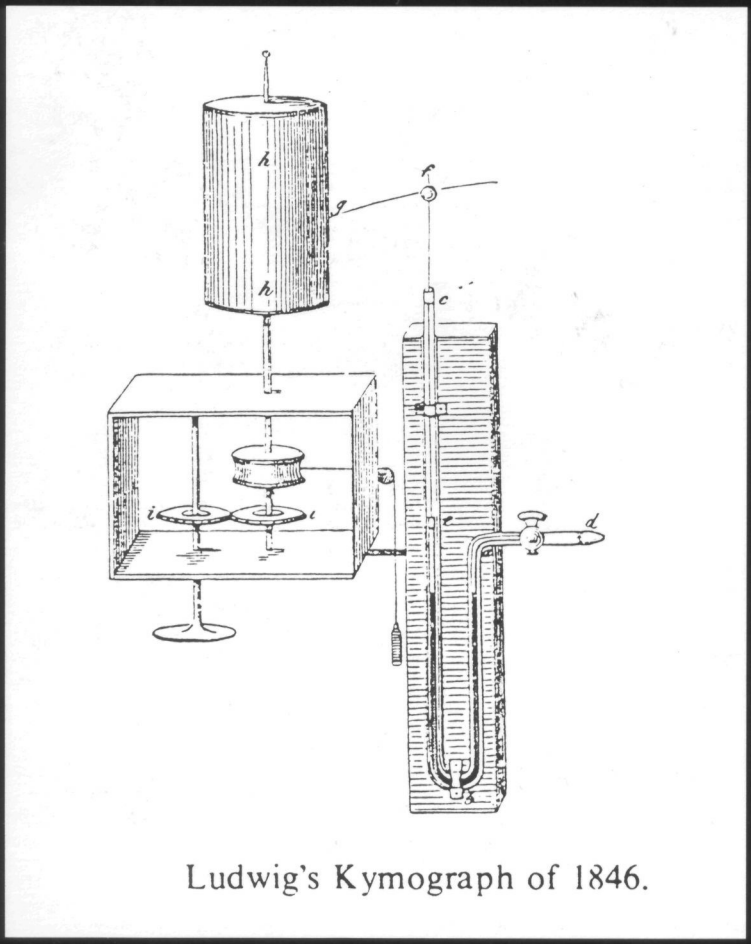
The History of Anesthesiology

Reprint Series: Part Seventeen

SELECTED STUDIES OF THE NINETEENTH CENTURY IN PHYSIOLOGY AND PHARMACOLOGY RELATED TO GENERAL ANESTHESIA



Ludwig's Kymograph of 1846.

The kymograph was the first recording instrument in the history of physiology. It was used for recording arterial blood pressure and was introduced by Carl Friedrich Wilhelm Ludwig (1816-1895) in 1846, the year of the introduction of general anesthesia.

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SELECTED STUDIES OF THE NINETEENTH CENTURY IN PHYSIOLOGY AND PHARMACOLOGY RELATED TO GENERAL ANESTHESIA

INTRODUCTORY NOTE

By

B. Raymond Fink, M.D.

Anesthesia was to 19th century medicine as the steam engine was to 18th century physics — a thriving bastard. Scientists did not claim to have sired either of them but did their best to endow both with legitimacy, undaunted by the unsophisticated state of methods and concepts, for in the 1840s the whole of nature seemed open to mechanical analysis.

The conservation of matter was a well-tested law, the conservation of energy, an emerging idea. Liebig's seminal volume on animal chemistry, published in 1842, inspired the venturers who sought a mechanochemical explanation for the latest wonder, inhalational anesthesia. Liebig contended that the intermediaries of a metabolic process could be inferred from the nature of the end products. This proved a fertile source of error, as when he asserted that the urea of the urine was derived from muscle and reflected the amount of the preceding muscular activity.

Such, in caricature, was the background for the first experimental attempt to find a chemical basis for ether anesthesia. It was undertaken by von Bibra and Harless in 1847 and published in a remarkable book that gave complete details of the argument and results. Ether was a fat solvent. Ergo ether dissolved the brain fat, thereby producing anesthesia; as expected, some of the fat turned up in the liver. The data are not worth reproducing here but the translated excerpts from the chapter on interpretations offer a fascinating historical insight into some of the misguided thinking of the time.

