XII.

In Figure XII there are four lines and a time line.

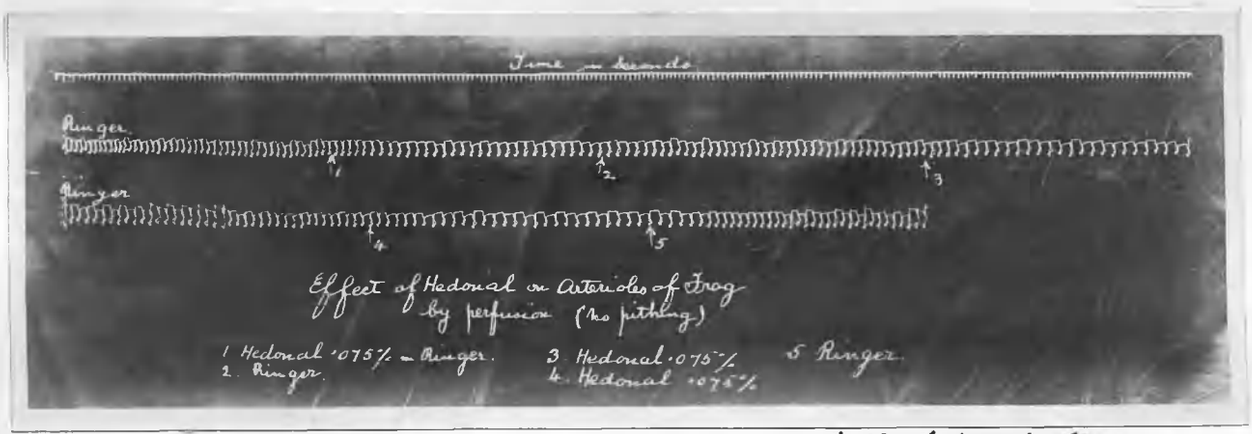
This experiment is interesting, in that a large number of perfusions have been made, the Hedonal always having acted as a vaso-constrictor, and the "Ringer" always as a restorative. The frog was not pithed. The Hedonal solution was one in 250 (.4%).

Figure XIII.



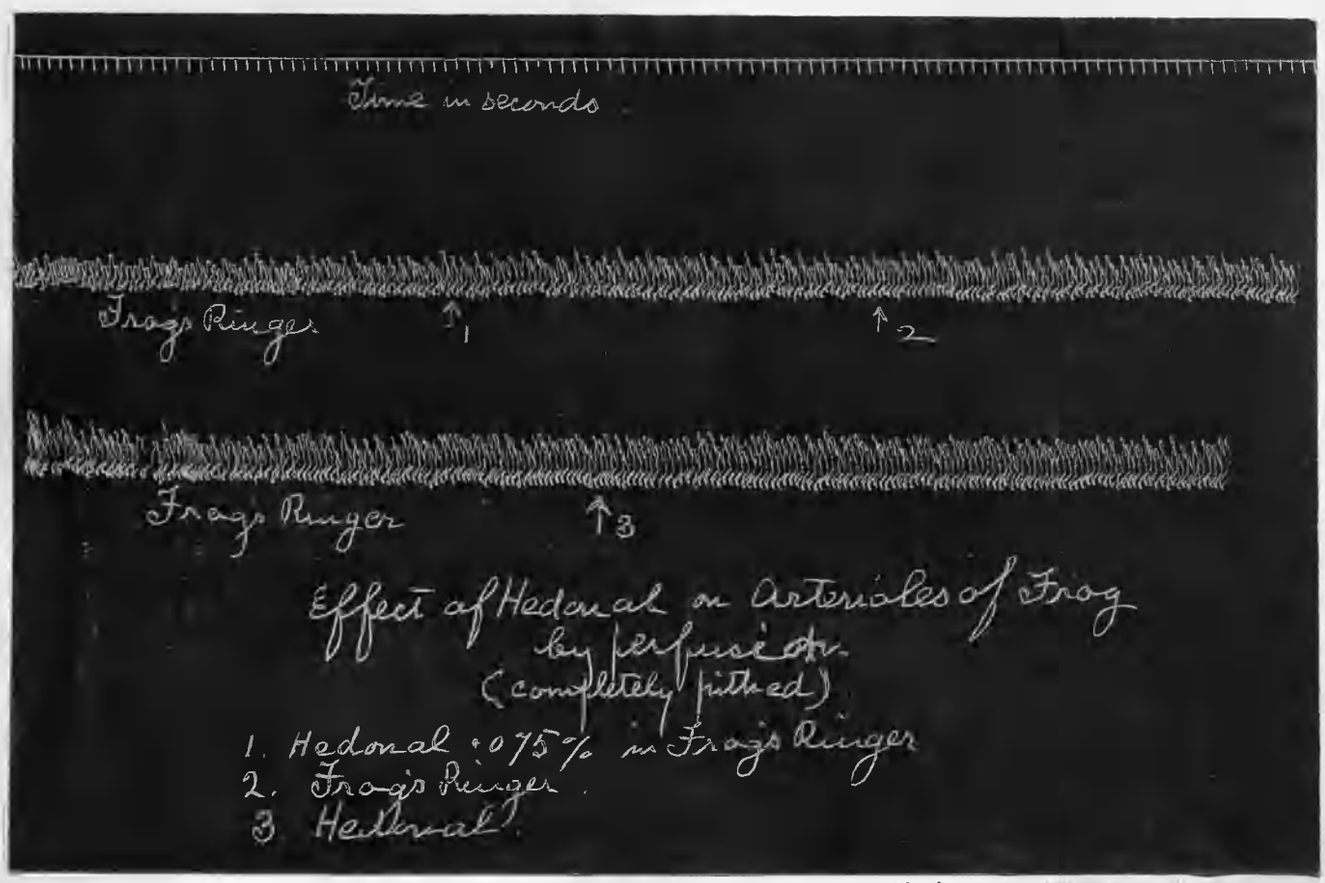
Half Natural Size.

Figure XIV.



Half Natural Size.

Figure XV.



Natural Size.

Line.	Solution perfused.	Drops in periods of 30 seconds.
1	"Ringer"	38
"	Hedonal	32
1	"Ringer"	38
2	Hedonal	31
"	"Ringer"	39
"	Hedonal	26
3	"Ringer"	34
"	Hedonal	21
"	"Ringer"	34
4	Hedonal	23
"	"Ringer"	34

The loss in output due to Hedonal and calculated on the first five couples is 27%.

FIGURE XIII.

In Figure XIII, the solution of Hedonal was 1 in 250 (.4%), and the frog was unpithed. There were nine different perfusions. In this experiment the first dose of Hedonal showed increased output from the arterioles. The explanation is that it was really a"Ringer" effect which was still increasing and the fluid had not been fully run off.

Line.	Solution perfused.	Drops in periods of 40 seconds.
1	"Ringer"	37
"	Hedonal	48
"	"Ringer"	50
"	Hedonal	43
2	"Ringer"	53
"	Hedonal	48
"	"Ringer"	50
"	Hedonal	20
3	"Ringer"	45

The loss in output due to Hedonal and calculated upon the first four couples, is 16%.

FIGURE XIV.

In Figure XIV a weak solution (.o75%) was used, the frog was pithed and the effect was a marked one.

Line.	Solution perfused.	Drops in periods of 44 seconds.
1	"Ringer"	35
"	Hedonal	23
"	"Ringer"	27
"	Hedonal	20
2	"Ringer"	27
"	Hedonal	21
"	"Ringer"	29

The loss in output due to Hedonal and calculated on the first three couples, is 28%.

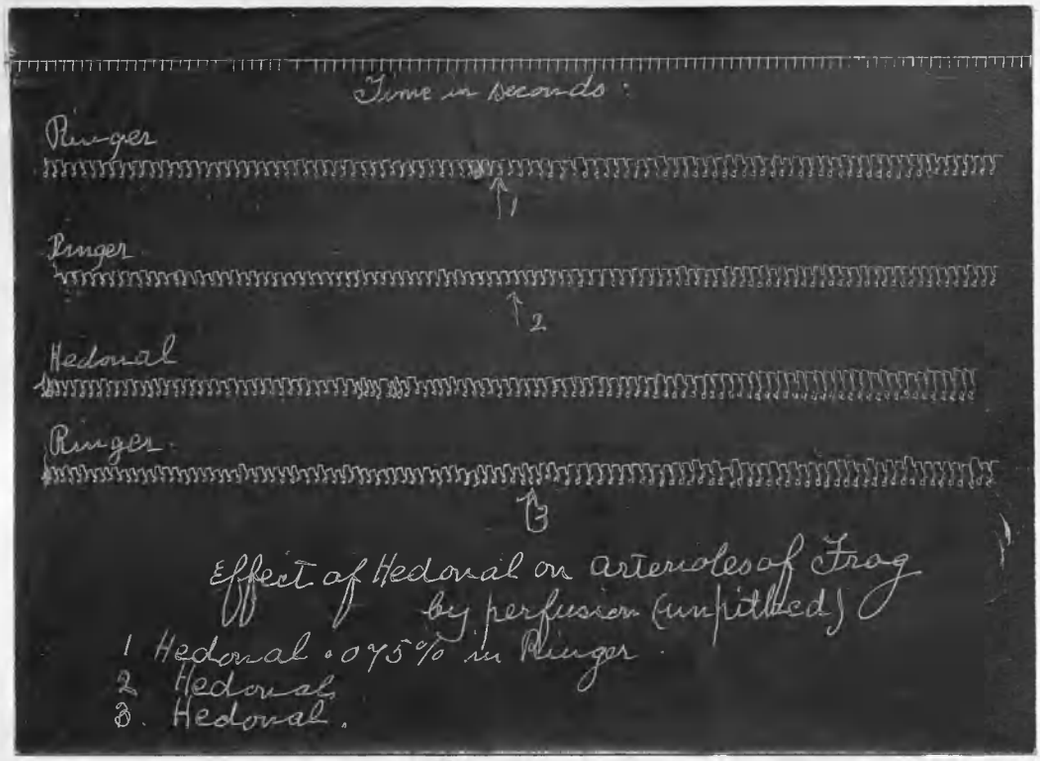
FIGURE XV.

In Figure XV the frog was pithed. A weak Hedonal solution was used (.075%).

Line.	Solution perfused.	Drops in periods of 28 seconds.
1	"Ringer"	59
"	Hedonal	53
"	"Ringer"	60
2	Hedonal	47

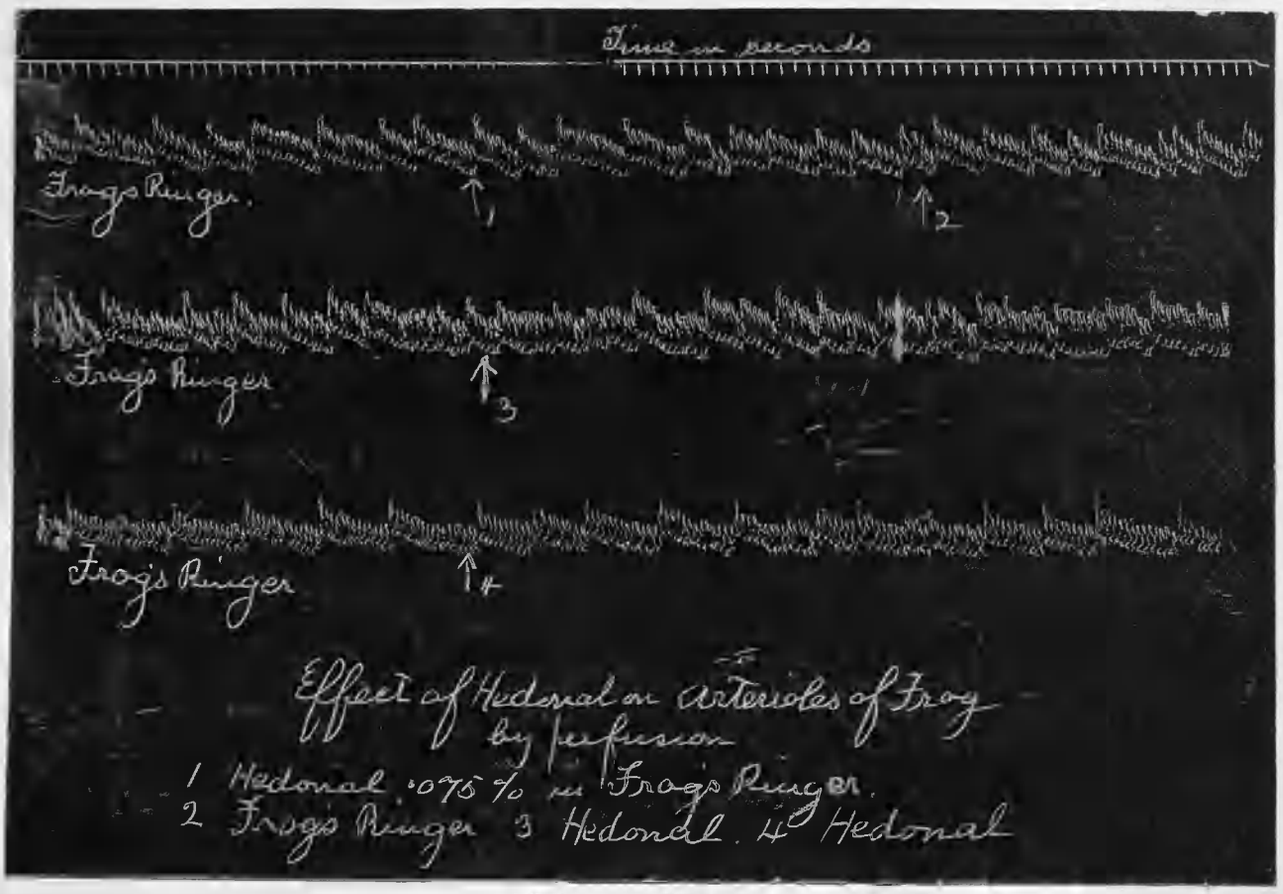
The loss in output is 15%.

Figure XVI.



Natural Size.

Figure XVII.



Natural Size.

FIGURE XVI.

Figure XVI shows four lines in the tracing and also a time line. The Hedonal solution was .075% in "Ringer", and the animal was unpithed.

Line.	Solution perfused.	Drops in periods of 38 seconds.
1	"Ringer"	37
"	Hedonal	36
2	"Ringer"	40
"	Hedonal	38
4	"Ringer"	42
"	Hedonal	36

The loss in out-put due to Hedonal is 7.5%.

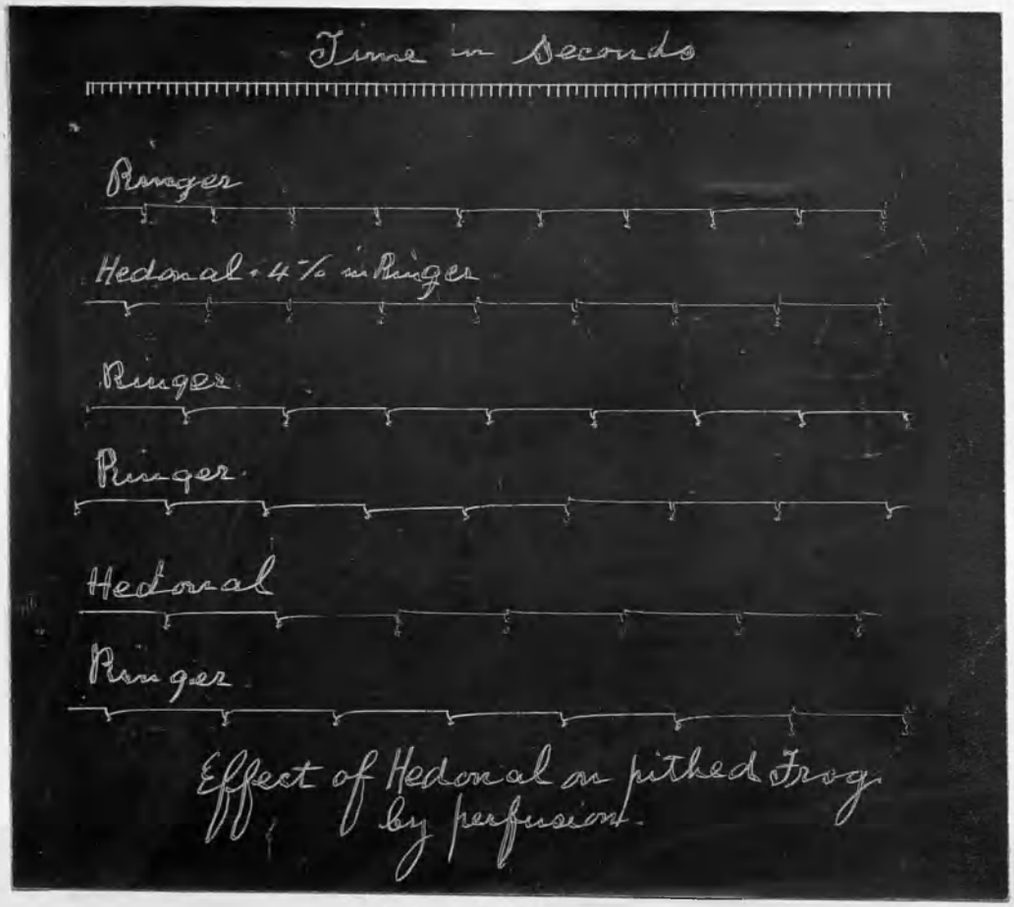
FIGURE XVII.

In Figure XVII, the frog was unpithed and the Hedonal solution was .075%. The appearance like that of respiration and pulse waves is very marked. The explanation has been already given. (see page 24.)

Line.	Solution perfused.	Drops in periods of 26 seconds.
1	"Ringer"	67
"	Hedonal	57
2	"Ringer"	67
"	Hedonal	60
3	"Ringer"	70
"	Hedonal	61

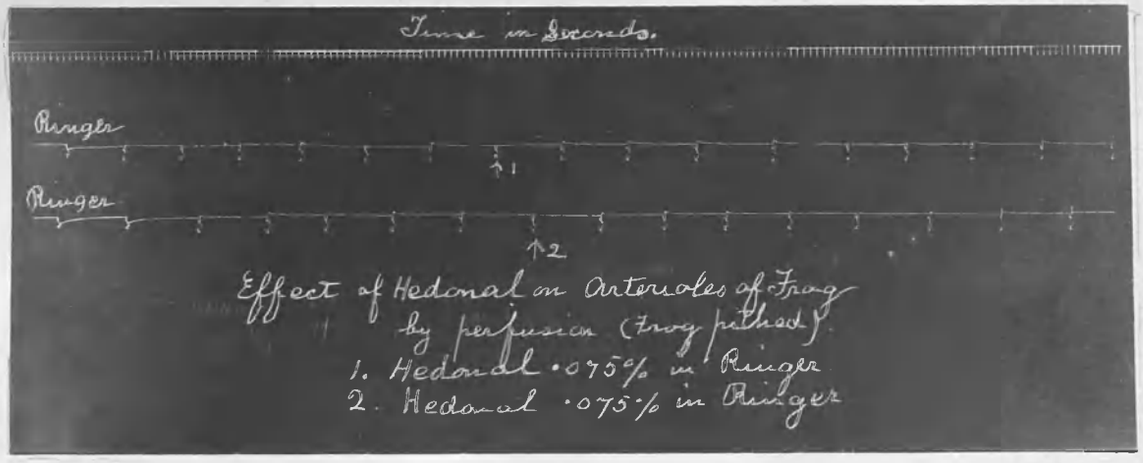
The loss in output due to Hedonal is 12%.

Figure XVIII.



Natural Size.

Figure XIX.

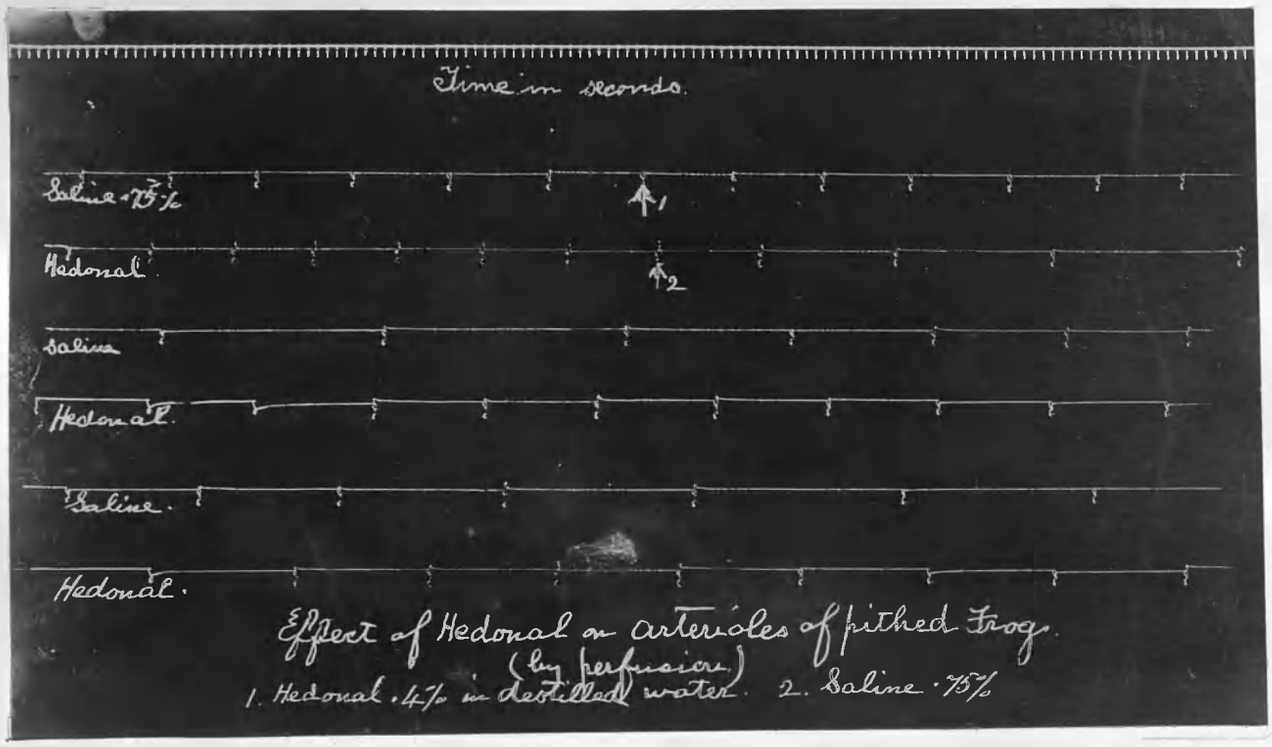


Scale:- 2/3rds Natural Size.

Two tracings are produced here in which Hedonal showed no effect at all. They were taken from the same frog, the animal first having been pithed. In Figure XVIII the Hedonal was .4%, and in Figure XIX it was .075%. In both cases the drug solvent and the restorative was "Ringer".