The physiology of the nervous system at the advent of general anesthesia was crude and still at the level of the gross divisions. The nature of the nerve impulse was unknown. These limitations silhouette the brilliance of Flourens' pioneering attempt to solve the puzzle of ether-suppressed function of the nervous system. Two of his first three contributions on the subject are presented here, apparently unavailable elsewhere in English. The last includes some interesting subsequent discussion — Flourens had deduced that the subdivisions of the central nervous system constituted a hierarchy of sensitivities to asphyxia and anesthetics.

The dissection of physiological function by means of toxic agents was the invention of Claude Bernard. I have translated and included here the communication at the Academy of Sciences in which he introduced that idea, beginning with curare. His demonstration of the site of action of curare beautifully illustrates the economy of method and acuteness of reasoning that went into his newly created science of experimental medicine. Elsewhere Bernard warned explicitly that curare was not an anesthetic agent in any true sense but only produced the appearance of anesthesia, the animal being capable of feeling but incapable of showing it.[1]

Pharmacology as a discipline was then not only non-existent but undreamed of. The search for better anesthetics was initially a search for lucky breaks, by trial and error. The first attempt to correlate variation of physiological effect with variation of chemical structure had been the abortive one of Blake,[2] and he examined substitutions of inorganic components in compounds long before the advent of the periodic table. Some twenty years elapsed before Richardson, well past the middle of the century, adapted Blake's approach to the field of organic chemicals and, as intimated in the included reprint, systematically compared change in structure with pharmacological effect on the nervous system.

The accelerated progress of the next two decades was authoritatively surveyed by Lauder Brunton in the Croonian lectures of 1889. It is the third of these three lectures which has the greatest interest for the present purpose. One gathers that by no coincidence at all the early structure-action studies often include anesthetics. It could hardly be otherwise, for only relatively simple synthetic organic compounds were available for tests of biological effect. This fact explains why inhalational general anesthesia virtually *had* to be the leading pharmacological discovery of the century and why it preceded the advent of antiseptic surgery. First, the small mass of small molecules meant that they could be volatile and inhaled. Second, inhalation meant that dosage was perforced gradual and therefore, in principle, always initially safe. Third, it was paramount that inhalation was intrinsically the only essentially germ-free form of administration and consequently unattended by the mortal perils of infection and sepsis.

Ventricular fibrillation elicited by electrical stimulation was remarked by Ludwig and Hoffa as early as 1850. McWilliam eventually took the lead in examining its physiology and was not unaware of a possible relevance to anesthesia. Unfortunately his paper, as can be seen, states that the animals were completely anesthetized but omits to name the anesthetic. At all events he failed to spot the relation to sudden death from chloroform anesthesia. There soon followed the lengthy experimental study by Gaskell and Shore, part of which is also reproduced here. It was undertaken because an epidemiological survey had been unable to decide which type of failure, respiratory or circulatory, was primarily responsible for the chloroform disasters. This experimental work, though expert, remained inconclusive because the primacy of the heart could not be clearly understood until after the discovery of epinephrine and its role in sensitizing the ventricles to chloroform.[3]

The last selection closes the century, aptly enough, with Meyer and Overton's correlation between partition coefficient and anesthetic potency. Meyer's article conveniently slipped in under the secular wire whereas

Overton's book[4] did not. No matter. The bastard child of the healing arts was clearly becoming certifiably scientific.

1. Bernard, C: Lecons sur les effets des substances toxiques et médicamenteuses. Paris: Baillère, 1883, p. 333.
2. Blake, J: On the physiological action of medicines. Report of the 16th meeting of the British Association for the Advancement of Science. London: John Murray, 1847, pp. 27-31.
3. Levy, AG: Sudden death under light chloroform anaesthesia. (Preliminary communication) J. Physiol (London) 42: iii-vii, Jan. 21, 1911.
4. Overton, CE: Studien ueber die Narkose; zugleich ein Beitrag zur allgemeinen Pharmakologie. Jena; G. Fischer 1901, 195 p.

M. J. P. Flourens

Note touchant les éffets de l'inhalation
éthérée sur la moëlle epinière

Note concerning the effect of ether
inhalation on the spinal cord

* * * * *

Note touchant l'action de l'éther sur les
centres nerveux

Note concerning the effect of ether
on the central nervous system

(C. R. Acad. Sci [Paris] 24: 161-162, 340-344, 1847)

Translated by

B. Raymond Fink, M.D.

Note concerning the effect of ether inhalation on the spinal cord.

by Mr. Flourens

1st experiment: on a dog. — After about thirty or thirty-five minutes, the animal subjected to the inhalation of ether became utterly insensible. The spinal cord was then exposed at a point in the dorsal region. The animal gave no sign of pain during this cruel operation.

After exposure of the spinal cord, the posterior roots (nerves of sensibility) were pinched and cut and the animal felt nothing. The anterior roots (nerves of movement) were pinched and cut, and not one of the muscles innervated by these roots moved. Finally, the spinal cord itself was injured, torn, cut, without the least sign of pain or convulsive reaction from the animal.

2nd experiment: on a dog. — Same experiment as the previous one, and same general result. Except that each time the anterior roots (nerves of movement) were cut a slight jerky movement by the animal occurred with the section of each one.

3rd experiment: on a dog. — After the external parts had become insensitive, the spinal cord was exposed. A posterior root was sectioned: no pain; The corresponding anterior root was sectioned, slight jerk by the animal. Inhalation of ether continued several minutes more, at the end of which time another anterior root was cut, and jerks no longer occurred.

4th experiment: on a rabbit. — After fifteen to twenty minutes of inhalation of ether the animal was completely insensible. The spinal cord was exposed: section of the posterior roots provoked no pain whatsoever; section of the anterior roots caused a slight jerk by the animal.

Ether has the amazing ability to abolish, for a limited time, the principles of feeling and of movement in the spinal cord. Moreover, the principle of feeling always disappears before that of movement.

I need hardly add that, after the effect of the ether had dissipated, the spinal cord recovered all of its lost powers, except at the points of section or excessive damage inflicted by the experiment. The parts of the body situated below these points remained paralyzed.

It is a pleasure to acknowledge the help of Mr. Auguste Dumeril, son of our famous colleague, and Mr. Philppeaux, my two naturalist assistants at the Museum of Natural History.

Note concerning the action of ether on nerve centres.

by Mr. Flourens

I. My recent experiments[1] have shown that the action of ether on nerve centers follows a certain sequence. Ether acts first on the cerebrum proper (cerebral hemispheres or lobes) and impairs the intellect;[2] it acts, in the second place, on the cerebellum and impairs[3] motor equilibrium. Next, it acts on the spinal cord where it extinguishes in succession the principle of feeling and the principle of movement. Last of all, it acts on the medulla oblongata, and in so doing it extinguishes life.

II. In my latest experiments I allowed the action of ether on the nerve centers to increase until life was extinguished.

Experiment 1. on a dog. — The animal is subjected to the action of ether. Etherization is complete in six or seven minutes (translator's note: apparatus used is described in a long footnote). After 30 minutes, death appears imminent. The medulla oblongata is exposed; touching it lightly produces a slight movement of the animal. A second touch produces no movement, the animal is already dead.

Experiment 2: on a dog. — Etherization sets in within five or six minutes. The dorsal region of the spinal cord is exposed. A posterior root is pinched, then cut: no sensibility. An anterior root is pinched, then cut: no movement. As in the two categories of roots, so also in the two regions of the spinal cord. The posterior region has become insensitive, the anterior region no longer elicits movement.

Etherization is maintained for almost one hour. When the animal seems about to succumb the medulla oblongata is exposed.

When the medulla oblongata is touched, the animal convulses slightly. A second touch, a second small jerk. The moment the medulla oblongata ceases to react, the animal dies.

Experiment 3: on a dog. — Same sequence, same survival of medulla oblongata longer than spinal cord, same sudden death of the animal when the action of the medulla oblongata ceases.

III. It follows, as I have said, that ether acts successively on the cerebrum (cerebral lobes or hemispheres), the cerebellum, the spinal cord, the two regions of the cord and categories of roots, and the medulla oblonga-

ta. In so doing it successively impairs and extinguishes intelligence, motor equilibrium, sensitivity, motricity, life.