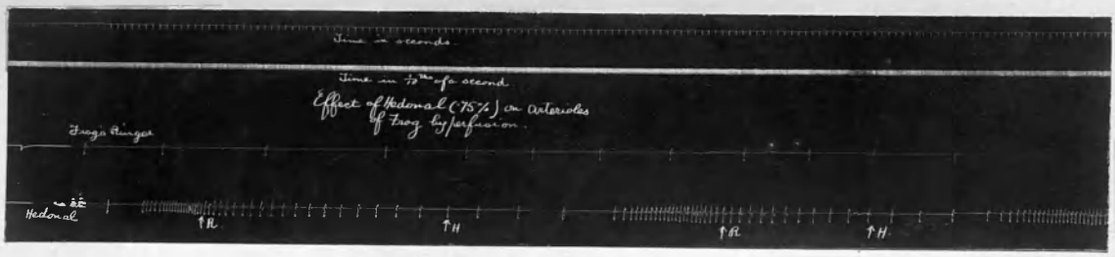
In opposition to all the foregoing results there is now produced Figure XX, which shows Hedonal to have been a vaso-dilator. It was a pronounced effect. The conditions of the experiment, however, should be noted. The Hedonal (.4%) was dissolved in distilled water, which is not isotonic with the blood. The control solution or restorative differed from the drug-solvent. It was .75% normal Saline. These facts are important in so far as they might explain how an entirely different result could be recorded by different experimenters.

Figure XX.



¾ Natural Size.

Figure XXI.



⅓ Natural Size.

FIGURE XX.

In the tracing, Figure XX, every dose of Saline has diminished the output, and every dose of Hedonal has increased the output, always showing vaso-dilatation. The calculation has been made on the last four lines, as each line represents only one solution and occupies approximately two minutes.

Line.	Solution perfused.	Drops in periods of 120 seconds.
3	Saline .75%.	7
4	Hedonal .4% in distilled water.	10
5	Saline.	6
6	Hedonal	9

The increase in output is therefore 46%.

FIGURE XXI.

This last tracing has been shown for similar reasons to those of the preceding one. It shows vaso-dilatation byHedonal. There are two lines in the tracing, and two time lines,one in seconds and one in tenths of a second. The frog was pithed. The following conditions also require to be noted.

1. The solvent of the drug was normal Saline.
2. The restorative was "Frog's Ringer".
3. The effect of Hedonal did not show for 24 seconds after the perfusion of Hedonal was started.
   The effect of Hedonal was a very marked effect.

SECTION X.

NERVE EXCITABILITY.

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NERVE EXCITABILITY.

(Frog's Sciatic).

Ten experiments showing:-

(1) Partial paralysis of the nerve due to Hedonal locally applied.

(2) Restoration of the partially paralysed nerve, by a bath of Ringer's solution.

(3) Hedonal effect on the nerve, produced a second time, i.e., after restoration had first been obtained by "Ringer".

(4) The calculated increase in the latency period due to Hedonal.

------oOo------

The results of Experiments:-

The general effect of Hedonal on the sciatic nerve of the frog has always been that of diminished excitability: in some cases such as is seen in Figures 1 and 2, immersion of the nerve for 1 minute in .37% Hedonal stopped all response to the electric current in use.

In Figures 3 and 4, a second minute in the Hedonal bath abolished response to the current: in Figure 5 response ceased after the third dose.

Again it has been found that a partially paralysed sciatic nerve or one which has shown no response at all to the current used after Hedonal treatment, may have its excitability very much restored by placing it in a bath of Frog's "Ringer". This is well demonstrated in Figures 6, 9 and 10.. In Figure 9 after restoration the Hedonal effect was produced a second time.

In the last two tracings, viz., Figures 7 and 8 both "make" and "break" contractions are shown.

In Figure 8, the Hedonal effect is very gradual and is exceptional in this way. To the general statement regarding diminished excitability due to Hedonal the following must be added.

In a few cases the very first dose of Hedonal to the nerve, produced when it was electrically stimulated, a higher curve, or greater excitability than the previous normal. Every subsequent application of the drug, however, always rapidly diminished the excitability until, indeed, no response whatever was obtained. This initial increase in excitability may be seen in Figures 7 and 8.

The explanation of the primary increased excitability has not been exactly determined. It may be that the nerve when stimulated after the Hedonal bath, in some cases was more excitable at first from the increased moisture, apart from the drug altogether, and when the drug had not had time to affect it. Later on the real effect was a drug effect rather than moisture. Apart from this suggestion, we may recall the fact that in some other sections, there has been a similar early evidence of increased function, for example, the effect of Hedonal on the heart of the frog showing a primary stimulation - the cardiac rate usually being increased at first.

Again we have seen that the reduction in blood pressure in the rabbit and dog due to Hedonal was nearly always preceded by an initial increase. Our three-fold experience may then be due to the same cause.

It has always been found, that the Hedonal solution applied to the nerve, increased the latency period. This has been calculated in four cases, the increase varying from 50% to 75% (see Figures 3, 4, 5 and 6.)

The Method adopted in these Experiments;-

The excitability of the frog's sciatic nerve was tested in the usual way. A nerve-muscle preparation was mounted on the frog-board. The gastrocnemius at one end was attached to a thread leading to the short arm of the myograph lever. The long arm of the lever was suitably pointed to take a tracing on the revolving drum.
A Du Bois-Reymond's inductorium was used for stimulating the nerve. The secondary coil had a measure in centimeters placed along its side, so that the current could be accurately measured.

The two wire terminals from the secondary coil were placed under the central part of the sciatic nerve. The electric current was then tested experimentally by giving shocks to the muscle through the nerve, until the "make" was obliterated and a maximal "break" shock was obtained. A normal curve was then traced without Hedonal. A second or even third normal curve was made with an interval of one minute to see what natural change might take place. The nerve was then placed in a small bath made of paraffin wax - about 1 inch long and containing Hedonal solution (.37%) in normal saline. The effect was tested with 1 minute intervals, the same current being used throughout the whole experiment, with the exception of Figure 10 where the current was increased.

In all the experiments in this section, the long arm of the lever measured 170 millimeters: there was no weight suspended. The weakest current used was with the secondary coil standing at 38 centimeters and the strongest at 10 centimeters.

The position of electrode during stimulation is seen below.

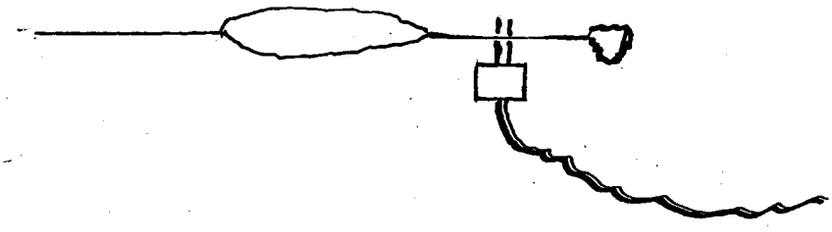
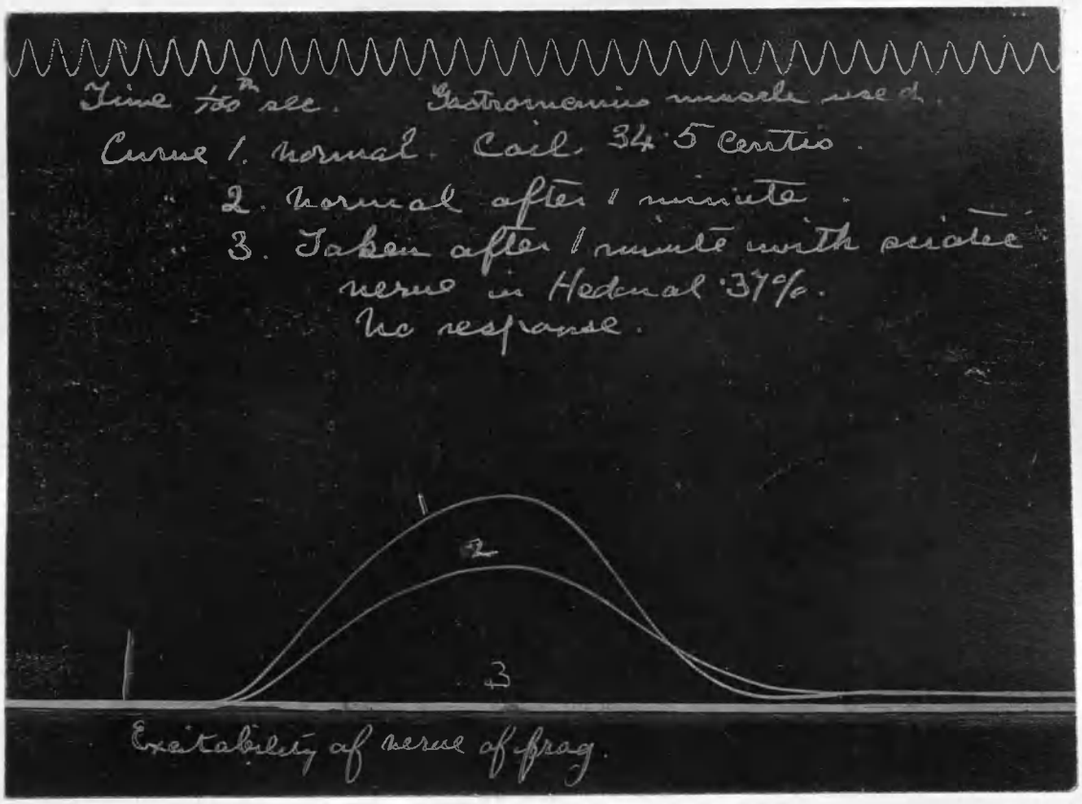
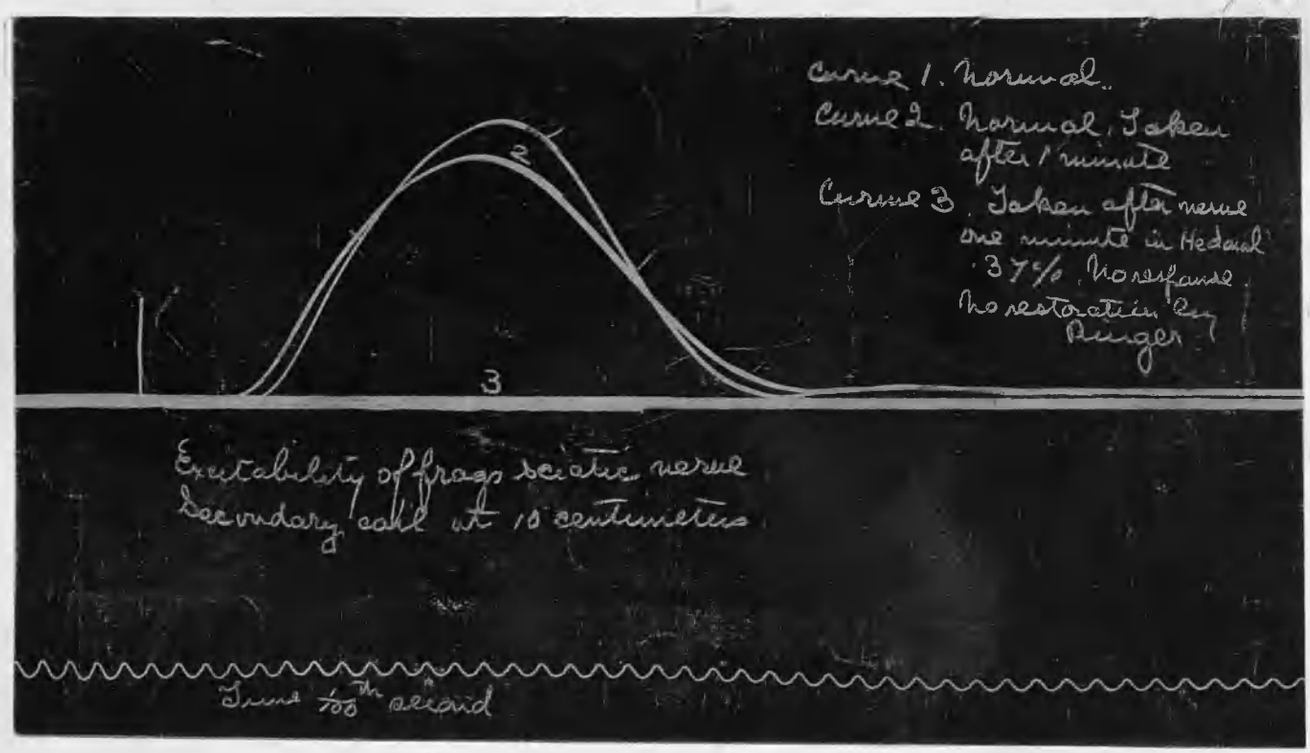


FIGURE I.



Natural Size

FIGURE II.



Natural Size.

Figure I.

In this experiment the nerve failed to respond to electric stimulation after 1 dose of Hedonal for 1 minute. The maximal "break" shock was obtained at 34.5 centimeters.

Curve 1. Normal. Height 28 m.m.

Curve 2. Normal. Height 19.m.m. - taken after an interval of 1 minute.

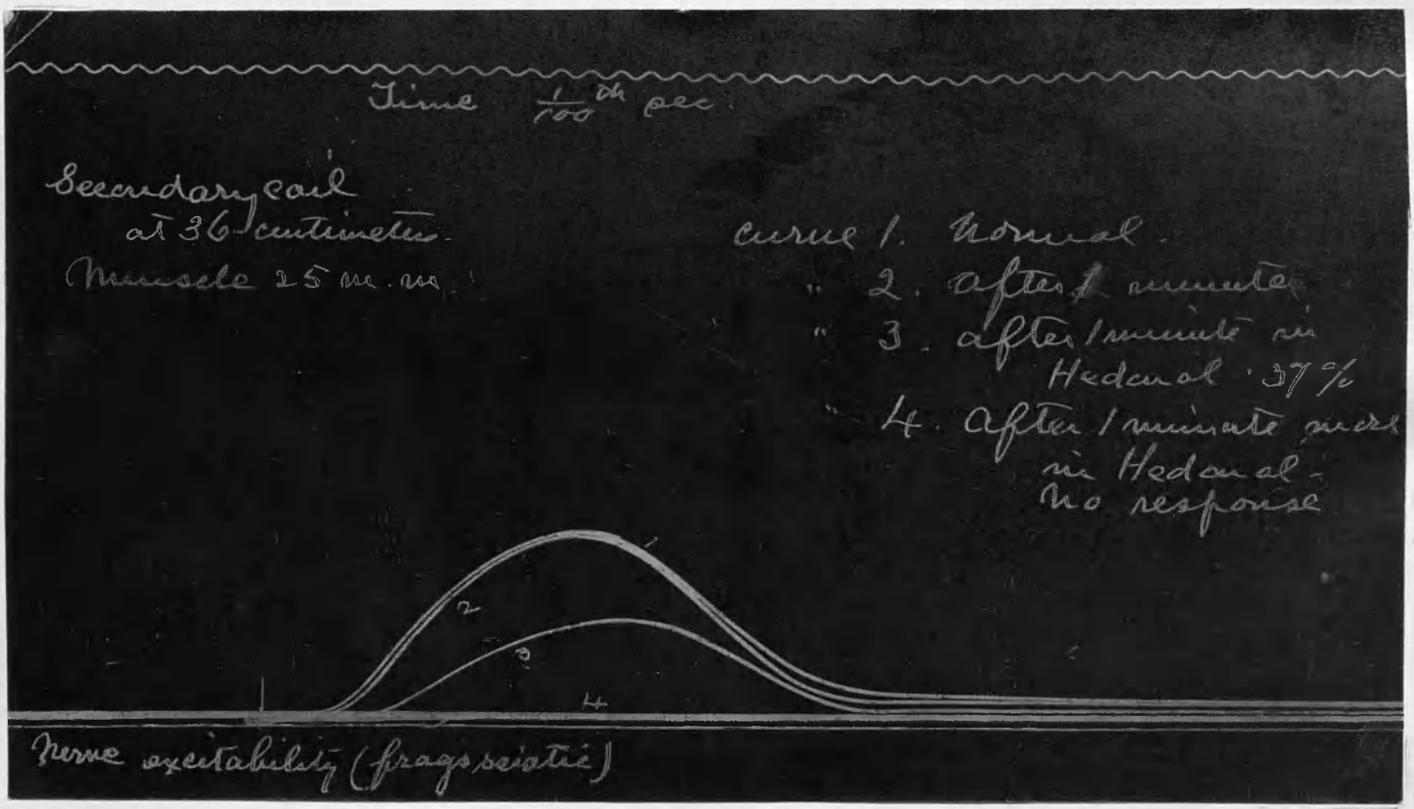
Curve 3. Stimulation was attempted after the nerve had been 1 minute in the Hedonal bath. No response.

Figure II.

In Figure II, the nerve has failed to respond after immersion for 1 minute in the Hedonal bath as in Figure I.

Two normal curves were first traced. The nerve after failing to respond was placed in a bath of "Ringer"; in this case no restoration took place.

FIGURE III.



Natural Size.

Figure III.

Figure III shows failure of the nerve to respond to electric current after the second dose of Hedonal. The Hedonal has distinctly increased the latency period.

A normal latency period was found to be (Curve 2) 2⅓ /100ths of a second. With one dose of Hedonal, it became 4/100ths of a second, or an increase took pla ce from .023 second to .040 second. The real increase is = .017 of a second or 73%.

The maximal shock was obtained with the coil standing at 36 centimeters.

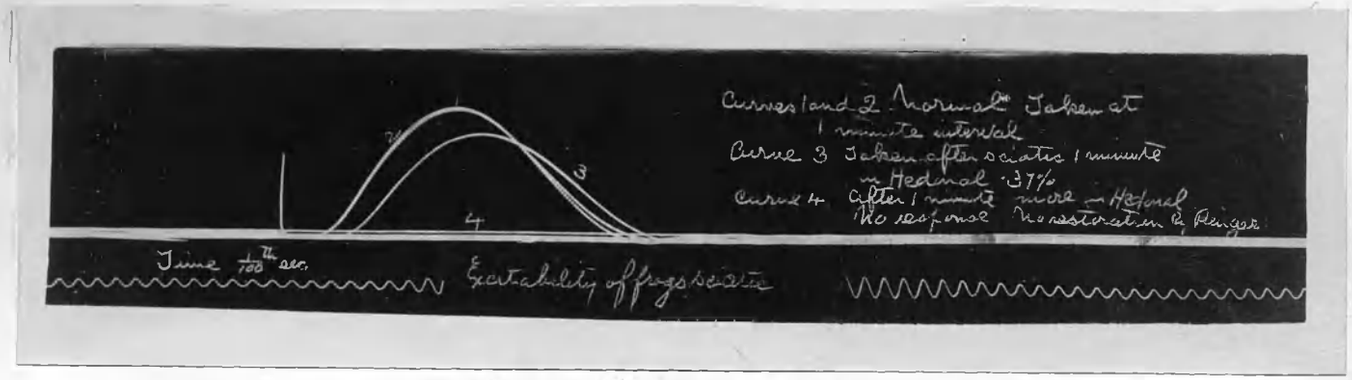
Curve 1. Normal curve. Height 27 m.m.
Latency period 2/100ths of a second (.02 sec.).

Curve 2. Normal. Taken 1 minute later. Height 26 m.m.
Latency period 2⅓ 100ths of a second (.023 sec.).

Curve 3. Hedonal curve. Height 14 m.m. - a loss of 46%.
Latency period 4/100ths of a second (.04 sec.).
The increase in the latency period is .017 second or 73%.

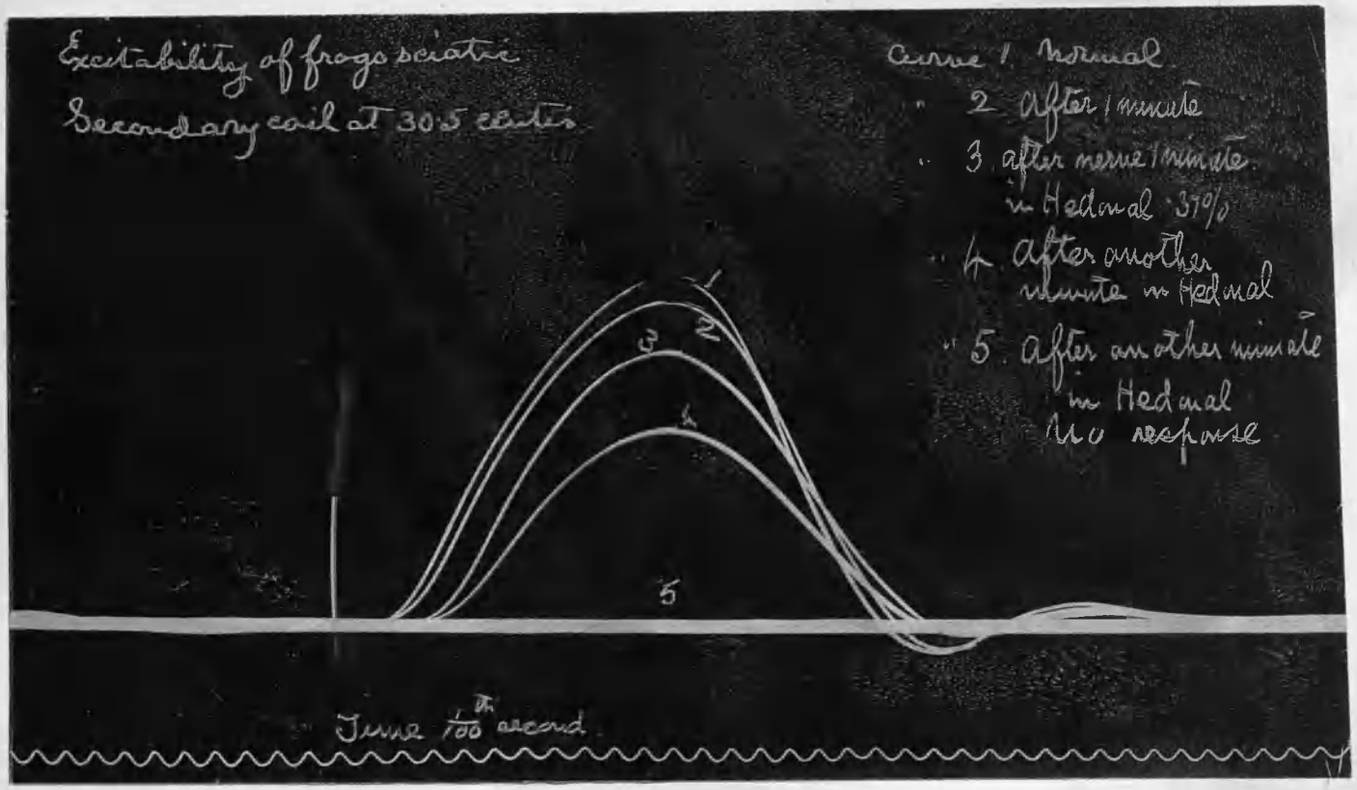
Curve 4. This was attempted after another minute in Hedonal.
There was no response. A "Ringer" bath was then used. No restoration.

FIGURE IV.



Scale 2/3rds Natural Size.

FIGURE V.



Natural Size.

Figure IV.

There are two normal curves in Figure 4, which occupy practically the same position, but which were taken with an interval of one minute. The first Hedonal dose produced a definite effect. With the second dose no response resulted, the same current being used.