IV. It will be remembered that I obtained the same results with hydrochloric ether as I did with sulfuric ether. Hydrochloric ether led me to try the novel compound known as chloroform.

Within a very few minutes (six in a first experiment, four in a second and third), the animal subjected to inhalation of chloroform became fully etherized. The spinal cord was then exposed. The posterior region and the posterior roots were insensitive; of five anterior roots tested in succession only two had retained their motricity, the other three had lost it.

V. It is impossible to witness even one etherization without being struck by the resemblance of the new phenomenon to the phenomenon of asphyxia. Almost all observers have noticed the resemblance, and some have carefully studied it.

I subjected two dogs to the simplest form of asphyxia, by causing them to consume the oxygen in a limited volume of air. This requires the small apparatus described in the footnote.[4] By beginning, continuing, interrupting or ending the procedure as needed, the animal is brought to a state of asphyxia strongly resembling etherization.

In the two dogs discussed here asphyxia reached the required degree, at which time the spinal cord was exposed. The animal felt nothing. The sensory region of the cord was pierced, pinched, cut and still the animal felt nothing; the motor region was pierced and pinched, sometimes eliciting weak muscular contractions.[5]

VI. Thus a true relation and close analogy exists between etherization and asphyxia. However, in ordinary asphyxia the nervous system is disabled under the influence of dark blood — blood deprived of oxygen — whereas in etherization the nervous system is first disabled by the singular agency which then subsequently determines the asphyxia.

VII. That is the nature of the difference. Otherwise, both in etherization and in asphyxia there is the same loss of feeling and voluntary movement, the same persistence, at least for a time, of repiratory movements, in one word, the same survival of the medulla oblongata.[6] Etherization lays bare the underlying mechanism of asphyxia, by which I mean the asphyxial death of nervous centres in succession.

VIII. My considered opinion is that the march of death through a suc-

cession of nervous centers is the truly important point of the new experiments.

IX. In 1822, in the memoirs I presented at that time to the Academy, I said: "The various parts of the nervous system all have different properties, special properties, specific roles which do not overlap.[7]

I also said: "Everything goes to show that there is an essential independence between the intellectual and motor faculties, between the coordination of movements and the excitation of muscular contraction. The organ of perception and volition is not that of coordination of movements, etc.[8]

I now say that, as in the case of those experiments which employed mechanical methods, so also etherization isolates the intelligence, the coordination of movements, the sensory sensibility, the motor power, and life.

XI. The isolation of life, of the vital point or node of the nervous system, is in fact the most striking result of these new experiments.

In an etherized animal one area survives alone, and as long as it does survive the other parts retain at least a latent life and can resume a complete life; once that area is dead, all is dead.

Etherization thus isolates and disengages the primary force, the elementary, the basic, the vital force of the nervous system. The vital force of the nervous system is the force proper of life itself.

After Mr. Flourens' communication Mr. Roux arose and spoke at some length, saying among other things that while he fully recognized the merit of Mr. Flourens' experiments he very respectfully was unable to accept all the deductions presented to the Academy, for the following reasons.

While animal experiments might indicate a successive as distinct from simultaneous action on various parts of the nervous system, the many observations of recent months on man seem to contradict or at least modify this. At human operations, all the manifestations of etherization sometimes occur simultaneously. More often, on the contrary, self-awareness, consciousness, the capacity to understand questions and to answer them with voluntary gestures endure right up to the moment of onset of insensibility. Secondly, he disagreed that etherization is a kind of asphyxia: a changed color of arterial blood is not always seen at surgical operations. Even when insensibility is extreme one can usually distinguish quite readily between

the crimson arterial and dark venous bleeding that occurs when arteries and veins have been severed simultaneously. And what a difference between the florid skin of an etherized individual and that of one stricken with asphixia!

Mr. Despretz drew attention to the fact that the air breathed by patients subjected to the action of ether contains only half as much oxygen as ordinary air. At a temperature of 20 degrees, which seems to be the temperature during surgery, the elastic force of ether vapor is equal to about half of the mean pressure of the atmospheric (assuming the ether to be pure). If, beforehand, one doubled the amount of oxygen by adding to the air a quantity of oxygen equal to one fifth of its volume, the air breathed with the ether would be as rich in oxygen as ordinary air, and the chances of asphyxia would be lessened.