The latency period was increased by the first dose of Hedonal by 75%.

Curves 1 and 2. Normal. Height 25 m.m.
Latency period 2/100ths of a second in each (.02 sec.).

Curve 3. Hedonal effect. Height 19 m.m. - a loss of 24%.
Latency period 3½/100ths of a second or .035 second. This equals an increase of .015 second, or 75%.

Curve 4. Hedonal effect. No response.
In this case "Ringer" failed to restore excitability.

FIGURE V.

In Figure V two normal curves are shown and three for Hedonal. The third dose of Hedonal showed failure to respond.

The latency period as calculated in Curve 3 (first dose of Hedonal) and compared with the preceding normal curve showed an increase of 50%. The secondary coil stood at 30.5 centimeters.

Curve 1. Normal. Height 48 m.m.

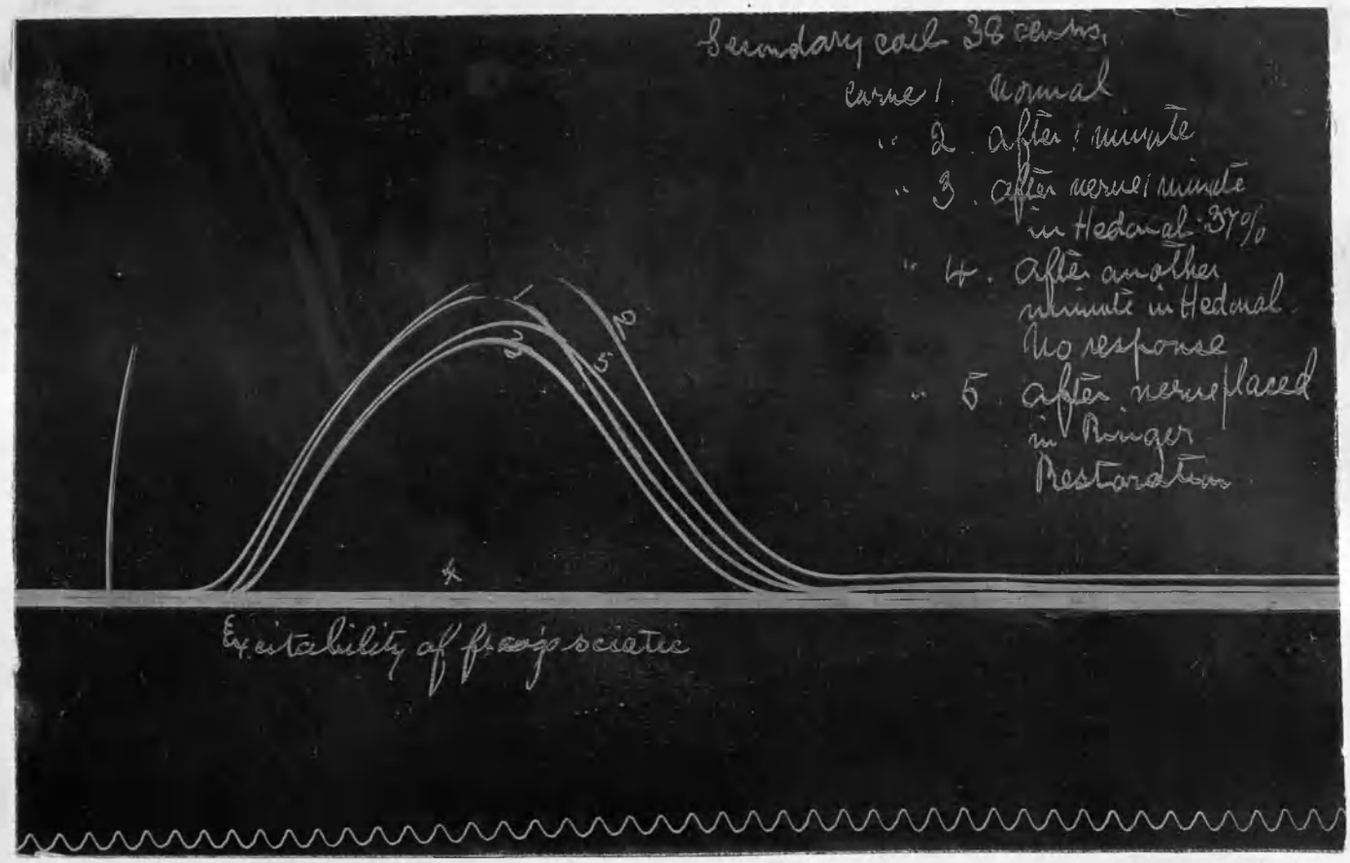
Curve 2. Normal. Taken after another minute. Height 44 m.m.
Latency period 2/100ths of a second or .02 second.

Curve 3. Hedonal curve. Taken after the nerve was one minute in Hedonal. Height 36 m.m. - a loss of 8 m.m.
Latency period 3/100ths of a second or .03 second.
This period has been increased by 50%.

Curve 4. Taken after the nerve was another minute in Hedonal.
Height 26 m.m.
Latency period 3⅓ rd/100ths of a second or .033 second.

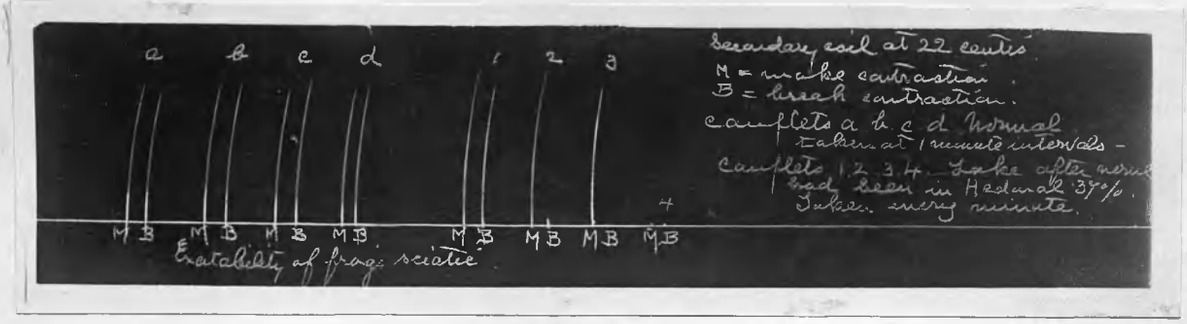
Curve 5. This attempt met with no response.

FIGURE VI.



Natural Size.

FIGURE VII.



Scale :- 2/3rds Natural Size.

FIGURE VI.

This figure is produced to show the power of "Ringer to restore the excitability of the frog's sciatic nerve, after it had been partially paralysed by Hedonal, so that it had failed to respond to the electric current formerly applied. The "Ringer" curve rose higher than the Hedonal curve, viz., a height of 37 m.m.

The first dose of Hedonal increased the latency period by 50%. The secondary coil stood at 38 c.m.

Curve 1. Normal. Height 40 m.m.

Curve 2. Normal. Height 45 m.m. Taken after one minute; it is higher than the former one. The latency period was 3/100ths of a second or .03 second.

Curve 3. Hedonal curve. Height 34 m.m. - a loss of 11 m.m. or 24%. The latency period was 4½/100ths of a second or .045 sec.. This is an increase of 50%.

Curve 4. Hedonal effect. No response.

Curve 5. "Ringer" curve. Restoration effect. Height 37 m.m..

FIGURE VII.

To prevent mingling of several curves, the drum in Figure VII was stationary, so that each contraction of the lever on stimulation traced a line separated from all others. Both a "make"and a "break" contraction was recorded, so that in the tracing, couplets are seen in each case. The current was used when the secondary coil stood at 22 c.m..

The first four couplets, a,b,c,d, are normal curves taken at 1 minute intervals.

Couplets 1, 2, 3, 4, are Hedonal curves taken every minute.

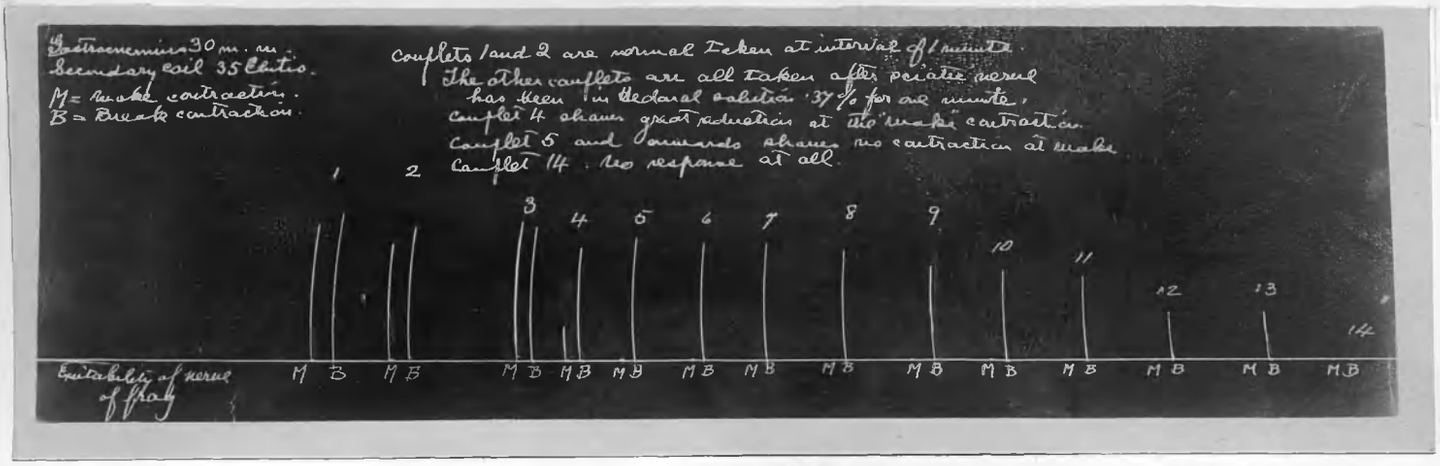
In couplet d, (normal) the "make" curve is 29 m.m. high and the "break" 30 m.m..

In couplet 1,(Hedonal) the "make" is 32 m.m. and the "break" is 30 m.m. The increased height of the curves in this couplet has been explained on page 48.

Couplets 2 and 3 both show failure to respond to the "break" shock.

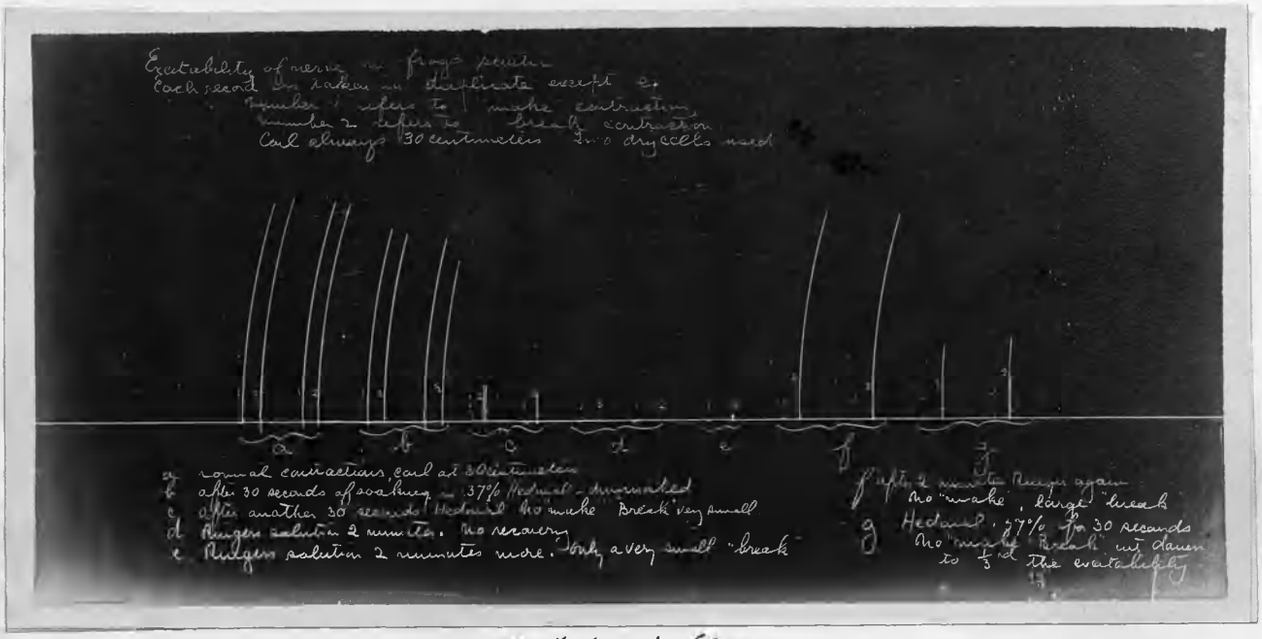
Couplet 4 shows no response whatever.

FIGURE VIII.



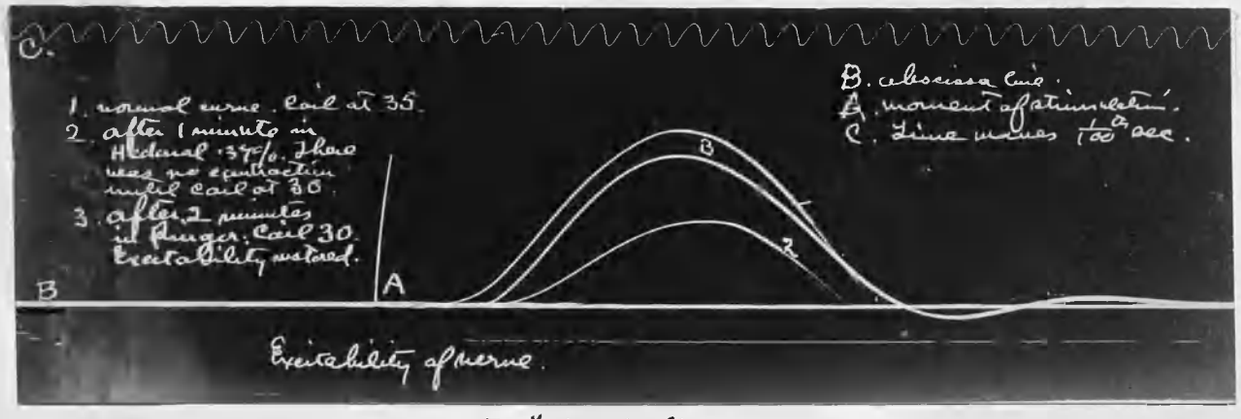
Half Natural Size.

FIGURE IX.



·6 Natural Size.

FIGURE X.



·7 Natural Size.

FIGURE VIII.

As in Figure VII the drum in this case has been stationary. "Make" and "break" contractions are recorded in couplets. The secondary coil stood at 35 c.m.. In this experiment there was unusual resistance to the effect of Hedonal; the result has been very gradual.

In couplet 2, which is a normal one, the "make" contraction is 31 m.m., and the "break" 37 m.m..

In couplet 3 (first Hedonal one), the "make" contraction is 38 m.m., and the "break" contraction 37 m.m.. This is actually an increase over the former normal couplet.

In couplet 4, the "make" is very much reduced, and quite absent in all the succeeding couplets, until in couplet 14 no response to either shock is obtained.

FIGURE IX.

In Figure IX the "make" and "break" shock effects are produced in duplicate, the drum being stationary.

There is seen a profound effect from immersion of the frog's sciatic in Hedonal .37% for 30 seconds. When the nerve at last failed to respond to the electric current, immersion in "Ringer" began to restore the excitability. The curves in Couplet f are fully as high as the first normal ones.

Treatment by Hedonal again cut down these restored curves as seen at g.

FIGURE X.

Figure X is produced to show restoration of excitability in the sciatic nerve by "Ringer" after loss of excitability due to immersion in Hedonal.

The current first used was with the secondary coil standing at 35 c.m..

Without measuring the height of the curves, the results may be readily understood.

Curve 1. This was a normal one taken with the coil at 35 c.m.. The nerve was then immersed in Hedonal .37% for one minute and then stimulated with the same current as above. No response took place. The current was then increased to 30 c.m. and the nerve was stimulated.

Curve 2. This curve shows the result. This Hedonal curve is much reduced as compared with the normal curve 1, and yet the current is much stronger. The nerve was then immersed for 2 minutes in "Ringer" and the same current repeated (30 c.m.)

Curve 3. This curve shows great restoration.

SECTION XI.

CONDUCTIVITY OF NERVE AS SEEN IN THE FROG'S SCIATIC.

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Conductivity of Nerve.

The frog's gastrocnemius with the sciatic nerve attached were prepared and placed on the frog-board. The muscle was then attached to the short arm of the lever, the long arm being directed to the smoked drum surface. An induction coil was used to give the electric stimulations, a mercury key being introduced into the circuit.

In five of the tracings the drum remained stationary when many stimulations were made. In these five both "make" and "break" shocks were recorded; in the other four exppriments the drum was revolving fast.

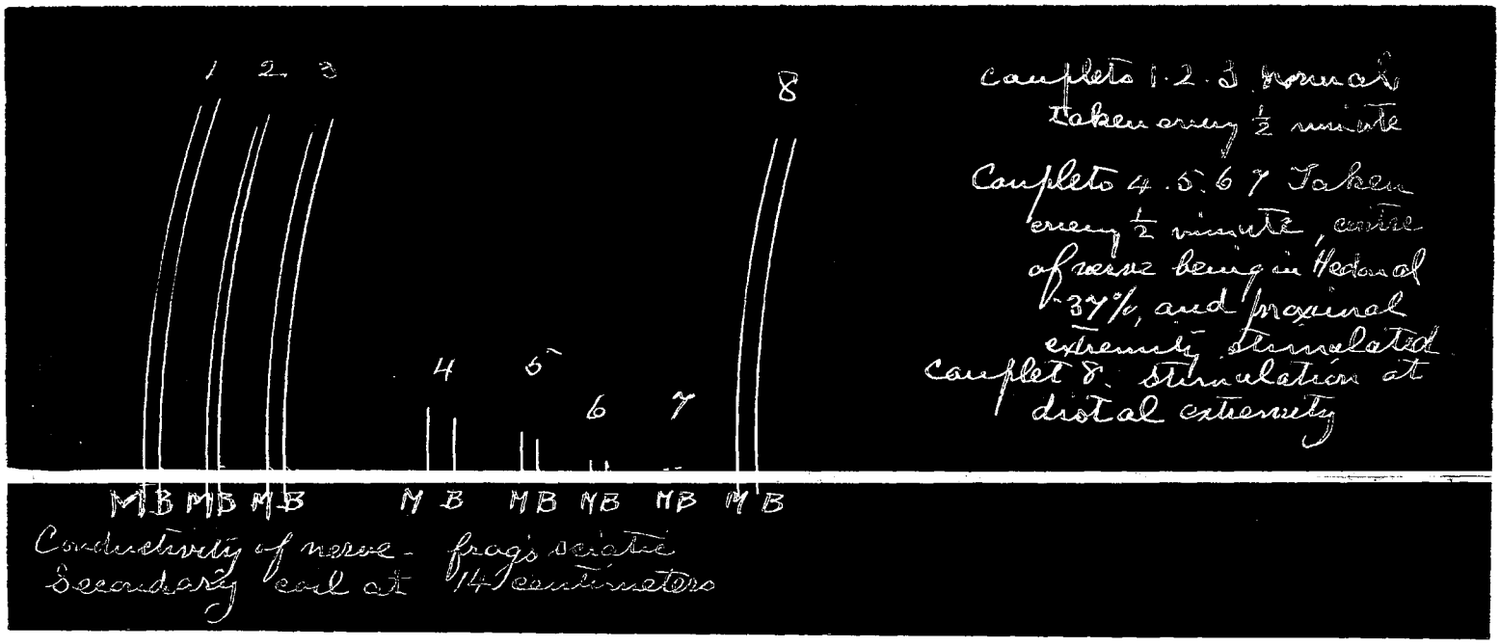
The method adopted:-

The small bi-polar electrode was placed under the sciatic nerve, as near its spinal attachment as possible. The nerve was then stimulated electrically at equal intervals ($\frac{1}{2}$ to 1 minute) with a measured current which was used all through the experiment. In this way several normal curves were traced to show, apart from further treatment of the nerve, what natural change might be expected in its response.

The central portion of the nerve was then allowed to fall into a small bath made of paraffin wax and containing Hedonal solution which in some cases was .37% and in others .75% in normal saline. In some of the experiments the nerve was allowed to remain immersed for 30 seconds and in others 60 seconds. After each immersion in Hedonal the nerve was stimulated electrically as a rule until no response was obtained. The electrode was then placed beneath the distal extremity of the nerve and stimulation again carried out.

The experiments all show diminished conductivity and finally no conductivity at all of the nerve impulse with the current used when the central portion was treated with Hedonal.

FIGURE I.



Natural Size.