Translater's Comment: Humphry Davy in 1800 had suggested the use of oxygen with nitrous oxide in surgery, but this was not tried until 1868 by Andrews in Chicago, nor made widely practical until 1892, by Hewitt in England. This gives one some idea of the prescient brilliance of Davy. The vapor pressure of ether (and alcohol?) was apparently first measured by Gay-Lussac, around 1811. Dalton had measured the vapor pressure of water in 1802. Despretz' intervention in the discussion reminds one of the interdisciplinary nature of the meetings of the Academy of Sciences of Paris. Leverrier, who had reported his discovery of Neptune six months earlier, was the first speaker at this session. César-Mansuète Despretz (1791 - 1863) was a distinguished Belgian physicist, born in Lessines, 25 miles from Brussels, who had worked on the vapor pressure of ether in 1819 and eventually became president of the Paris Academy. It was not until 1951 that Faulconer initiated the practice of trickling a 500 ml per minute flow of oxygen under the open drop ether mask.

FOOTNOTES

1. C. R., 22 February 1847, p. 253
2. I say IMPAIRS advisedly. One cannot in general doubt that intelligence and coordination of movement are the functions first affected. Some dogs resist either and in them ether does not go so far as to produce insensitivity and motor unresponsiveness of the spinal cord; ether dazes these dogs (that's the effect on intelligence) and makes them stagger drunkenly (that's the effect on coordination of movement). With some ethers (oxalic ether, acetic ether) I have been unable to extinguish the sensitivity and motoricity of the spinal cord, but dogs subjected to these ethers have always been dazed and seemed drunk.
3. Again, I say IMPAIRS deliberately. One cannot test the state of the cerebrum or cerebellum directly by a mechanical lesion, as one can with the spinal cord. The brain and cerebellum are insensitive (see my Recherches experimentales sur les proprietes et les fonctions due systeme nerveux, 2nd edition, pp. 18 and 20). One can only evaluate their state from their functioning. In any case for my present objective, the states of the cerebrum and cerebellum are secondary matters. If you remove the cerebrum you destroy the animal's intelligence but the animal survives; if you remove the cerebellum, the animal's motor equilibrium is lost but the animal survives. (ibid. p, 31 and 37). The main subject of the present work is to demonstrate that the medulla oblongata surprisingly survives longer than the spinal cord. This remarkable survival is a new discovery.
4. The apparatus consists of a flask with two tubes. One has a tap that prevents or permits entry of external air into the flask when shut or open, and the other leads to a firmly attached bladder. At the other end of the bladder is an opening for the head of the animal. The bladder is tightened around the muzzle in such a manner that the animal is obliged to inhale and rebreathe from the flask.
5. One of the dogs died during the experiment; the other was returned atmospheric air and recovered.
6. By way of further analogy, the viscera of animals dead of etherization and dead of asphyxia are almost in the same state. The lungs of both are a little pale, the liver and kidneys on the contrary are engorged with dark blood that escapes freely from an incision, the heart is dilated and flaccid, the blood in the two ventricles is dark, etc.
7. Recherches experimentales sur les propriete's les fonctions du systeme nerveux. 2nd edition, p. 15.
8. ibid, p. 13.

E. von Bibra, E. Harless

DIE WIRKUNG DES SCHWEFELAETHERS IN CHEMISCHER UND PHYSIOLOGISCHER BEZIEHUNG

Erlangen, Carl Heyer, 1847

Chapter 8, pp 157-165

Chemical Physiological Theory of the Action of Inhaled Ether

(Excerpts)

Translated by

B. Raymond Fink, M.D.

Chapter VIII. Chemical Physiological Theory of the Action of Inhaled Ether. (Excerpts).

. . . It was shown above that the primitive sheath of nerve is composed of an albuminous substance that also contains fat,* and that this diversity of composition exists both in the fibers of the peripheral and those of the central nervous systems as well as in ganglia, although in the latter the proportion of fat is smaller. All physiologists are agreed that the essential vital characteristic of nerve resides in its composition.

Ability to dissolve fat is the most important property of ether; it does so the more readily the nearer its temperature is to its boiling point. A further property of anhydrous ether is its ability to attract water. These properties enable it endo-and exo-osmotically to permeate all tissues without exception. But this action does not necessarily require that ether reach nervous tissue via the blood vessels. Sulfuric ether quickly penetrates all tissues from every cavity in the body and, unlike nitric ether, is not prone to undergo transformation in the capillaries.

With all its chemical attributes intact ether in the nervous system first affects the components for which it has the greatest affinity, the fatty ones. It partly dissolves them, and the solution gets taken up by the venous blood after traversing the capillaries by endosmosis.

Partial dissolution of the fat by ether must of course necessarily alter the components of the nervous tissue and nullify their mode of action. This accords with the slight, difficult-to-measure depletion of spinal cord fat. There was also uncertainty about the fat content of the brain, where macroscopic sections failed to demonstrate any structural changes, nor was it possible to ascertain whether the change of fat content was in proportion to the physical disturbance. Perhaps I attempted too much in trying to relate fat content of the brain and psychic manifestations; however, it was never my intention to seek correspondence between sensory impressions, such as music, and the brain's content of fat.

While it is quite certain that amount of fat is an important factor in manifestation of brain activity, many finer qualitative differences accompanying the intimate details of mental activity at present escape our scrutiny, perhaps forever. We certainly do not claim that our analyses of the fat content of the brain have uncovered the secret workshops of the psyche.

The conditions for demonstrating the cerebral loss of fat quantitatively were created only by prolonging the inhalation of ether for as long as possible. Premature death of the animals was avoided by allowing brief inter-

vals of recovery; after the reflexes were abolished, the animal was taken out of the apparatus until the first signs of voluntary movement returned and was then returned to the ether vapor. In this manner the uptake of ether was continued for several hours in a number of animals, thereby making it possible to measure the associated effect on metabolic exchanges.

If a deficit of fat develops in the brain it must be recoverable as an excess in some other organ. Since the dissolved fat gets carried through the capillaries into the venous part of the circulation, we looked for it in the liver, an organ whose secretion is always rich in fat. Although we did not expect to find there all the fat that had been removed from the brain, we did expect to find some of it, and indeed succeeded in doing so. Ether may also cause other glands to deliver a secretion enriched in fat. At all events, it is clear from our analyses that the fat content of the liver of etherized animals always exceeded that of the healthy controls. To avoid the individual variability in the fat content of brain and liver all our comparisons were made between animals of the same sex and similar age. Although some may believe that the observed individual differences were too great to be produced by anesthesia, it strains credulity to think that the chance choice of animals would in every case have favored our theory. Our confidence in the large numerical differences is strengthened by the fact that, appropriately enough, they occurred from the outset exclusively in carnivorous species. We recognized that the rate of metabolism affected the amount of metabolites accumulating during anesthesia. In mammals, for example, substances entering the circulation and carried to the organs are transformed more rapidly than in amphibia. The extent of this differs in carnivores and herbivores and another instance of this previously noted difference is that the difference in liver fat content between anesthetized and unanesthetized animals was less striking in herbivores. In the blood, however, no difference in fat content could be demonstrated between the narcotized and unnarcotized animals — no doubt for the same reason that prevents us from finding any difference in the level of blood urea. The velocity of the circulation is such that excess dissolved fat in the blood entering the liver at any moment is always extracted there, so that the fat content of the blood always remains within the limits of normal variation.

. . . Reviewing the collected results of the amount of carbon dioxide given off during ether inhalation, here again a deficit in a product of metabolism becomes apparent. The deficit may be attributed to the inhalation of ether on two grounds. First, a purely mechanical one, is that a mixture of atmospheric air and ether vapor will contain a decreased quantity of oxygen; as Liebig has shown, decrease of inspired oxygen leads to decreases in metabolic transformation. And the slower the metabolism, the greater will be the decrease in products of metabolism, deemed to consist

of urea and carbon dioxide, both of which we find to be diminished during anesthesia.

Second is the fact that the nervous system exercises a great influence on the entire metabolism. Rest and motor activity leave behind detectable traces in the products of respiration as well as in secretions, particularly the kidneys. In mammals the end product of organic oxidation, urea, is found especially in the actively mobile carnivora and decreases in amount as soon as their activity is curtailed.