In the present series of experiments, the method chosen for stimulation of the Nerve under different conditions, is shown diagrammatically below:-

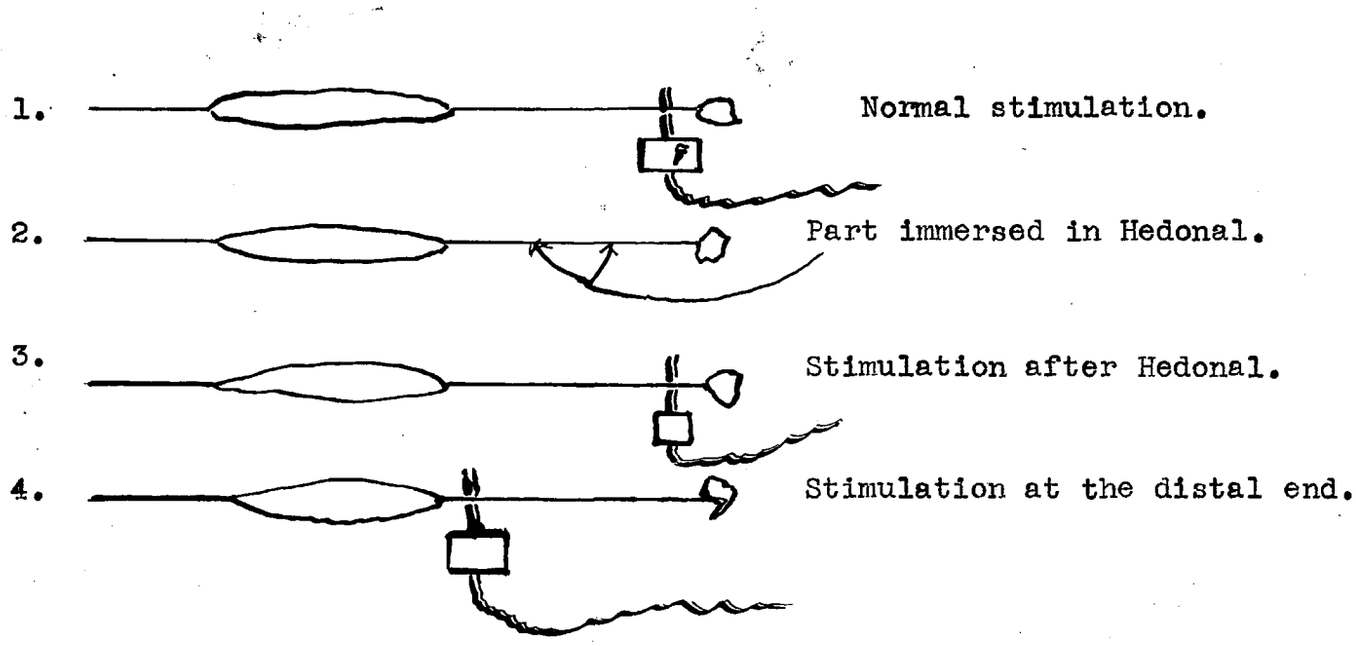
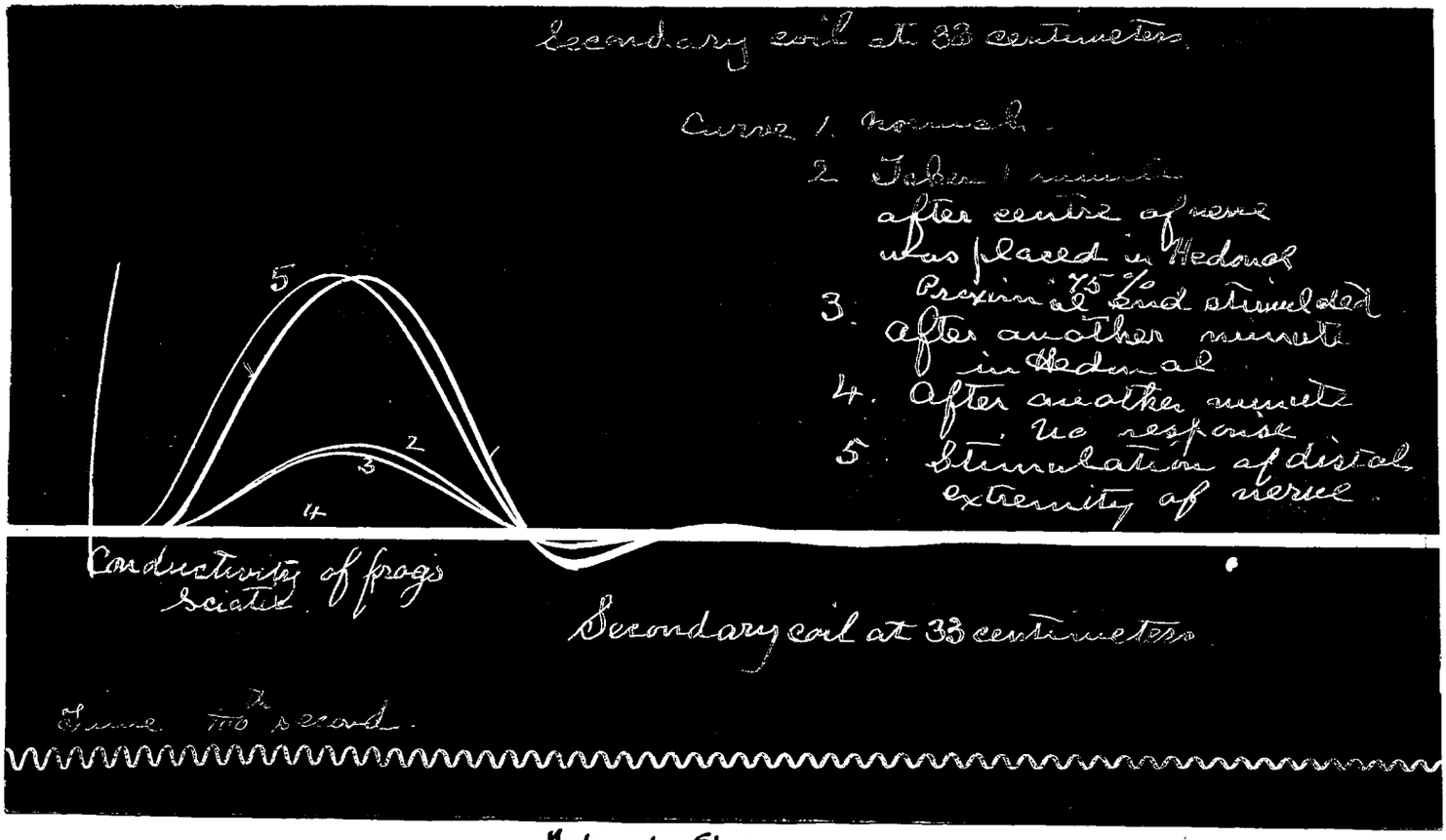


FIGURE 1.

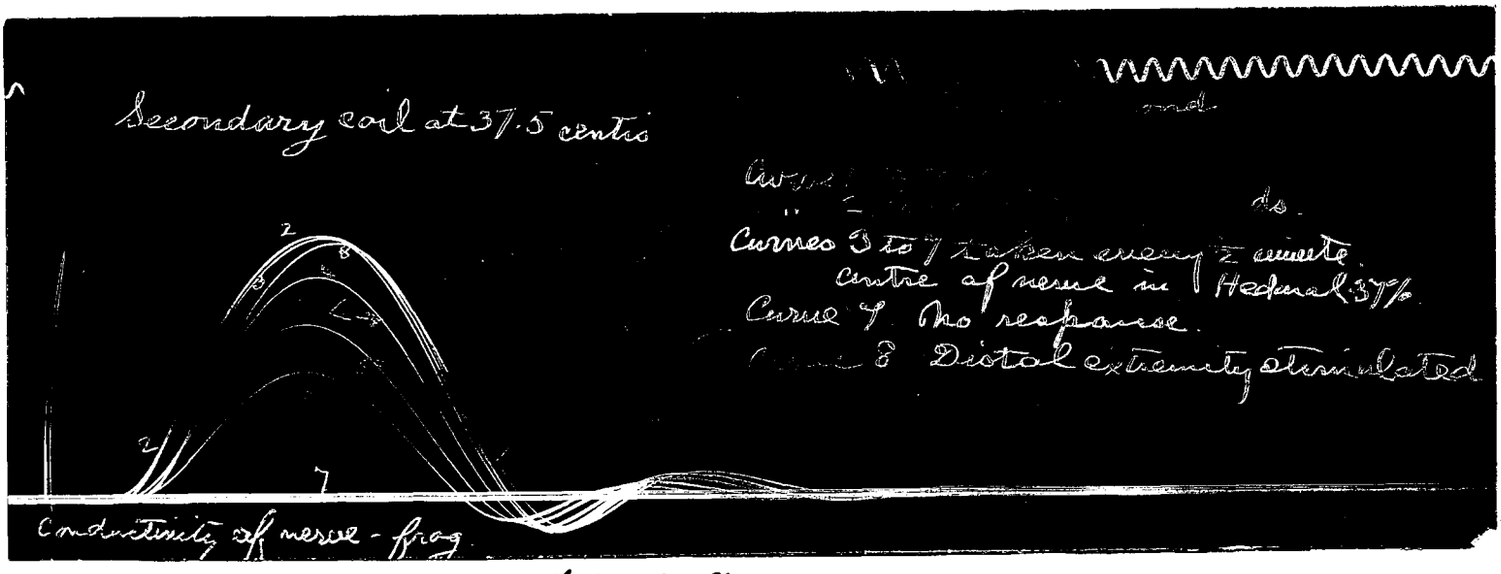
In Figure I the drum was stationary. Both "make" and "break" contractions were recorded. This experiment shows a very striking result. There are three normal couplets; the last one for comparison measuring 48 m.m. and 50 m.m. for the "make" and "break" shocks respectively. Then 4 Hedonal couplets are seen. The first of these (4) measures only 9 m.m. and 7 m.m., so that after the centre of the nerve had been immersed in Hedonal .37% for 30 seconds, the "make" and "break" contractions lost respectively 81% and 86%. The fourth Hedonal dose (7) is followed by no response to the electric current used. The nerve was then stimulated at the distal extremity and there was traced a normal couplet (8) 46 m.m. high.

FIGURE II.



Natural Size.

FIGURE III.



Natural Size.

FIGURE II.

In Figure II the electric stimulations were applied every minute. A maximal "break" shock was obtained with the secondary coil at 33 c.m. and the drum was revolving fast.

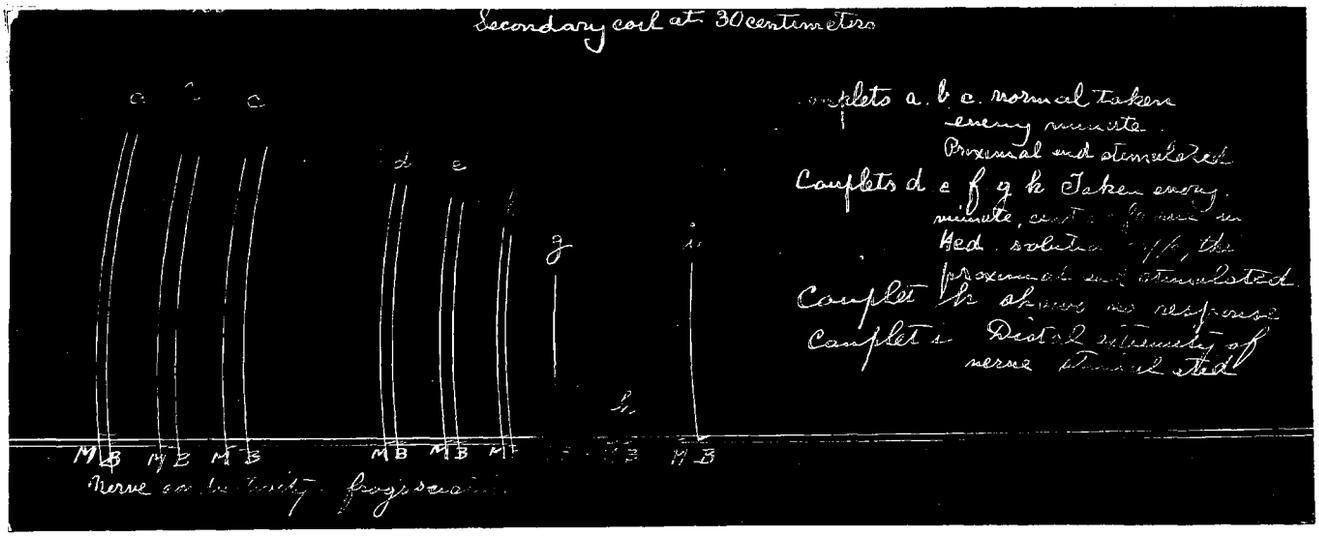
The first dose of Hedonal produced marked loss in conductivity (Curve 2). The third dose (4) stopped all response. Curve 5 was traced when stimulating at the distal extremity of the nerve. Here again there is a normal curve rising exactly to the height of Curve 1, which was taken at the proximal extremity before treatment. It is also interesting to notice that the latency period in Curve 5 was, as we should expect, less than Curve 1.

FIGURE III.

In Figure III the normal curves 1 and 2 are of the same height. The first Hedonal curve (3) has fallen only 1 m.m.. Each Hedonal curve then shows marked diminution in the conductivity until Curve 7 which shows no response. Stimulation at the distal extremity of the nerve then shows a high curve (8).

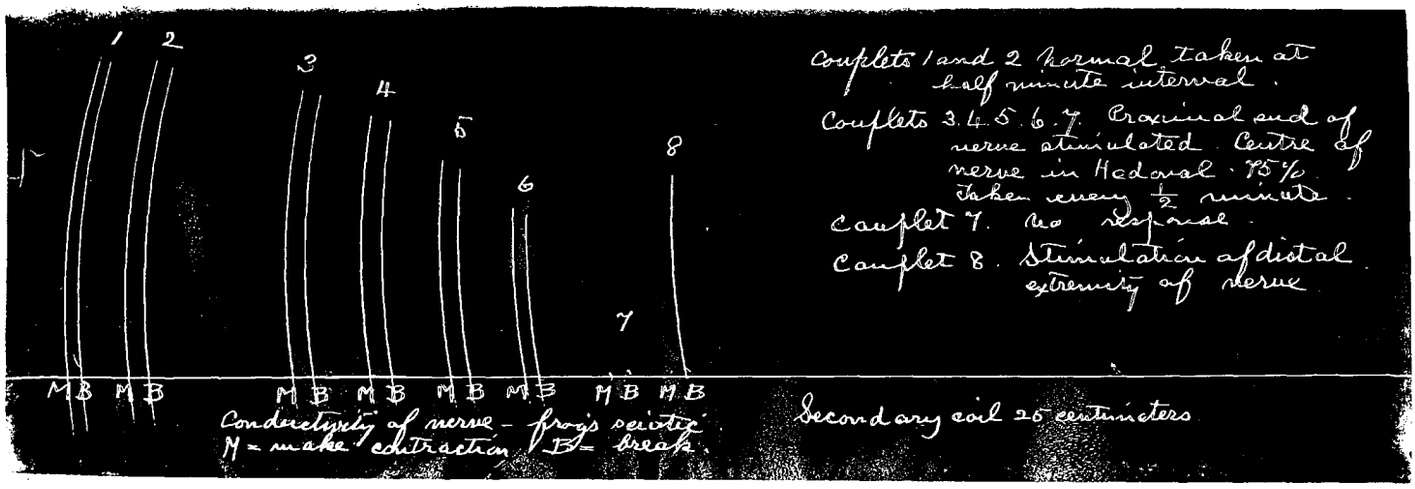
In this experiment the maximal "break" shock was obtained at 37.5 c.m.. A revolving drum was employed.

FIGURE IV.



Scale 2/3rds Natural Size.

FIGURE V.



Scale 2/3rds Natural Size.

FIGURE IV.

The drum was stationary in this experiment, so that both "make" and "break" shocks were recorded. Three normal couplets are shown. In the last one (c) the "make" measured 58 m.m. and the "break" 60 m.m.. The first three Hedonal couplets are each diminished in height a few millimeters. In the fourth Hedonal couplet (g) the "make" had not shown any contraction. At (h) no response was seen to electric stimulation. The stimulation at the distal extremity showed only the "break" shock; but it was greatly restored.

FIGURE V.

In Figure V the couplets have been traced every half minute, the Hedonal solution being .75%. The drum was stationary.

In looking at the tracing the general effect is seen at a glance. The treatment of the centre of the nerve with Hedonal has caused the curves 3, 4, 5, 6, to be regularly and definitely cut down. No response has been obtained for couplet 7. The effect of the drug has been similar in both the "make" and "break" curves.

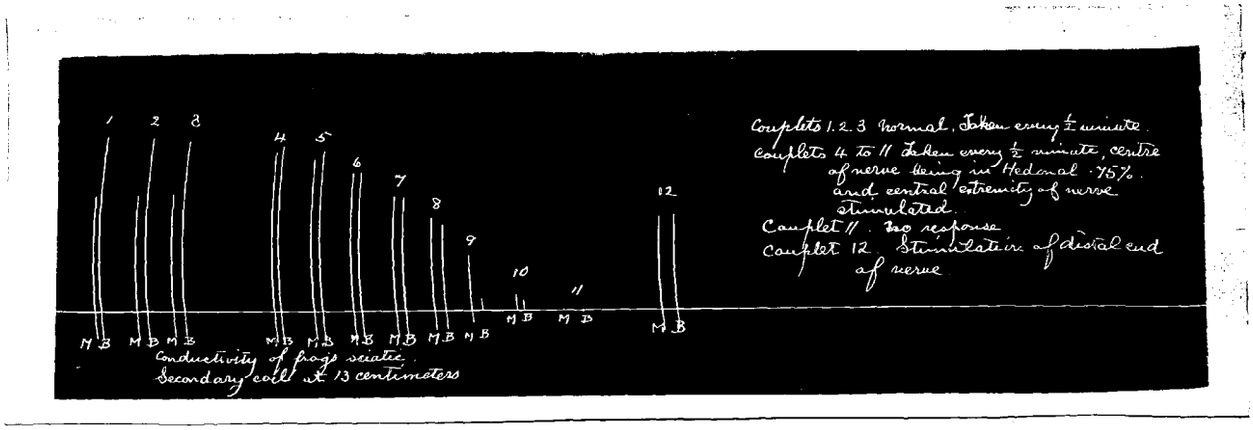
When the distal extremity was stimulated, the "break" curve which is shown was quite normal, but the "make" is absent. This part of the nerve has not, of course, been under the influence of Hedonal.

The actual measurements are seen below.

	Couplet.	"Make"	"Break"	Loss in height of curve.	
				"make"	"break"
Normal	1	67 m.m.	66 m.m.		
"	2	67 m.m.	66 m.m.		
Hedonal	3	59 m.m.	58 m.m.	8	8
"	4	54 m.m.	53 m.m.	5	5
"	5	45 m.m.	43 m.m.	9	10
"	6	35 m.m.	34 m.m.	10	9
"	7	0	0	35	34

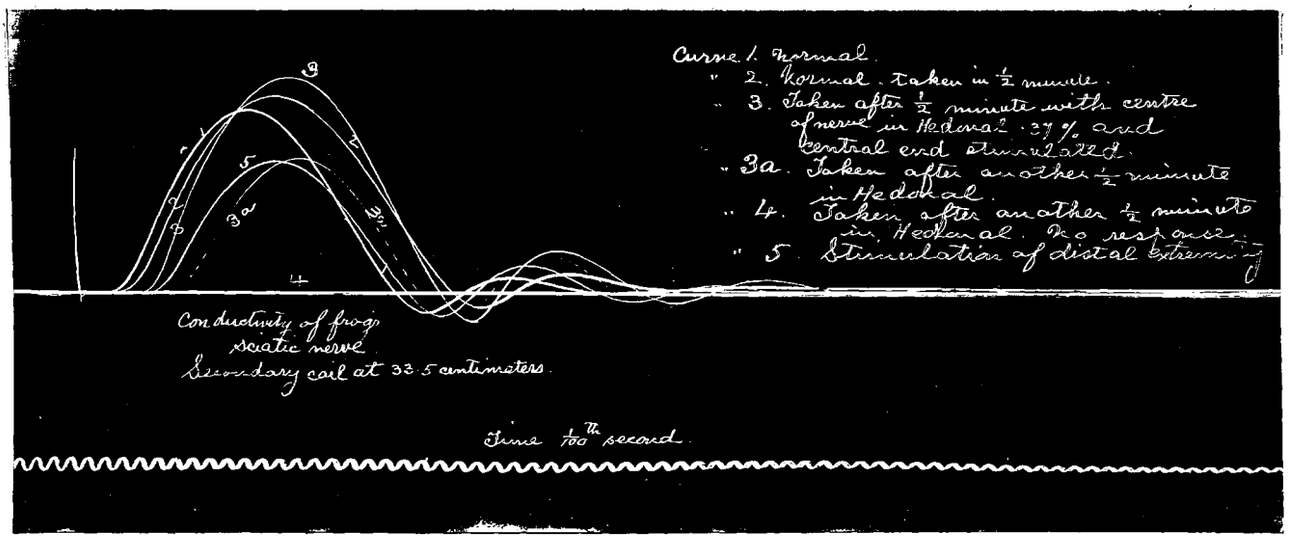
Couplet 8 represents stimulation at the distal extremity of the nerve, and taken after Couplet 7. It shows response for the "break" shock, which is probably quite normal, this part of the nerve not having been treated by Hedonal.

FIGURE VI.



Half Natural Size.

FIGURE VII.



Scale:- 2/3rds Natural Size.

FIGURE VI.

Figure VI is very similar to Figure V, the curve of the "make" contraction in the normal couplets, however, is shorter than the "break". A regular Hedonal effect is seen, until no response is obtained when stimulating at the proximal extremity. The couplet 12 shows normal response at the distal extremity, this part of the nerve being unaffected by the drug.

Note:-

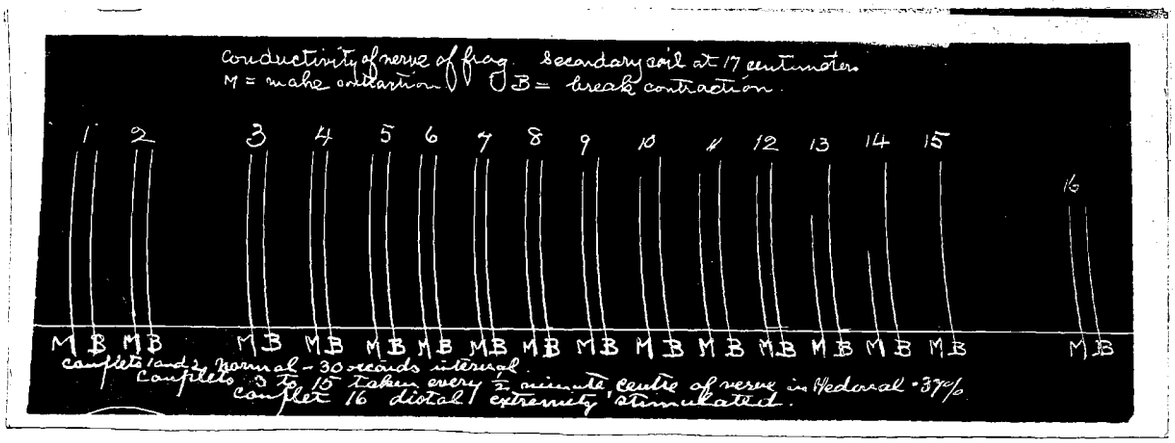
It is seen in Figures 5 and 6 that the curves fall below the abscissa line. These curves have started at the moment of stimulation on the abscissa. What falls below is the recoil, as can also be seen when examining the curves taken with a revolving drum instead of a stationary one, as was the case in Figures 1, IV, V, VI and VIII.

FIGURE VII.

In Figure VII, a revolving drum has been used. The curves have been traced every half minute, the Hedonal solution being .37%.. The maximal "break" shock was obtained with the secondary coil at 33.5 c.m..