In man the amounts of urea and uric acid formed at rest are less than in brisk activity. So too, the amount of carbon dioxide exhaled increases during energetic activity and decreases during inactive rest. That this view, so brilliantly developed by Liebig, is correct is here again fully confirmed. There is no need to ascribe the change in carbon dioxide and urea production to the action of the sympathetic, since, as shown above, the latter is maintained long after the brain and cord have become paralyzed.

In the voluntary muscles there is not only a cessation of visible movement but a decline of the tonus at relative rest, normally a rich source of stimulated chemical activity. This change in a major source of body heat accounts for the conspicuous fall of temperature observed during anesthesia, as demonstrated above. An additional factor in this temperature decrease is the diminished oxygen intake accompanying ether anesthesia. . . .

Claude Bernard

Analyse physiologique des propriétés des systèmes musculaire et nerveux au moyen du curare

(C. R. Acad. Sci. [Paris] 43:825-829, 1856)

Physiological analysis of the properties of the muscular and nervous systems by means of curare

Translated by

B. Raymond Fink, M.D.

Mr. Koelliker's presentation at the last meeting of the Academy reminded me of my experiments with curare and the physiological conclusions to which I was led by the study of this unique substance.

In 1844, Mr. Pelouze gave me some curare which he had obtained from Mr. Goudot. The poison came from New Granada and had the same characteristics and properties as the curare examined by Messrs. Boussingault and Roulin.

In the course of experiments on living animals I was struck by a new observation. I found that, immediately after death in animals poisoned by curare, the nervous system loses its ability to act on the muscular system by producing convulsions. For instance, if one poisons a frog by placing a little dry or dissolved curare on its back, one sees that reflex movements become completely abolished as the poison takes hold. If one then immediately prepares the frog by the Galvani method of skinning the hind legs and isolating the lumbar nerves, one obtains no leg contractions with an electrical stimulus applied directly to the nerves, whereas the same stimulus applied directly to the muscles elicits violent convulsions. The loss of excitability prevails not only in the nerve trunks but also in fine branches pursued as closely as possible to the muscle.

From this experiment it follows that muscular contractility is entirely distinct and independent of the nervous action which evokes it, since curare preserves the former but abolishes the latter. Hence I concluded that the independent irritability of muscle, whose existence has been debated ever since Haller, was definitively established by the precise physiological effect of the curare. This experiment was mentioned in a communication made to the Academy by Mr. Pelouze and me in 1850, concerning the chemical and physiological properties of curare (Compte Rendu, Vol. 31, 14 October 1850). (Translator's note: The experiment was mentioned, but not the observation!)

In 1852 I again demonstrated this physiological distinction between the nervous and muscular systems. I reported that in animals poisoned by curare muscular irritability, far from being diminished, was, on the contrary, enhanced. For I had noted that the muscles of frogs killed by curare were generally redder and remained electrically excitable longer than the muscles of other unpoisoned frogs. However, in view of the possibility of individual variations in muscular excitability, it was necessary to confirm the result by comparing corresponding muscles in the same animal.

Here is how I performed this further experiment. I tied the blood vessels of one of the hind legs of a large frog, taking care to leave the sciatic

nerve intact. I then poisoned the animal by introducing a little curare through an incision in the skin of the back. The entire muscular system of the animal thus received the influence of the curare via the circulation, except for the muscles of the ligated limb, which muscles could accordingly be considered normal relative to the others. In this experiment I observed that the muscles of the limb that had not received the poison always became unirritable much sooner than those of the poisoned limbs.

Pursuing these experiments, it further came to my attention that the unpoisoned limb remained completely sensitive and always responded reflexly to pinching. More remarkable still, on stimulating the skin of other parts of the body, to which the poison had penetrated, similar reflex movements occurred, strictly restricted to the unpoisoned limb.