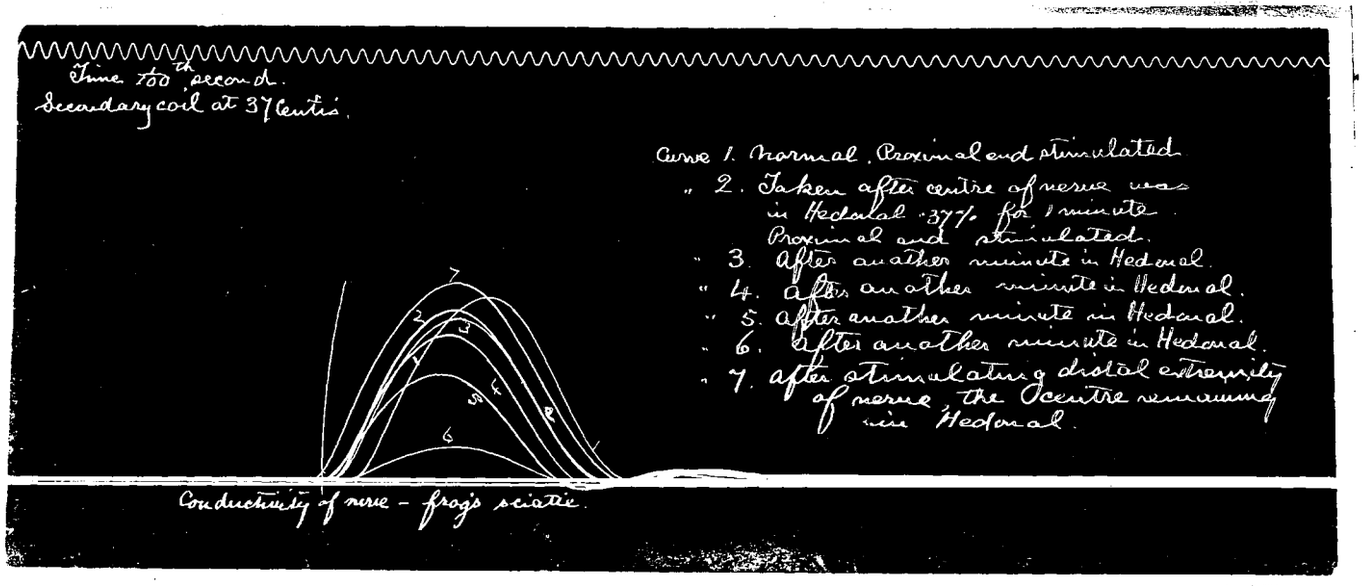
It may be noticed that the first curve (3) taken after treatment by Hedonal and stimulation being at the proximal extremity, has actually exceeded the height of the normal curves which were taken before Hedonal was used at all.. This result has occasionally been seen as a first effect after Hedonal, more especially if the Hedonal immersion was very short - ½ a minute, as in this case. All the later curves regularly show the Hedonal effect by reduction in height, more than normal curves would show in the same time, and this equally applies to all the experiments. Curve 3a then shows a considerable fall and no response is obtained for Curve 4. Stimulation at the distal extremity showed a normal response.

FIGURE VIII.



Scale 2/3rds Natural Size.

FIGURE IX.



Scale 2/3rds Natural Size.

FIGURE VIII.

In Figure VIII the drum was stationary, "make" and "break" curves being shown.

This tracing is produced, as it shows this particular sciatic nerve to have strongly resisted the action of Hedonal, contrary to the usual experience. The conductivity of the nerve has been certainly affected, however, in that the "make" curve has disappeared entirely and has made its appearance again when the distal (untreated) extremity was stimulated. The Hedonal solution chosen was the weaker one, and the intervals were short.

FIGURE IX.

In Figure IX the Hedonal solution was .37% and the stimulations were made at intervals of one minute. A maximal "break" shock was obtained with the coil at 37 c.m.

Curve 1. Normal. Height 37 m.m.
Curve 2. Hedonal. Height 34 m.m.
Curve 3. Hedonal. Height 32 m.m.
Curve 4. Hedonal. Height 29 m.m.
Curve 5. Hedonal. Height 21 m.m.
Curve 6. Hedonal. Height 6 m.m.
Curve 7. Taken after stimulation at the distal extremity. Height 40 m.m.

In this experiment, conduction of the nerve impulse has become more impossible, due to Hedonal. The effect has not been pushed until no response was obtained, to prevent mingling of curves.

The distal extremity when stimulated (curve 7) has responded even more strongly than the normal curve taken at the proximal extremity of the nerve.

The latency period is also much less in Curve 7 (distal) than in Curve 1 (normal), the distance for the nerve impulse to travel being less.

SECTION XII.

EFFECT ON THE RATE OF NERVE IMPULSE AS SEEN IN THE FROG'S SCIATIC.

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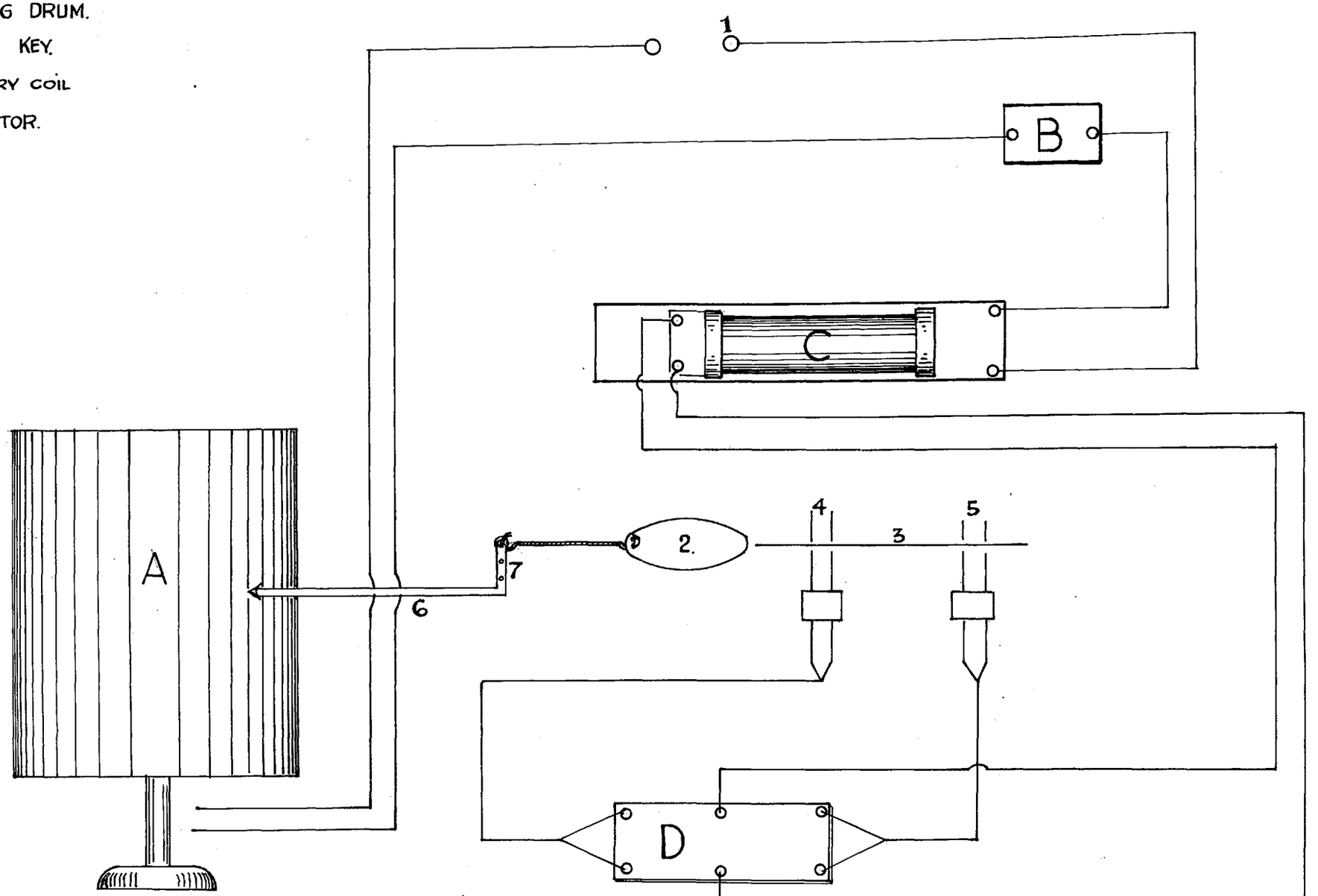
A. REVOLVING DRUM.
B. MERCURY KEY.
C. SECONDARY COIL
D. COMMUTATOR.



1 POWER.
2 MUSCLE.
3 NERVE.
4, 5 } ELECTRODES.
6 LONG ARM OF MYOGRAPH LEVER
7 SHORT Dº Dº Dº

ELECTRICAL APPARATUS FOR TESTING RATE OF NERVE IMPULSE.

The method employed in the following seven experiments, is the old one of Von Helmholtz. The normal rate was first taken, and then the nerve was immersed in Hedonal solution .37% in normal Saline and the test made again immediately, the rate being calculated as detailed below.

In the following experiment it may be noted that the rate of the nerve impulse after treatment of the nerve by Hedonal has been calculated after only one dose. As may be seen in other sections on this subject, the initial dose of Hedonal has sometimes produced a curve higher than the normal one, although usually a lower curve; so that in the present case if the calculation had been made after longer or subsequent periods of immersion, the effect would have been greater in the same direction.

The method in detail:-

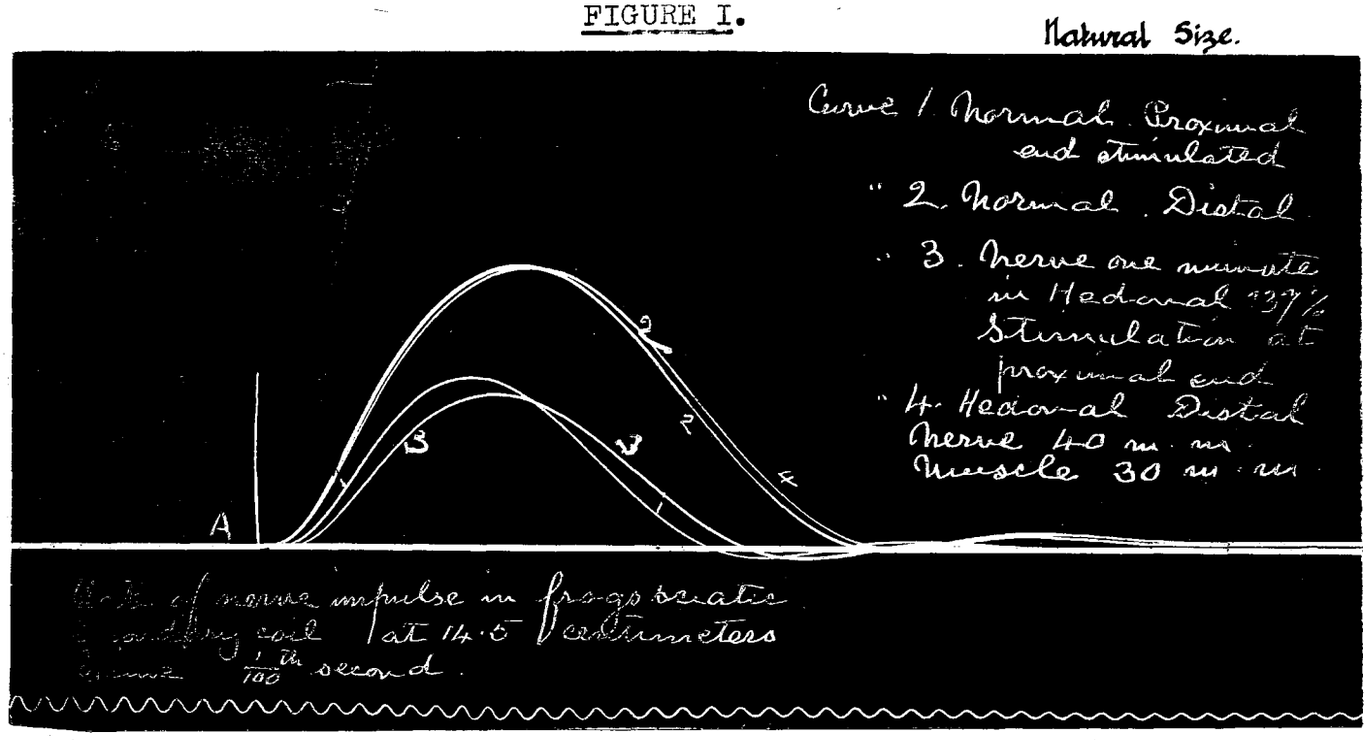
The frog's gastrocnemius with the sciatic nerve attached, was prepared and placed on the frog board. The muscle tendon was then attached to the short arm of the myograph lever. The long arm had a stylet at its extremity which reached the fast-revolving drum. A Du Bois-Reymond inductorium was used for the current, and a mercury commutator was introduced into the secondary circuit. No weight was suspended on the long arm of the lever. By testing with the electric current a single maximal "break" shock was obtained, and the position of the secondary coil was then retained throughout the experiment.

An electrode was placed under each end of the nerve so that by means of the commutator either end could be stimulated without changing the position of the electrode. One end of the nerve was electrically stimulated, a curve obtained and the moment of stimulation marked. Then the other end was stimulated. The distance between the starting points of both curves on the abscissa line was measured in millimeters.

The/

The calculation was then made for the normal rate of nerve impulse as it was found in this nerve. A diagram of the electric arrangement is here shown page 76.

FIGURE I.



In Figure 1 the length of the nerve was 40 m.m. The time record showed notches each measuring 4 m.m. and representing 1/100th of a second. The secondary coil stood at 13.5 m.m.

Calculation of the normal rate:-

Distance from moment of stimulation to start of curve 1 (proximal end)	5 m.m.	Difference 2.5 m.m.
Distance from moment of stimulation to start of curve 2 (distal end)	2.5 m.m.	

The measurement 2.5 m.m. represents the time occupied in transmission of the nerve impulse. The further estimation is shown below by the equational method.

$$\frac{x \text{ m.m.}}{40 \text{ m.m.}} \Big| \frac{2.5 \text{ m.m.}}{1 \text{ sec.}} \quad \frac{1/100\text{th sec.}}{4 \text{ m.m.}} = 6400 \text{ m.m. per second or } 6.400 \text{ meters.}$$

Calculation of the rate after treatment by Hedonal:-

Distance from moment of stimulation to the start of Curve 3 (proximal end) 7 m.m.

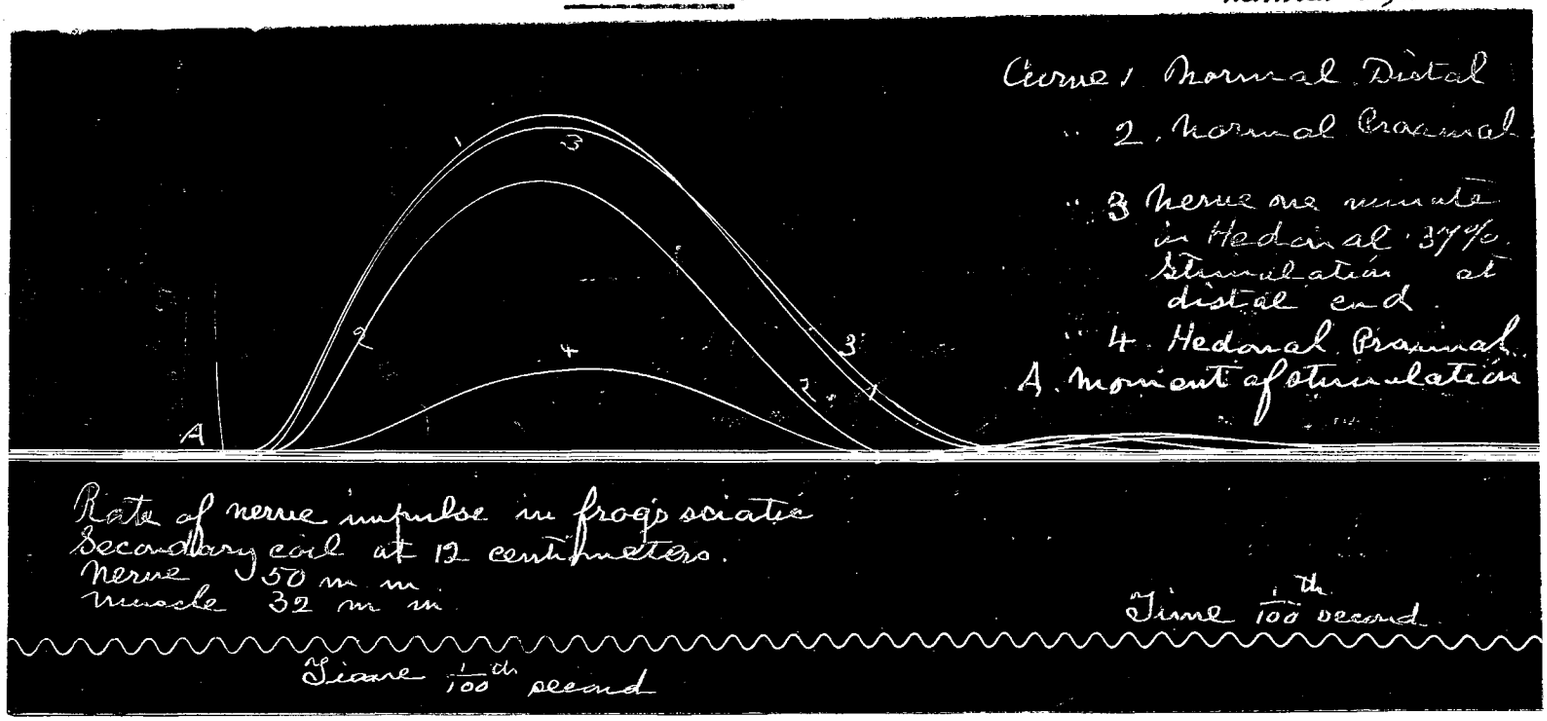
Distance from moment of stimulation to the start of curve 4 (distal end) 3.5 m.m.

Difference 3.5 m.m.

$$\frac{x \text{ m.m.} \mid 3.5 \text{ m.m.} \quad 1/100\text{th second}}{40 \text{ m.m.} \mid 1 \text{ sec.} \quad 4 \text{ m.m.}} = 4571 \text{ m.m. per second or } 4.571 \text{ meters per second.}$$

There has been a difference of the loss in rate of 28%.

FIGURE II. Natural Size.



The nerve was 50 m.m. long in Figure II. The time line showed notches measuring 5 m.m. and representing 1/100th of a second.

To calculate the normal rate of nerve impulse:-

The latency period for curve 1 (distal) = 4 m.m.
for curve 2 (proximal) = 8 m.m. Difference 4 m.m

Therefore we have

$$\frac{x \text{ m.m.} \mid 4 \text{ m.m.} \quad 1/100\text{th second}}{50 \text{ m.m.} \mid 1 \text{ sec.} \quad 5 \text{ m.m.}} = 6250 \text{ m.m. per second or } 6.250 \text{ meters.}$$

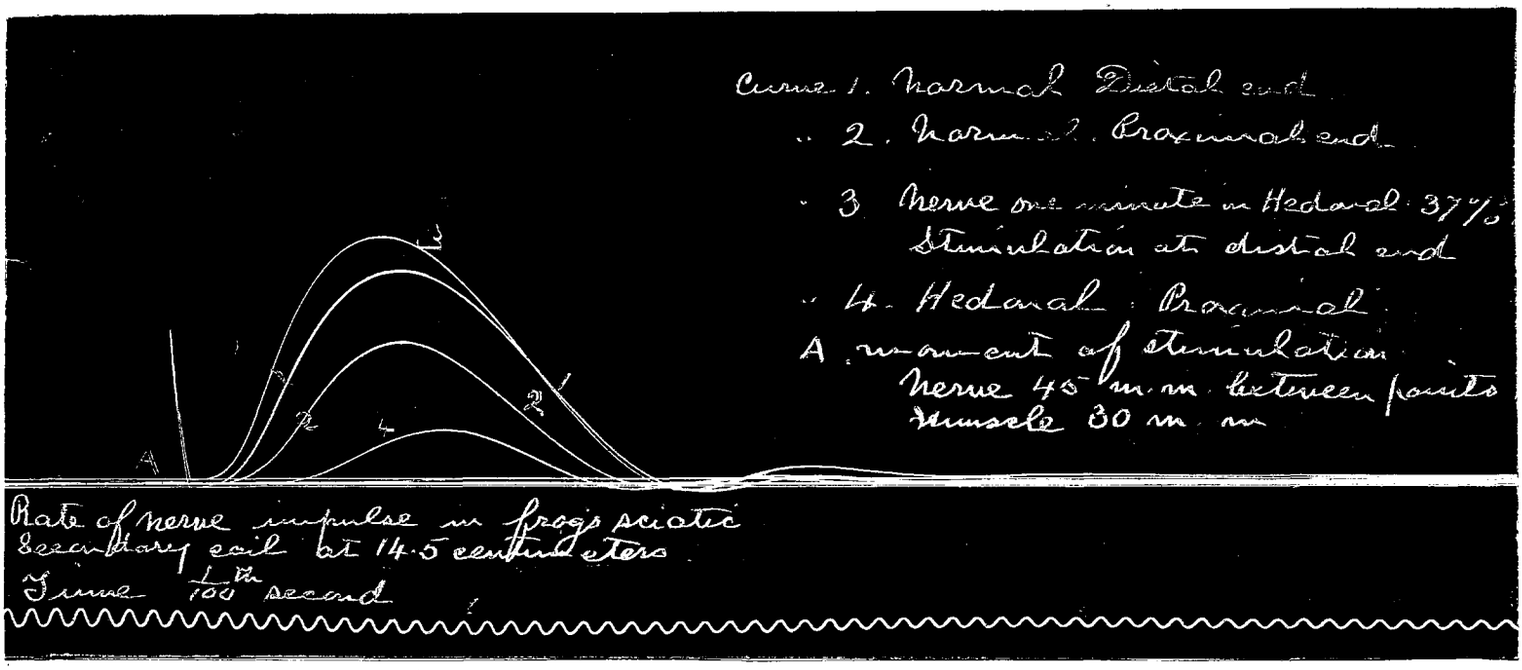
To calculate the rate after Hedonal was applied.

Latency Period of curve 3 (distal) = 7 m.m.

" " " curve 4 (proximal) = 12 m.m. Difference 5 m.m.

5 m.m. = rate of nerve impulse; but each time wave measuring 5 m.m. is equal to 1/100th of a second, therefore 50 m.m. (the length of the nerve) have been travelled in 1/100th of a second, or 5000 m.m. per second. (5 meters). The difference of the loss in rate is 20%.

FIGURE III.



Natural Size.

In Figure III, the time line is in waves measuring 4 m.m., each of which represents 1/100th of a second. The nerve between the points of stimulation was 45 m.m. long.

Curves 1 and 2 are the normal curves traced when the nerve was stimulated at the distal and proximal extremities respectively.

The latency period for curve 1 = 3 m.m.

" " " curve 2 = 5 m.m.

The difference in the periods = 2 m.m.

The rate is calculated below.

$$\frac{x \text{ m.m.}}{45 \text{ m.m.}} \Big| \frac{2 \text{ m.m.}}{1 \text{ sec.}} \quad \frac{1/100\text{th sec.}}{4 \text{ m.m.}} = 9000 \text{ m.m. per second or 9 meters.}$$

After the nerve was immersed in Hedonal, the rate was calculated.

Latent period of curve 3 = 7 m.m.

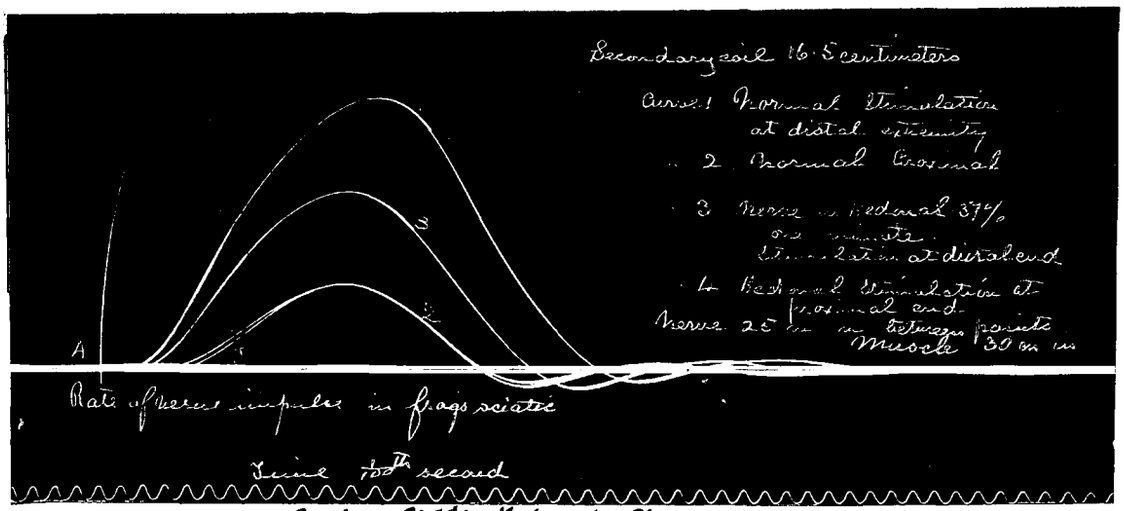
" " " 4 = 17 m.m.

The difference in the periods = 10 m.m.

$$\frac{x \text{ m.m.}}{45 \text{ m.m.}} \mid \frac{10 \text{ m.m.}}{1 \text{ sec.}} \quad \frac{1/100\text{th second}}{4 \text{ m.m.}}$$ = 1800 m.m. per second or 1.8 meters.

There has been a loss in the rate of nerve impulse equal to 80%., due to the nerve being immersed in Hedonal .37% for one minute.

FIGURE IV.



In Figure IV each time wave measures 5 m.m. and represents 1/100th of a second. The Hedonal solution was .37%. The nerve measured 25 m.m. The difference in the latent period of curves 1 and 2 = 8 m.m.

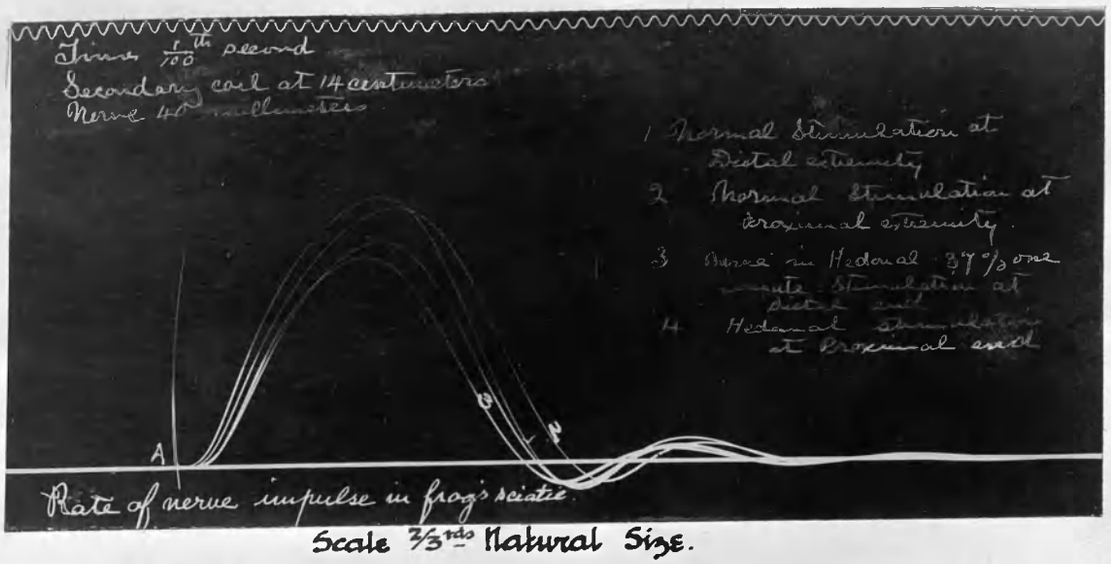
$$\frac{x \text{ m.m.}}{25 \text{ m.m.}} \mid \frac{8 \text{ m.m.}}{1 \text{ sec.}} \quad \frac{1/100\text{th second.}}{5 \text{ m.m.}}$$ = 1562 m.m. per second or 1.562 meters.

After the nerve was immersed in Hedonal solution for 1 minute it was again stimulated. The difference in the latent periods of curves 3 and 4 = 9 m.m.

$$\frac{x \text{ m.m.}}{25 \text{ m.m.}} \mid \frac{9 \text{ m.m.}}{1 \text{ sec.}} \quad \frac{1/100\text{th second.}}{5 \text{ m.m.}}$$ = 1388 m.m. per second or 1.388 meters.

There has therefore been a loss in the rate of the nerve impulse equal to 11% due to the nerve being immersed in Hedonal solution .37% for one minute.

FIGURE V.



Scale 2/3rds Natural Size.

In Figure V each time wave measured 4 m.m. and represented 1/100th second. The Hedonal solution was .37%. The nerve measured 40 m.m.

The difference in the latent period of the normal curves 1 and 2 is equal to 1 m.m. To calculate the normal rate of impulse:-

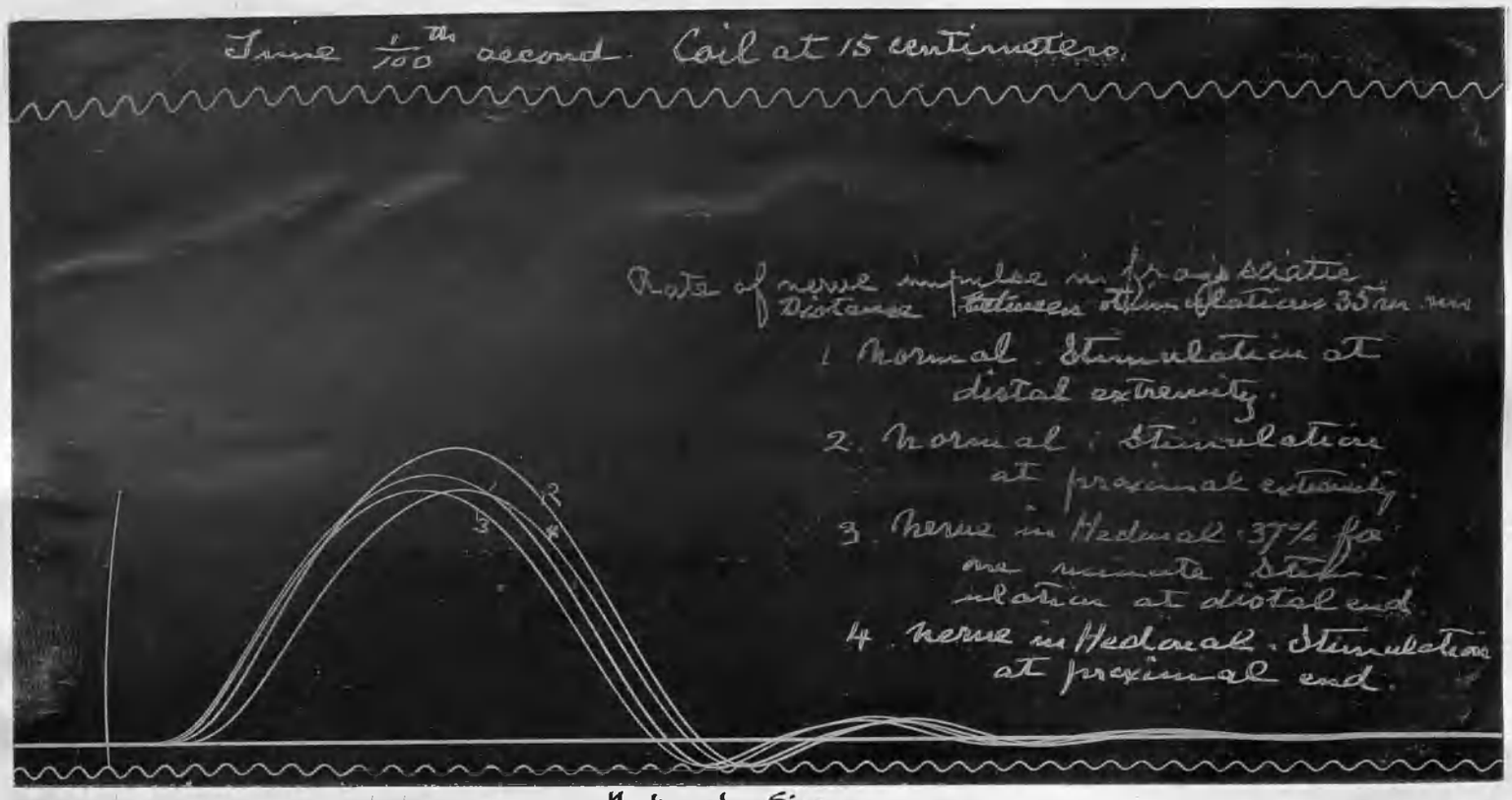
$$\frac{x \text{ m.m.}}{40 \text{ m.m.}} \mid \frac{1 \text{ m.m.}}{1 \text{ sec.}} \quad \frac{1/100\text{th second.}}{4 \text{ m.m.}} = 16{,}000 \text{ m.m. per second or 16 meters per second.}$$

The difference in the latent periods of the two Hedonal curves 3 and 4 is equal to 1.5 m.m.

$$\frac{x \text{ m.m.}}{40 \text{ m.m.}} \mid \frac{1.5 \text{ m.m.}}{1 \text{ sec.}} \quad \frac{1/100\text{th second.}}{4 \text{ m.m.}} = 10{,}666 \text{ m.m. per second or 10.666 meters.}$$

Therefore the nerve has shown a loss of 33% by being immersed in Hedonal .37% for one minute.

FIGURE VI.



Natural Size.

In Figure VI the nerve measured 35 m.m., the Hedonal solution was .37%., and each wave of the time line measured 40 m.m. representing 1/100th second.

To calculate their normal rate:-

The difference in the rates of the normal curves 1 and 2 is equal to 3 m.m.

$$\frac{x \text{ m.m.}}{35 \text{ m.m.}} \Big| \frac{3 \text{ m.m.}}{1 \text{ sec.}} \quad \frac{1/100\text{th second}}{4 \text{ m.m.}} = 4666 \text{ m.m. per second or } 4.666 \text{ meters.}$$

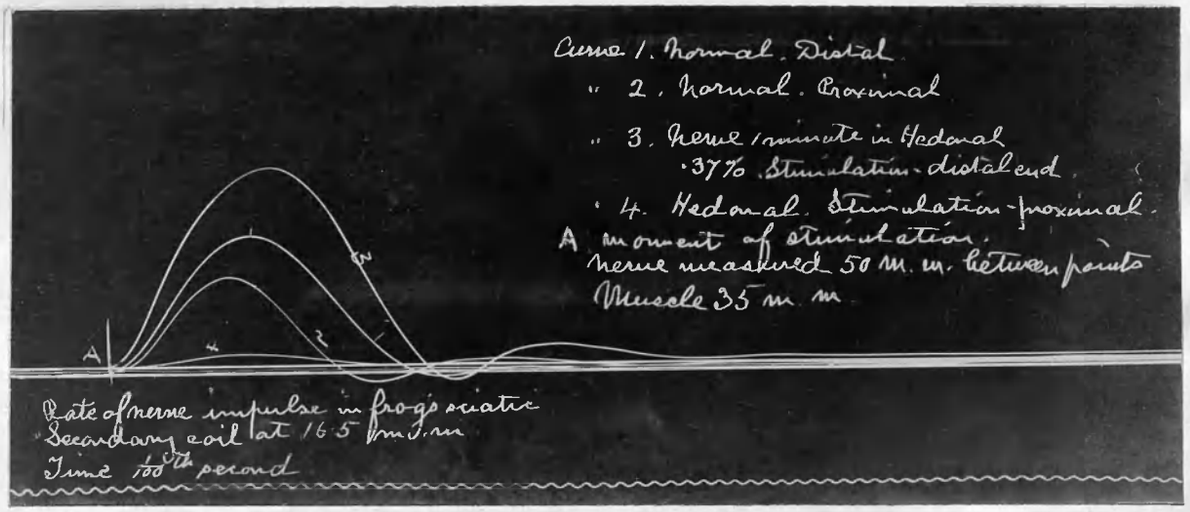
To calculate the rate after Hedonal treatment:-

The difference in the latent periods of the Hedonal curves 3 and 4 equals 4 m.m.

$$\frac{x \text{ m.m.}}{35 \text{ m.m.}} \Big| \frac{4 \text{ m.m.}}{1 \text{ sec.}} \quad \frac{1/100\text{th second}}{4 \text{ m.m.}} = 3500 \text{ m.m. per second or } 3.5. \text{ meters.}$$

The nerve by immersion in Hedonal solution .37% for one minute has lost 24.9% of the rate of nerve impulse.

FIGURE VII.



.68 Natural Size.

In Figure VII the nerve measured 50 m.m., the Hedonal solution was again .37% and the time waves measured 3.5 m.m. each., representing 1/100th second.

To calculate the normal rate of nerve impulse:-

The difference in the latent period of the two normal curves 1 and 2 = 2 m.m.

$$\frac{x \text{ m.m.}}{50 \text{ m.m.}} \;\middle|\; \frac{2 \text{ m.m.}}{1 \text{ sec.}} \quad \frac{1/100\text{th second.}}{3.5 \text{ m.m.}} = 8750 \text{ m.m. per second or } 8.750 \text{ meters.}$$

To calculate the rate after treatment by Hedonal:-

The difference in the latent periods of the Hedonal curves 3 and 4 = 8 m.m.

$$\frac{x \text{ m.m.}}{50 \text{ m.m.}} \;\middle|\; \frac{8 \text{ m.m.}}{1 \text{ sec.}} \quad \frac{1/100\text{th second}}{3.5 \text{ m.m.}} = 2187 \text{ m.m. per second or } 2.187 \text{ meters.}$$

The nerve, after 1 minute in Hedonal .37%, has lost in its rate of nerve impulse 75%.

SECTION XIII.

EFFECT OF HEDONAL ON MUSCULAR CONTRACTILITY AS OBSERVED IN THE FROG'S GASTROCNEMIUS.

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MUSCULAR CONTRACTILITY.

This has been investigated in the gastrocnemius of the frog.

(a) by direct stimulation of the muscle itself by electric current in normal conditions.

(b) by direct stimulation of the muscle after the muscle had been treated by Hedonal.

(c) by indirect stimulation, viz., through the sciatic nerve in the normal state.

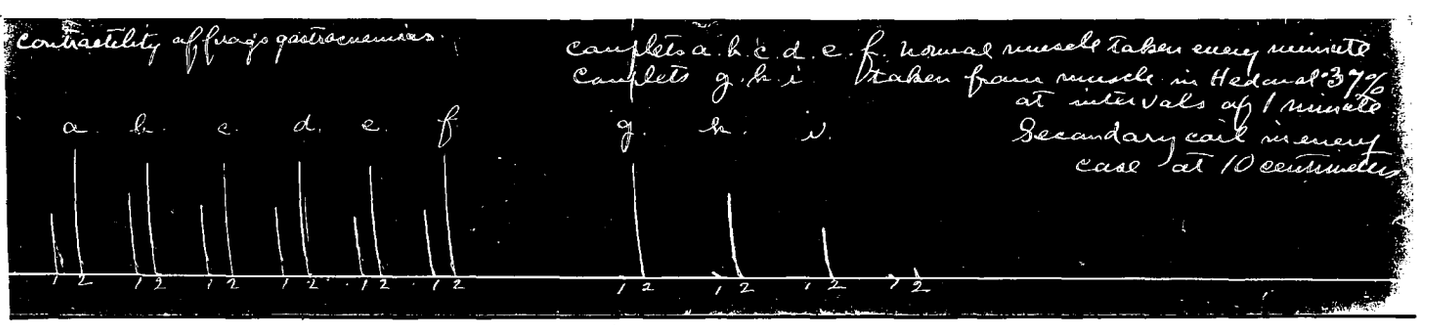
(d) by indirect stimulation of the muscle through the nerve after treating the muscle by Hedonal.

In this way it has been possible to mathematically calculate:-

1. The real contraction of the muscle when electrically stimulated before and after treatment by Hedonal.
2. The percentage of contraction before and after treatment.
3. The work done in gramme-millimeters both before and after treatment of the muscle by Hedonal.
4. The percentage of power lost by the muscle due to the effect of Hedonal.
5. Regarding the muscular contraction, the effect of Hedonal on the duration of the latent period.

Nine experiments are shown.

FIGURE I.



Scale 2/3rds Natural Size

This figure shows in a general way the action of Hedonal on the muscle. The work done by the muscle has not been estimated.

A muscle preparation was placed on the frog board, and connected through a lever with the smoked drum, which in this case was stationary. Both "make" and "break" shocks were applied directly to the muscle itself/

itself, which lay across the electrodes from a Du Bois-Reymond's inductorium.

Six normal couplets were first made at intervals of a minute, to show the normal amount of fatigue which might be expected apart from treatment.

Then four tracings were made after treatment of the muscle for one minute in a bath of Hedonal solution, .37%.

The result was that the "make" contraction was absent from every couplet after the treatment of the muscle by Hedonal. The "break" contraction was in each couplet cut down until the fourth showed no response.

In the normal couplets there was no reduction seen in the height of the curves. The "make" curve was about 13 millimeters and the "break" 26 millimeters high. Of the Hedonal curves, curve g = 24 m.m. (break)

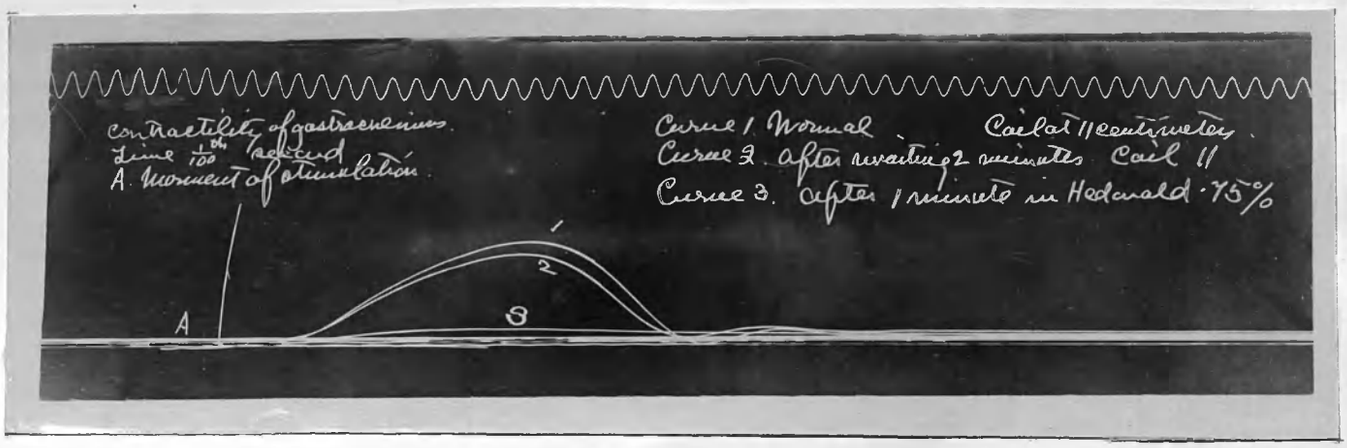
curve h = 18 m.m. ("break")

curve i = 10 m.m. ("break")

The next one showed no response.

Through the whole experiment the secondary coil stood at 10 centimeters. The muscle was 25 millimeters long. The Hedonal therefore had, after four doses, stopped all response to the electric current applied.

FIGURE II.



Scale: 2/3rds Natural Size.

In this experiment there has been calculated respectively:-

(a) The work done by the gastrocnemius estimated in gramme-millimeters.

(b) The work done after treatment by Hedonal.

(c) The actual loss of power of the muscle in gramme-millimeters.

(d) The percentage loss of power.

(e) The effect on the latent period after electric stimulation.

The following are the details of the experiment:-

Length of the muscle 30 m.m.

Length of the long arm of the myograph lever from fulcrum to tip = 170 millimeters.

Length of short arm of lever from fulcrum to power = 10 millimeters.

Distance from fulcrum to weight suspended = 20 millimeters.

Weight suspended = 5 grammes.

Current applied with the secondary coil standing at 11 centimeters.

The muscle specimen was mounted as before and a revolving drum was used, the current being applied from a Du Bois-Reymond's inductorium.

Two normal curves and one Hedonal curve were traced.

Curve 1. Normal. Vertical height 21 m.m.
Latent period was 3¼/100ths of a second,
or .032 second.

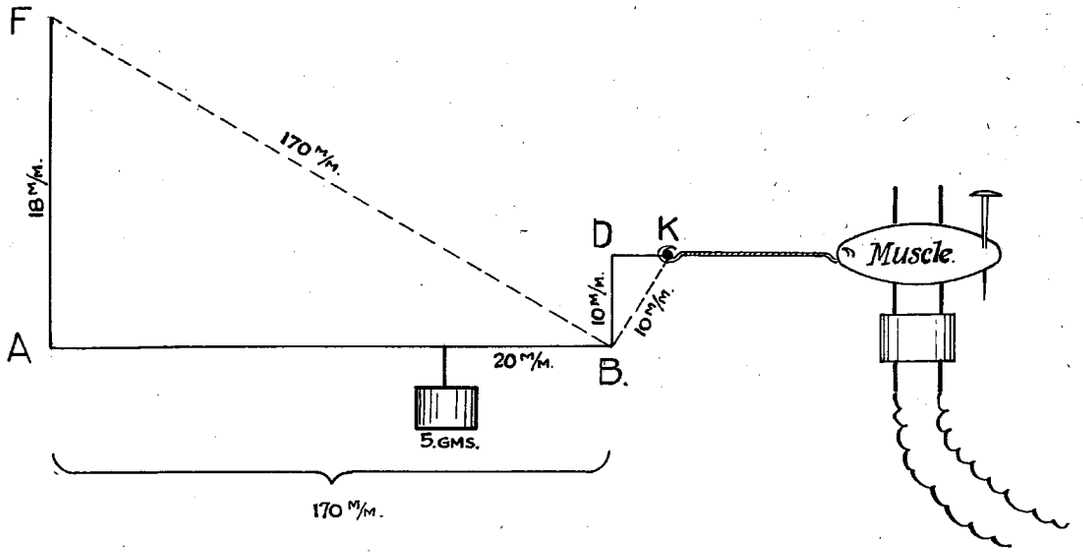
Curve 2. Normal, taken after waiting 2 minutes.
Height 18 m.m. - a fall of 3 m.m.
Latent period 3¼/100ths of a second, or
.032 second as before.

Curve 3. Hedonal curve. This was taken after the muscle had been placed for 1 minute in a small bath made of paraffin wax, containing Hedonal solution (.75%), and electrically stimulated as above.
The height was only 3 m.m. The muscle had lost 15 m.m. in the height of the curve as compared with curve 2 = 83%.
Latent period was 5¼/100ths, or .052 of a second.

There has therefore been an increase in the latent period from one dose of Hedonal, of .020 of a second, or 62%.

As curve 2 will be used as the normal one for comparison, it will be necessary first of all to estimate the work done as shown by this curve.

To find the actual shortening of the muscle, a drawing has been shown below which readily explains the method of calculation:-



When the muscle contracts, the myograph lever A. B. D. takes up the new position F. B. K., and F. is the height of the curve traced. This is the magnified contraction; the actual contraction is D.K. Two triangles are seen, B. A. F. and B. D. K. The base F. B. is to the base B. K. as A. F. (apparent contraction) is to D. K. (actual contraction). Stating these facts by the equational method we have

$$\frac{170 \text{ m.m.}}{18 \text{ m.m.}} \Big| \frac{x}{10 \text{ m.m.}} = 1.05 \text{ m.m. actual contraction.}$$

percentage 3.5.

To find the weight really lifted:-

$$\text{Weight really lifted} = \text{weight suspended} \times \frac{\text{Distance of weight to fulcrum}}{\text{Distance of power to fulcrum}}$$

$$= 5 \text{ grammes} \times \frac{20 \text{ m.m.}}{10 \text{ m.m.}} = 10 \text{ grammes.}$$

To find the work done by the muscle:-

Work done = weight really lifted x actual contraction.

= 10 grammes x 1.05 millimeters.

= 10.5 gramme-millimeters.

The muscle, normally and immediately, before further treatment, was able to do 10.5 gramme-millimeters of work, when stimulated by electric current, the secondary coil standing at 11 centimeters.

Estimation of the work done after the muscle was treated with Hedonal for one minute.

Curve 3 is now to be considered.

As before $\frac{170 \text{ m.m.} \times x}{3 \text{ m.m.} \quad 10 \text{ m.m.}}$ = .17 m.m. actual contraction percentage .56.

The weight lifted is as before = 10 grammes.

The work done = 10 grammes x .17 m.m. = 1.7 gramme-millimeters.

Before treatment, the muscle did 10.5 gramme-millimeters.

After 1 minute in Hedonal solution, it did only 1.7 gramme-millimeters.

The percentage of loss of power to do work is equal to 83.

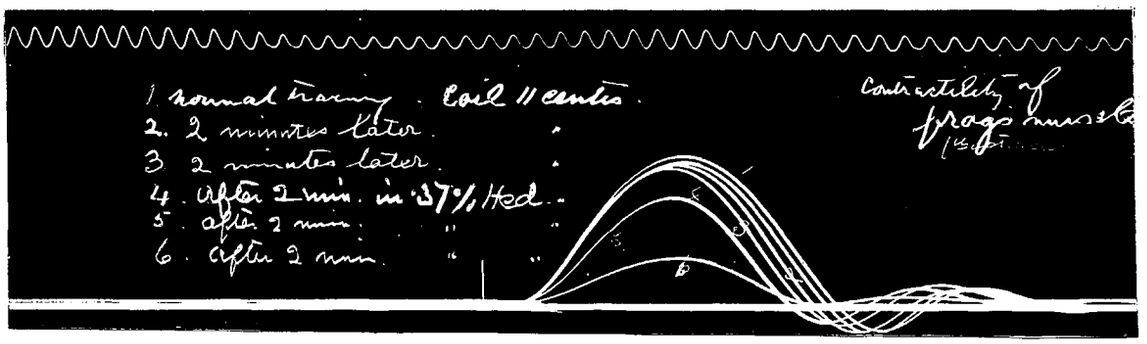
FIGURE III.

A muscle preparation was put in position and connected with the revolving drum by the lever. The muscle was directly stimulated by the electric current. In this experiment, all the details, including length of muscle and current used, were the same as in Figure II. The curves drawn, however, were at 2 minute intervals throughout. The strength of the Hedonal bath was .37 per cent.

The muscle treated showed greater contractility, as will be seen by the height of curve when stimulated. It showed more ability to resist the application of the Hedonal.

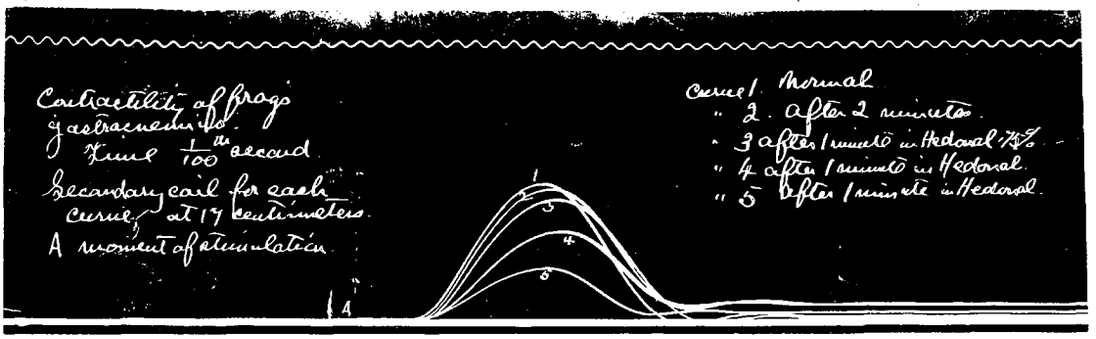
The latent period by the first dose was not so much increased as in Figure II, - practically not affected, although in later doses the increase was seen.

The tracing is seen below.



Scale 2/3rds Natural Size.

FIGURE IV.



Scale:- 2/3rds Natural Size.

In this Figure the conditions were the same as described before regarding the apparatus.

The muscle was 30 milli-meters long. A revolving drum was used. The current applied was from a maximal "break" shock with the secondary coil standing at 17 centi-meters, and was applied directly to the muscle. A solution of Hedonal (.75% in Saline) was employed in which to immerse the muscle.

Five curves were traced. The first two were normal. The calculations have been made with regard to the last four curves.

Curve 1. Normal. Height 28 m.m.

Curve 2. Normal. Height 27 m.m. It has fallen only 1 m.m. and was taken after two minutes.

Curve 3. Hedonal curve, - Taken after one minute in Hedonal (.75%). Height 24 m.m. It has fallen 3 m.m.

Curve 4. Hedonal curve. Taken after 1 minute more in Hedonal solution. Height 18 m.m.

Curve 5. Hedonal curve. Taken after another minute in Hedonal solution. Height 10 m.m.

In this experiment, the work done by the muscle before and after treatment has been calculated, so that the total effect of the three doses of Hedonal has been accurately measured.

Curve 2. To find the actual shortening.

$$\frac{170 \text{ m.m.}}{27 \text{ m.m.}} \mid \frac{x}{10 \text{ m.m.}} = 1.5 \text{ m.m. actual shortening.}$$

Percentage of shortening = 5.

The real weight lifted = 10 grammes.

Work done = 10 grammes x 1.5 millimeters = 15 gramme-millimeters.

Curve 3.

$$\frac{170 \text{ m.m.}}{24 \text{ m.m.}} \mid \frac{x}{10 \text{ m.m.}} = 1.4 \text{ m.m. actual shortening.}$$

Percentage of shortening = 4.6.

Work done = 10 grammes x 1.4 m.m. = 14 gramme-millimeters.

Curve 4.

$$\frac{170 \text{ m.m.}}{18 \text{ m.m.}} \mid \frac{x}{10 \text{ m.m.}} = 1.0 \text{ m.m. actual shortening.}$$

Percentage of shortening = 3.3.

Work done = 10 grammes x 1 m.m. = 10 gramme-millimeters.

Curve 5.

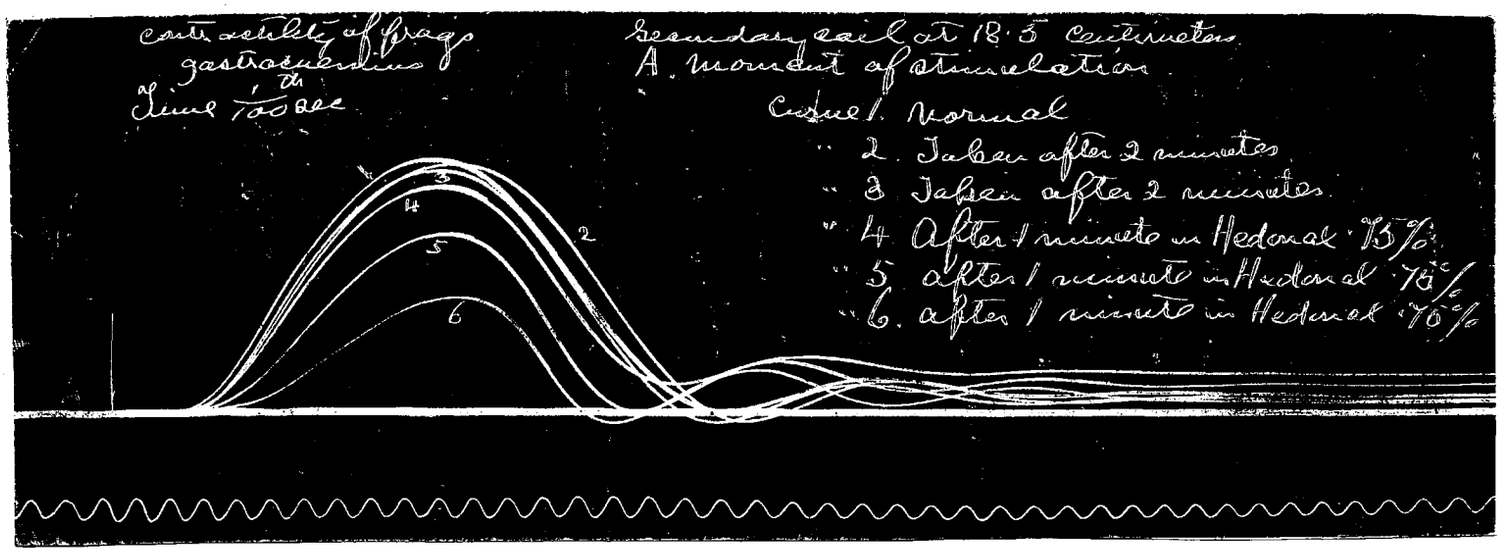
$$\frac{170 \text{m.m.}}{10 \text{ m.m.}} \mid \frac{x}{10 \text{ m.m.}} = .5 \text{ m.m. actual contraction.}$$

Percentage of contraction = 1.6.

Work done = 10 grammes x .5 m.m. = 5 gramme-millimeters.

The muscle has lost working power equal to 66% by immersion in Hedonal (.75%) for 3 minutes.

FIGURE V.



Natural Size

Figure V shows six curves, three being normal and taken at intervals of two minutes, to show what diminution in the height of the curve, would occur naturally. The last three curves have been traced after the muscle had been immersed in a bath of Hedonal (.75%). These have been taken at intervals of one minute. The muscle was 25 millimeters in length. It was stimulated directly by an electric current, with the secondary coil standing at 18.5 c.m.. A revolving drum was used. The other measurements in the apparatus were as before.

In the present case regarding the work done, the comparison has been made between Curve 3 (the last normal one), and Curve 6 (the last Hedonal one).

Curve 1. Normal. Height 35 m.m.
Latent period 2⅕th/100ths of a second or .022 second.

Curve 2. Normal. Height 35 m.m.
Latent period 2⅔rds/100ths of a second, or .026 second.

Curve 3. Normal. Height 33 m.m.
Latent period 2⅔rds/100ths of a second, or .026 second.

Curve 4. Hedonal curve. Height 31 m.m.
Latent period 2⅔rds/100ths of a second, or .026 second.

Curve 5. Hedonal curve. Height 25 m.m.

Latent period 3/100ths of a second, or .03 second.

Curve 6. Hedonal curve. Height 16 m.m.

Latent period 3 rds/100ths of a second, or .036 second.

To calculate the work done in Curve 3.

$$\frac{170 \text{ m.m.}}{33 \text{ m.m.}} \Big| \frac{x}{10 \text{ m.m.}} = 1.9 \text{ m.m. actual contraction.}$$

percentage of contraction = 7.6

Work done = 10 grammes x 1.9 millimeters = 19 gramme-millimeters.

Curve 4.

$$\frac{170 \text{ m.m.}}{31 \text{ m.m.}} \Big| \frac{x}{10 \text{ m.m.}} = 1.8 \text{ m.m. actual contraction.}$$

percentage = 7.2.

Work done = 10 grammes x 1.8 m.m. = 18 gramme-millimeters.

The work done is slightly less than in the normal Curve 3.

Curve 6.

The total loss of power is here estimated after 3 immersions of the muscle in Hedonal, each lasting one minute.

$$\frac{170 \text{ m.m.}}{16 \text{ m.m.}} \Big| \frac{x}{10 \text{ m.m.}} = .9 \text{ m.m. actual contraction.}$$

Work done = 10 grammes x .9 = 9 gramme-millimeters.

Therefore there has been a loss of work done equal to 10 gramme-millimeters, or 52% - the effect of 3 minutes' treatment of the muscle with Hedonal.

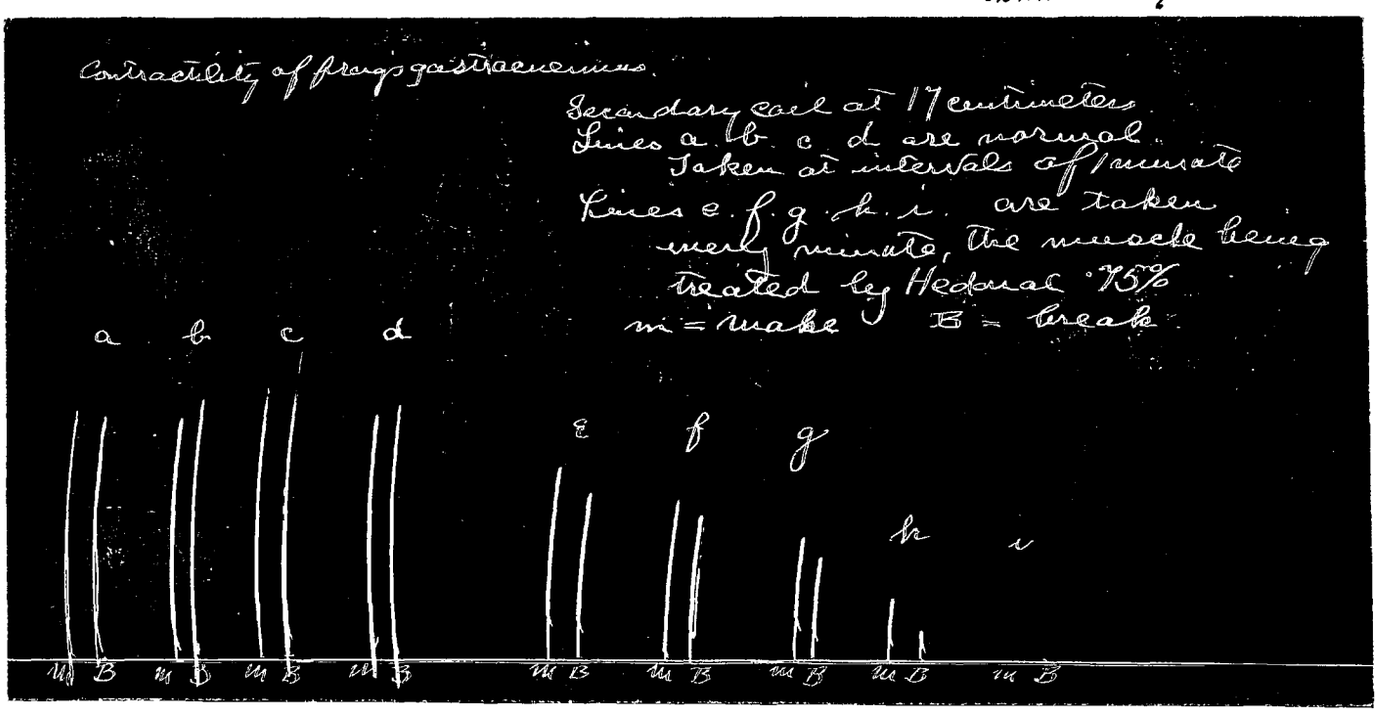
Regarding the latent period, it can be seen in the tracing that the difference between Curve 3 and Curve 4 is inappreciable.

Comparing Curve 3 with Curve 6 there is an increase in the latent period equal to 38% - the result of the immersion of the muscle for 3 minutes in Hedonal (.75%).

The following group of four experiments upon contractility of frog's muscle differ from the foregoing, particularly in one point, viz., the muscle has been electrically stimulated indirectly, i.e., through the sciatic nerve. A muscle-nerve preparation was therefore in each case mounted on the frog board. The electrode was placed under the centre of the sciatic nerve. When Hedonal was applied, the muscle alone was immersed. There was, as in the other experiments, a weight of 5 grammes suspended on the long arm of the myograph lever, 20 m.m. from the fulcrum. The short arm, from fulcrum to power, measured 10 m.m..

FIGURE VI.

Natural Size



In Figure 6 the muscle measured 30 millimeters. The solution of Hedonal was .75% in normal Saline. The current was used with the secondary coil standing at 17 centimeters. The drum was stationary to prevent mingling of curves, as there were both "make" and "break" shocks recorded.

Four normal couplets are seen in the tracing. These were taken at one minute intervals. Five Hedonal couplets were also formed. The muscle was placed for one minute in the Hedonal bath. It was then removed and the sciatic immediately stimulated. This was repeated at intervals of one minute.

The following can be noticed:-

Each immersion in Hedonal diminished the height of the curve, i.e., the contractility of the muscle.

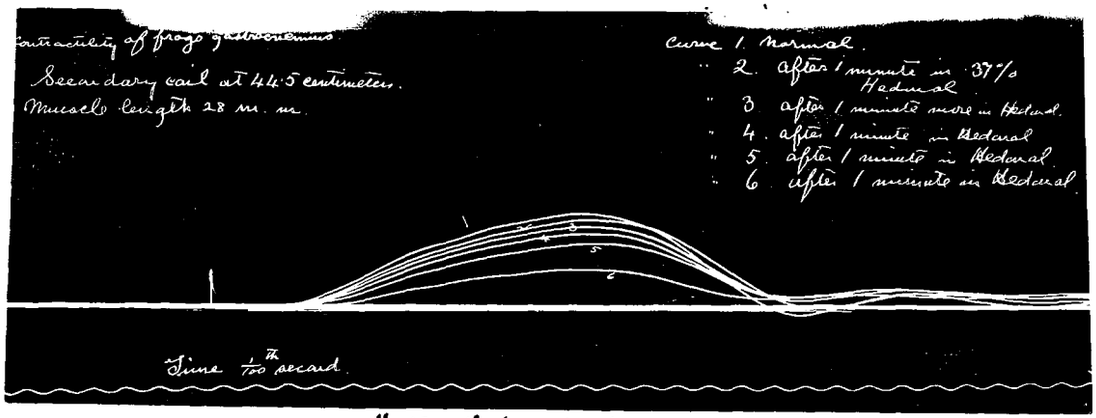
The "make" and "break" in this case were very equally affected.

In the fifth couplet, no response was obtainable with the current used.

TABLE OF MEASUREMENT OF CURVES.

Couplet.	"Make."	"Break."	
a	34 m.m.	33 m.m.	Normal curves.
b	34 "	36 "	
c	36 "	36 "	
d	32 "	33 "	
e	29 "	23 "	Hedonal curves.
f	22 "	20 "	
g	17 "	14 "	
h	10 "	5 "	
i	0 "	0 "	

FIGURE VII.



Half Natural Size.

A muscle-nerve preparation was mounted, the length of the muscle being 28 millimeters. The Hedonal solution employed was .37%. The secondary coil stood at 44.5 centimeters. A fast revolving drum was used, driven by a geared motor. The muscle was indirectly stimulated by electricity through the sciatic nerve.

Six curves were drawn, the first one only being the normal one. The others were taken at intervals of one minute, the muscle each time having been immersed in Hedonal.

Curve 1. Normal. Height 26 m.m.

Latent period 2⅓rd/100ths of a second or .023 second.

Curve 2. Hedonal. Height 24 m.m.

Latent period 3/100ths of a second or .03 second.

Curve 3. Hedonal. Height 32 m.m.

Curves 2, 3, and 4 are indistinguishable for the latent period, as the lines are too close for measurement.

Curve 4. Hedonal. Height 20 m.m.

Curve 5. Hedonal. Height 17 m.m.

Latent period 3⅓rd/100ths of a second, or .033 second.

Curve 6. Hedonal. Height 10 m.m.

Latent period 4/100ths of a second, or .04 second.

By treating the muscle with Hedonal, the latent period has been increased by .017 of a second, or 73%.

To estimate the work done by the muscle:-

Curve 1. (Normal.)

$$\frac{170\text{m.m.}}{26\text{ m.m.}} \Big| \frac{x}{10\text{ m.m.}} = 1.5\text{ m.m. Actual contraction.}$$

Percentage 5.3.

Work done = 10 grammes x 1.5 = 15 gramme-millimeters.

Curve 2. (Hedonal)

$$\frac{170\text{ m.m.}}{24\text{ m.m.}} \Big| \frac{x}{10\text{ m.m.}} = 1.4\text{ m.m. Actual contraction.}$$

Percentage 5.

Work done = 10 grammes x 1.4 m.m. = 14 gramme-millimeters.

The muscle by being immersed in Hedonal (.37%) for one minute has done 6.6 per cent. less work.

Curve 6. (Hedonal.)

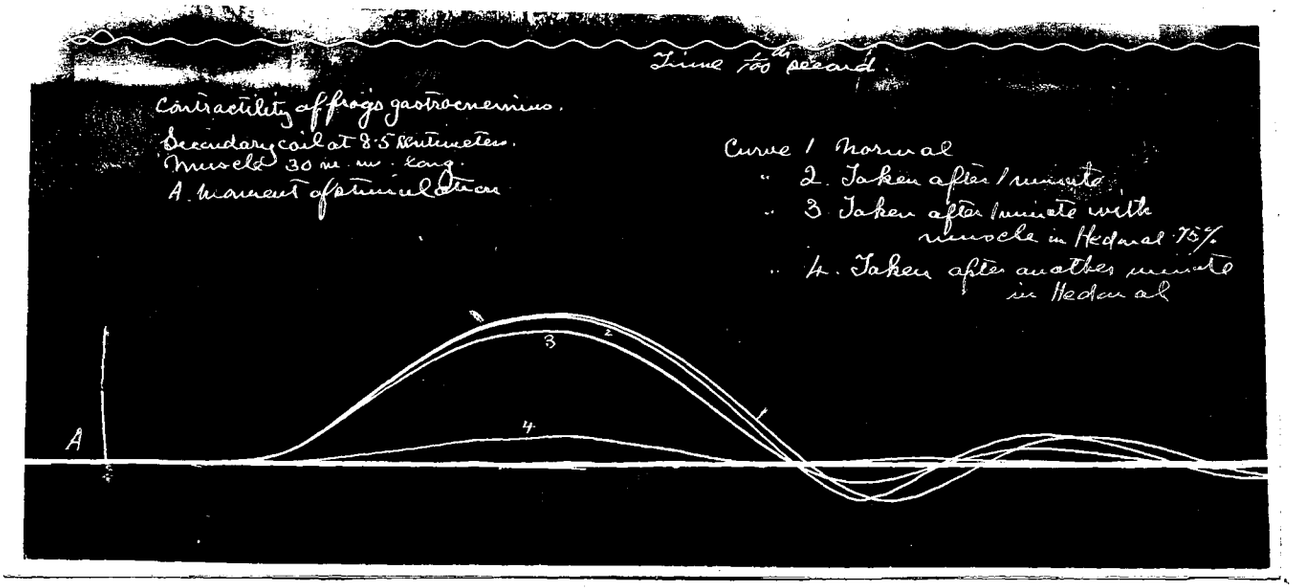
$$\frac{170\text{ m.m.}}{10\text{ m.m.}} \Big| \frac{x}{10\text{ m.m.}} = .5\text{ m.m. Actual contraction.}$$

Percentage 1.7.

Work done = 10 grammes x .5 = 5 gramme-millimeters.

At the end of the experiment the muscle showed a loss of work actually done equal to 66 per cent. as compared with the normal curve No.1.

FIGURE VIII.



Scale :- 2/3rds Natural Size.

A muscle-nerve preparation was made, the muscle measuring 30 m.m. Stimulation by electricity was indirect - through the nerve. The secondary coil stood at 8.5 centimeters. A fast revolving drum was used with McColl's control arrangement for keeping the revolutions constant in speed. The Hedonal used was .75 per cent.

The first two curves were normal ones taken with one minute intervals. Lines 3 and 4 were traced after the muscle had been in Hedonal.

Curve 1. Normal. Height 33 millimeters.
The latent period 3/100ths of a second or .03 second.

Curve 2. Normal. Taken 1 minute later. Height 32 millimeters.
The latent period 3/100ths of a second or .03 second.

Curve 3. Hedonal. Taken after the muscle was immersed in Hedonal for 1 minute. Height 29 millimeters.
The latent period 3/100ths of a second or .03 second.

Curve 4. Hedonal. Taken after the muscle was again immersed for 1 minute in Hedonal. Height 7 millimeters.
The latent period 4½/100ths of a second or .045 second.

The muscle having been immersed for two separate minutes in Hedonal solution, has shown, regarding the muscular contraction, an increase in the latent period of .015 second or 50%.

Estimation of the work done:-

Curve 2.

$$\frac{170 \text{ m.m.}}{32 \text{ m.m.}} \quad | \quad \frac{x}{10 \text{ m.m.}} \qquad = 1.8 \text{ m.m. actual contraction.}$$

Percentage 6.

Work done = 10 grammes x 1.8 m.m. = 18 gramme-millimeters.

Curve 3,

$$\frac{170 \text{ m.m.}}{29 \text{ m.m.}} \quad | \quad \frac{x}{10 \text{ m.m.}} \qquad = 1.7 \text{ m.m. actual contraction.}$$

Percentage 5.6.

Work done = 10 grammes x 1.7 m.m. = 17 gramme-millimeters.

The muscle has lost power equal to 1 gramme-millimeter.

Curve 4.

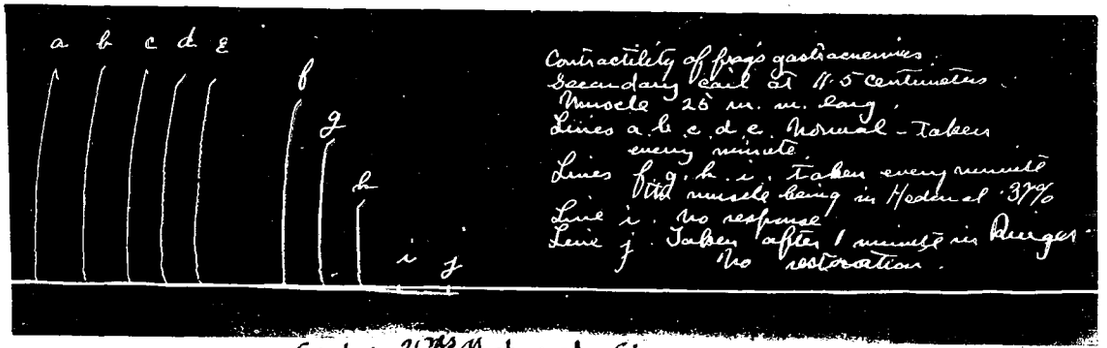
$$\frac{170 \text{ m.m.}}{7 \text{ m.m.}} \quad | \quad \frac{x}{10 \text{ m.m.}} \qquad = .41 \text{ m.m. actual contraction.}$$

Percentage 1.3.

Work done = 10 grammes x .41 = 4.1 gramme-millimeters.

The muscle, after having had two separate minutes in Hedonal solution, has lost contractility, as represented by 13.9 gramme-millimeters, or a loss of work done equal to 77%.

FIGURE IX.



The electrical stimulation of the muscle was indirect, viz., through the sciatic nerve. The current used was with the secondary coil standing at 11.5 centimeters. The Hedonal solution employed was .37%. The lines traced represent maximal "make" shocks. The drum was stationary.

Five normal lines were first traced at intervals of one minute; they altered very little.

Four Hedonal lines were attempted. The last one showed no response (i). Then the muscle was placed in "Ringer" solution for one minute. No restoration was obtained (j).

The height of the contraction is seen below.

Line a.	Height 46 m.m.	Normal lines.
b.	" 46 m.m.	
c.	" 46 m.m.	
d.	" 45.5 m.m.	
e.	" 45 m.m.	
f.	" 40 m.m.	Hedonal.
g.	" 32 m.m.	
h.	" 20 m.m.	
i.	No response.	
j.	No restoration.	Ringer.

BIBLIOGRAPHY.

****

(1) Zur Frage der intravenosen Hedonal narkose. A.T.Sidorenko. Centralblatt fur Chirurgie, 1910. p. 1219, 1220.

(2) Intravenous Hedonal Narcosis. P.Fedoroff. Verhandlungen Gesellschaft fur Chirurgie. 22 April, 1911, Vol.40.

(3) Intravenous Hedonal Narcosis. A.P.Jeremitsch. Deutsch Zeitschrift fur Chirurgie. 1911. Vol.108. p.551

(4) Hedonal Chloroform Narcosis. N.P.Krawkow. Archive fur Experimentelle Pathologie und Pharmakologie, 10 Oct., 1908.

(5) Intravenous Hedonal Anaesthesia, C.M.Page, Lancet, 11th May, 1912. Vol. I. p.1258.

(6) Intravenous Hedonal Narcosis - Technique. M.L.Lytschkowski. Centralblatt fur Chirurgie. 1910. p.1638.

(7) Intravenous Hedonal Anaesthesia, C.M.Page, British Medical Journal, 23rd Nov., 1912, p.1473.

(8) Intravenous Hedonal Narcosis, M.L.Lytschkowski. St.Petersburgh Medizinische Wochenschrift, Vol.36. Year 1911. p.209.

(9) Intravenous Anaesthesia. W.F.Honan, Annals of Surgery, 1913. p.901-917.

(10) Intravenous Hedonal Narcosis. P.Fedoroff. Journal fur Geburtsh und Gynecologie, 1910. Nos. 5 & 6. (Russ.)

(11) Hedonal, British Medical Journal, 15th June, 1912, p.1378.

(12) Complications following Hedonal Administration. Rawden Veale. British Medical Journal, 17th August, 1912. p.347-348.

(13) Ether Infusion Anaesthesia, F.S. Rood, Lancet, 23rd March, 1912.p.794.

(14) Intravenous Hedonal Narcosis. Honan & Hassler, Surgical, Gynaecological and Obstetrical Journal, Volume XVI. p.206,209, and 1856.

(15) Intravenous Hedonal Anaesthesia. Z.Mennell. Lancet, 9th Novr., 1912, p.1297.

(16) Intravenous Hedonal Anaesthesia, G.A.H.Barton, Lancet, 9th Novr., 1912. p.1297.

(17) Hedonal as a General Anaesthetic administed by Intravenous Infusion, Harold Upcott, (Hull), Lancet, 8th June, 1912, p.1568.

(18) Thrombosis following Adminstration of Hedonal. C.M.Page, Proceedings of Hunterian Society, Lancet,2nd Novr., 1912. p.1221.

(19) Hedonal Anaesthesia, Barrington Ward. British Medical Journal, 9th Novr., 1912, p.1310.

(20) Anaesthesia. Gwathmey, 1914, p.763.

(21) Local Anaesthesia, Brawn & Shields, 1914.

(22) Extra Pharmacopeia, Martindale, 1915

(23) Practical Physiology, D.Nöel Paton, and M.S.Pembrey, 1922.

(24) Physiological Action of Drugs, Pembrey & Phillips, 1901.

(25) Experimental Pharmacology, Dennis E.Jackson, 1917.

(26) The Action of Ions and Lipoids upon the Frog's Heart, A.J.Clark. Journal of Physiology, Vol.47. p.66-107.

(27) Textbook of Physiology, E.A.Schäfer, Vol.II. Vaso-motor Mechanism.

(28) Practical Physiology, Anrep and Harris, 1923.

(29) Jahresbericht der Medizine, Virchow, 1908 to 1916.

(30) Merck'shen Bericht, 1900 onwards.

(31) Action of Pituitrin on the circulation of the Bird. D.Nöel Paton. Journal of Physiology, Vol.XLIV. Nos. 5 & 6. p.410.15th July, 1912.

(32) Vaso-Motor System, William M.Bayliss,

(33) Infusion Anaesthesia, Felix S.Rood, British Medical Journal, 21st October, 1911, p.974-976.

(34) Anaesthesia in Man by Intravenous Injection of Chloral. Oré. De L'Academie des Sciences de Paris, 1874, Vol 78. p.515-516. (Originally appeared in the Proceedings of the Society of Surgery of Paris, 29th May, 1872.)

(35) Absolute Anaesthesia produced by one injection of Chloral Hydrate for Resection of Calcaneum. Ore. 1874. Vol.78. p.1311-1315.

(36) Action of Urethane, O.Schmiedeberg. Archiv. fur Experimentelle Pathologie und Pharmakologie, 1885-1886. Vol.XX. p.206.

(37) Intravenous Anaesthesia by H.Kummel. Lancet. 30th Dec. 1911.p.1848. (originally in Arch. fur Klinisch Chirurgie Band V. p.95.

(38) Intravenous Ether. Lancet, 30th Dec. 1911. p.1847. (originally in Beitrage zur Klinische Chirurgie Band 96. Heft 3).

(39) General Hedonal Narcosis, S.P.Fedoroff and A.P.Jeremitsch. Centralblatt fur Chirurgie 1910. Number 9. p.316-318.

(40) Intravenous Etherization. J.Blumfeld. Medical Press and Circular, 19th June, 1912. p.638.

(41) Hedonal Infusion Anaesthesia, C.M.Page. British Medical Journal, 16th March, 1912, p.611. (a paper read before the Royal Society of Medicine on 1st March, 1912.)

(42) Die Intravenose Hedonalnarkose, S.P.Fedoroff. Centralblatt fur Chirurgie 1910, No.19. p.675-676.

(43) Two New Hypnotics. (Urethane) British Medical Journal, 1886. Vol I. p.354.

(44) Chloroform Anaesthesia in the light of Physiological Research, George Herbert Clark, Glasgow Medical Journal. 1914.

(45) Intravenous Chloroform Narcosis, Ludwig Burkhardt, Münchener Medizinische Wochenschrift, Book LVI. Vol.2. Year 1909. p.1678-1681.

(45a) Hedonal as an Anaesthetic, Lancet 14th August, 1915. (up to date opinion)

(46) Hedonal as an Anaesthetic. H.P.Fairlie. Medical Press and Circular. 14th Sept. 1915.

(47) Hedonal in Therapeutics. E.Cataldi. Bollètino della Societa Lancisiana degli Ospedali di Roma. Fasc. IV. 1905.

(48) Hedonal by Burkhardt (Nurnberg). Proceedings of International Medical Congress. British Medical Journal, 16th August, 1913. p.393.

(49) Kinetic Theory of Shock, George W. Crile, Lancet, 5th July, 1913. Vol.II. p.7.

(50) Anoci-Association , George W.Crile, British Medical Journal, 16th August, 1913. p.394, 2nd Column.(read at International Medical Congress).

(51) Histological Changes in the Liver and Kidney after Chloroform administered by different channels. George Herbert Clark. Proceedings of the Royal Society of Edinburgh, Session 1908. Vol. XXIX. Part 5. No.26.

(52) Delayed Chloroform Poisoning. Stiles & McDonald, Scottish Medical and Surgical Journal, August, 1904. p.97.

(53) Regarding a new Hypnotic from the Urethane Group. H.Dreser (Elberfeld) Transactions of the Company of German Natural Philosophers and Physicians, 71st Assembly at Munich, 2nd part, 2nd half Medical Sections, 1900. pp.46 and 49. Leipzig.

(54) A new Hypnotic from the Urethane Group. H.Dreser. Münchener Medizinische Wochenschrift, 46th year of issue, No.40.p.1310.

(55) Rectal Etherisation. Dudley Buxton. Proceedings of International Medical Congress. British Medical Journal, 16th August, 1913.p.393.

(56) Anaesthesia. Gwathmey, p.533.

(57) Intravenous Infusion of Ether. L.Burkhardt. A Report before the 17th International Congress of Medicine, Lancet, 23rd August, 1913.p.555.

(58) A practical Course of General Physiology. D.Noël Paton and George Herbert Clark, 1911.

(59) The Behaviour of the Blood Pressure in Chloroform And Ether Anaesthesia with special reference to Shock, H.P.Fairlie. The Practitioner. February. 1911. Page 265-274.

(60) Ether, T.Pridgin Teale. Encyclopaedia Medica, Vol.I.

(61) Hedonal Anaesthesia. Z.Mennell. Proceedings of Royal Society of Medicine. Section on Anaesthetics, British Medical Journal. 1912. Vol.II. p.1311.

(62) Intravenous Infusion Anaesthesia, Felix Rood. Annual Meeting of British Medical Association. British Medical Journal, 1912, Vol.II. p.608.

(63) Hedonal Narcosis in Young Children. Paul Drevermann. (Freiburg). Münchener Medizinsche Wochenschrift. No.36. 7th Sept.,1923.

(64) A Supplement to the Subject of the Combined Narcosis. (Hedonal-Chloroform) E.Karlowicz. (Warsaw). Deutsche Zeitschrift fur Chirurgie. Leipsig. Vol.105. May 1910. 1st and 2nd parts.

(65) Hedonal Chloroform Narcosis. E.Karlowicz. A Treatise on Experimental Work done in Petrograd, 1905.

(66) Clinical Experiences with Spinal Analgesia, Arthur E. Barker, British Medical Journal, 23/3/1907. p.665.

(67) Hedonal-Chloroform Narcosis, Krawkow, (translated from Russki Wratsch, 1910) Therapeutische Monatshefte, Year 1910. Vol 24.p.444.

(68) Hypodermic Medication, Bourneville and Bricon (translated from the French by A.S.Currie) 1887.

(69) Anaesthesia produced in Man by Intravenous Injection of Chloral, Oré. De L'Academie des Sciences de Paris, 1874. Vol.78. p.515.

(70) Intravenosen Hedonal-Narkose, A.P.Jeremitsch, Deutsch Zeitschrift fur Chirurgie. Band 108. H.5 and 6, Year 1911.

(71) Lancet, 13th July, 1912. C.M.Page.

(72) Hedonal Anaesthesia, C.M.Page. British Medical Journal, 23rd Nov.,1912. p.1473.

(73) Hedonal Anaesthesia, B.G.A.Moynihan, Lancet, 15/6/1912.Vol.I.p.1631.

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SUMMARY.

1. ANAESTHESIA.

A rabbit requires for maintenance of anaesthesia by intravenous perfusion, 2.2 grains of Hedonal per hour per kilogramme of body weight.

The effect on the eye is similar to that of chloroform. Small doses of .17 grain per kilogramme stimulate the sympathetic, dilating the pupil, the light reflex being retained: large doses of .57 grain per kilogramme paralyse the third cranial nerve, dilating the pupil, the light reflex being abolished.

The action on the corneal reflex varies extremely. It may be abolished by .11 grain per kilogramme, while .43 grain has failed to make it disappear.

The nature of the anaesthesia produced by Hedonal differs from that of other anaesthetics: it resembles more the sleep of a true hypnotic. A deep drowsiness continues for a long time after the animal has shown response to a needle. With chloroform or ether, after such response has been observed, the patient usually wakes up in a few minutes if the anaesthetic is discontinued.

Regarding the cause of death, it has been shown that respiration ceases before the heart; the heart stops in diastole.

2. EFFECT ON HEART OF RABBIT.

The heart of the rabbit always shows decrease in the amplitude of contraction of the auricle, and more so of the ventricle. Complete recovery of the auricle and ventricle takes place after perfusion of .16 grain of Hedonal per kilogramme. Complete recovery does not always take place after a dose of .2 grain per kilogramme.

The cardiac rate remains unaltered.

3. EFFECT ON EXCISED HEART OF FROG.

The excised heart of the frog shows diminished amplitude of contraction when a solution of Hedonal is perfused. The weakest solution/

solution to show this effect is 1 in 2,000: the strongest solution used, viz., 1 in 250, frequently stopped the heart.

The cardiac rate is reduced. Weak solutions (1 in 2,000) increase the rate at first: the rate is in a few seconds reduced. With a stronger solution (1 in 1,000), the initial increase in rate is not so apparent. Solutions of 1 in 250 show hardly any initial increase, and may stop the heart altogether.

When all movement of the heart has ceased, the action may be restored by perfusing Sherrington's solution;[1] it may even be restored by gently touching it with a glass rod. This is important for the clinician in cases of collapse in tabula; massage of the heart through the diaphragm may well be attempted in cardiac failure.

The heart of the frog stops in diastole.

A solution of .37% dropped on the surface of the heart will stop all movement, which movement may be again restored by the external application of normal saline.

4. EFFECT ON THE ARTERIOLES OF RABBIT AND DOG.

To ascertain the effect on the arterioles of the rabbit and dog, there was chosen the kidney or the bowel with mesentery. The organ was dissected out, and placed in an oncometer of suitable size. All the experiments showed vaso-dilatation when Hedonal was perfused. The results were more apparent in the dog than in the rabbit, and when using the intestine than when using the kidney. The dose varied from .15 grain per kilogramme to .5 grain per kilogramme.

5. EFFECT ON ARTERIOLES OF FROG.

Upon the arterioles of the frog, Hedonal acts as a vaso-constrictor when the drug-solvent and restorative are identical, the drug being perfused through the intact heart. Solutions of normal saline, Sherrington's solution, and frog's "Ringer"[2] respectively were used. The same effect was obtained in all these conditions.

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1. For composition see p. 18, vol II.

2. For composition see p. 18, vol.II.

The effect is independent of the brain and spinal cord, Hedonal may act directly on the circular muscle fibres in the wall: or again, it may act through the local nerve supply, either stimulating the vaso-constrictor fibres, or inhibiting the vaso-dilators.

From the above it may be noted that the action of Hedonal on the arterioles of the mammal is entirely different from the action on the arterioles of the frog, viz., in the former, there is vaso-dilatation; but in the latter vaso-constriction.

6. EFFECT ON BLOOD PRESSURE IN RABBIT AND DOG.

The blood pressure was tested in the rabbit and the dog. In both animals it is reduced by perfusing Hedonal. There is for a few seconds an initial increase in pressure, just as there may be observed a stimulating first effect in the case of some other anaesthetics. The initial increase is more apparent in the rabbit; but it may also be seen in the tracings from the dog. A dose of 6 c.c. (.75% Hedonal) or .69 grain, when perfused by the jugular vein of a rabbit weighing 1.800 grammes, caused a fall of pressure of from 15-22 m.m., while it was found that 1 c.c. or .11 grain in a rabbit of 1,300 grammes caused a fall of 20 m.m.. A dose of 6 c.c. or .69 grain in a dog weighing 4,400 grammes caused a fall of 7 m.m..

7. EFFECT ON RESPIRATION.

The effect on Respiration was examined in the rabbit. On simply glancing at the tracings, one might conclude that the respiration is most regular, and that there is no change from any one dose: but when one takes the whole tracing into account, the aggregate effect is certainly a loss in the amplitude of expansion of the thoracic wall, and a reduction in the respiration rate.

The facts are here stated. Single small doses of .2 grain of Hedonal per kilogramme show practically no change in the amplitude of expansion nor in the rate. A single dose of .26 grain per kilogramme showed a reduction in the amplitude of expansion equal to 25%, and in rate equal to 21%. In an experiment on the rabbit,

where/

where the quantity of Hedonal was similar to that found necessary to maintain anaesthesia, viz., .7 grain per kilogramme during 17 minutes, the reduction in the amplitude of expansion was 38%, and, in the respiration rate 53% during this time.

I am of opinion that the effect of Hedonal on respiration is not a dangerous one, and that the early deaths in the clinic which occurred after operation, were not of central origin, but due to the great muscular relaxation affecting the tongue, leading to obstruction of the air-way mechanically.

8. EFFECT ON VAGUS NERVE-ENDINGS IN RABBIT AND DOG.

The effect of Hedonal on the Vagus nerve-endings was examined in the rabbit and the dog.

The results in the rabbit may be seen in the following tracings:-

(a) The auricle and ventricle of the heart,

(b) The respiration and blood pressure.

The results in the dog are shown in the tracings of the blood pressure taken from the carotid.

The physiological action of the vagus nerve-endings is not materially affected by Hedonal.

9. EFFECT ON EXCITABILITY OF NERVE.

The Excitability of Nerve was tested in the frog, the sciatic nerve attached to the gastrocnemius being used.

Hedonal diminishes the Excitability.

Restoration of the Excitability may be attained by placing the nerve in frog's "Ringer"; this loss of Excitability, with Restoration following, may occur twice in succession.

Occasionally there was found an initial increase in excitability due to Hedonal, but this was always followed by a loss of Excitability.

10. EFFECT ON CONDUCTIVITY OF NERVE.

The Conductivity of the frog's sciatic nerve was also tested, using a similar preparation to the above.

It was found in every case that Hedonal diminished the conductivity of the nerve.

11. EFFECT ON RATE OF NERVE-IMPULSE.

The Rate of the Nerve impulse was measured in the frog by the method of von Helmholtz.

The normal rate was first calculated. The sciatic nerve was then treated with Hedonal solution (.37%) for one minute, and the rate again ascertained.

In every experiment, Hedonal reduced the rate. In one case, where the nerve had been in the solution for one minute, the reduction was as great as 80%.

12. EFFECT ON MUSCULAR CONTRACTILITY.

The effect of Hedonal on Contractility of Muscle was investgated in the frog's gastrocnemius by electric stimulation, both directly, (through the muscle), and indirectly, (by the nerve). The same measured current was employed in each separate experiment.

(a) The actual contraction of the muscle when electrically stimulated was reduced by placing it in Hedonal solution.

(b) After treating the muscle with Hedonal and stimulating it electrically the latent period was increased.

(c) The work done by the muscle was much reduced.

The compositions and experiments in the present work are the result of my own efforts
John Scott

T H E S I S

by

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presented under the regulations
for the degree of Ph.D. of the
University of Glasgow.

PART I

Temper-Brittleness.

PART II

Ac_1 and Ar_1 in Special Steels