Evidently the last-mentioned reflex movements in the healthy limb were occasioned by stimulation in the poisoned regions transmitted by sensory nerves that had remained intact. This led me to conclude that the curare had abolished only the properties of motor nerves while preserving those of sensory nerves, and that although one elicited no reflex on pinching the skin of a totally poisoned animal, this did not prove that the animal was insensitive, but only that the motor nerves had everywhere become unable to act on the muscles either via reflex sensory excitation or by the influence of the will. Motor paralysis thus may have two causes. First, an animal may refrain from moving because it is not motivated or does not feel any neurally transmitted sensation; this is immobility due to sensory paralysis. Second, the animal may also remain immobile in spite of wishing to move or being impelled by an external sensation; such occurs when the nerves are unable to transmit the motor stimulus to the muscles. This is immobility due to paralysis of the motor nerves.

The latter is the mode of action of curare. This already becomes clear from the manifestations of poisoning in higher mammals, in dogs for example. One sees that the limbs refuse to obey the will before sensibility or intellect are abolished. When one calls to a dog whose limbs have become paralyzed, one readily recognizes from certain movements, such as those of the eyes or tail which resist the poison longer, that the animal can hear but is unable to perform movements that would bring him to the speaker.

I was able to demonstrate directly the unique property of curare of extinguishing the properties of motor nerves while preserving those of sensory nerves by the following experiment. I made an incision at the bottom of the back in order to expose the lumbar nerves. Next, I passed a ligature under the nerves, encircling the entire body of the animal except for those nerves. In this manner the anterior half of the animal was cut off from

communication with the posterior half except by the lumbar nerves, since the ligature occluded the aorta and all the blood vessels. I then poisoned the animal by placing a little curare under the skin near the head and saw the upper half of the animal gradually become paralyzed by the toxin. But a pinch applied to the upper part of the animal immediately elicited movement in the lower half, sometimes strong enough for the frog to leap while pushing forward the poisoned, inert half of its body.

From this second series of experiments I concluded that curare effects a physiological analysis that is not restricted to exposing the properties of the muscular system. It also distinguishes between the properties of the motor and sensory nerves, since it preserves the properties of the sensory nerves but abolishes that of the motor ones. Curare acts on the externally-directed motor nervous system more rapidly than on the inwardly-directed or sympathetic nervous system. But it also finally affects the latter when the poisoning is complete, and I noted that it was then no longer possible to stop the heart by galvanic stimulation of the vagus nerve. Finally, I observed that curare acts on motor nerves so as to extinguish them starting from the periphery and proceeding centrally, or inversely from the ordinary paralysis of those nerves.

In my lectures at the *College de France* on "The effects of toxic and medicinal substances," currently in the press, I have dwelt at length on these remarkable properties of curare. My most recently reported experiments and the conclusions I have drawn from them have long since been known in France, through reports in newspapers and by word of mouth from persons who attended my lectures or visited my laboratory.

In support, I will merely cite a passage summarizing my opinions on the effects of curare, taken from very interesting work on this poison which Mr. Vulpian, a young physiologist well known to the Academy, presented last April to the Societe de Biologie.

"To the experiments of Mr. Bernard," said Mr. Vulpian, "is due our knowledge of the preservation of muscular irritability and sensibility during poisoning by curare; but this sensibility remains silent, all power of expression via the motor nerves having been lost. (C. R. Soc. Biol, April meeting, Gazette medicale, no. 31, 1856.)

Mr. Koelliker's experiments are thus entirely consonant with mine. It is clear that Mr. Koelliker was not aware of my recent researches on curare, so the agreement between our results is an additional guarantee of their exactitude.

REPORT

OF THE

THIRTY-SIXTH MEETING

OF THE

BRITISH ASSOCIATION

FOR THE

ADVANCEMENT OF SCIENCE;

HELD AT

NOTTINGHAM IN AUGUST 1866.

LONDON:
JOHN MURRAY, ALBEMARLE STREET.
1867.

Report on the Physiological Action of certain Compounds of Amyl and Ethyl. *By* BENJAMIN W. RICHARDSON, *M.A., M.D., F.R.S.*

IN two previous Reports to the Association, I dwelt especially on the action of certain of the compounds of amyl. The first Report dealt exclusively with the substance known as the nitrite of amyl. The second Report had further reference to the same body, and also to amylene, amylic alcohol, and the acetate and iodide of amyl. In some degree these Reports were complete as far as they went; that is to say, the facts presented were sufficient to demonstrate what visible physical influences were exerted on dead and on living matter by these representatives of the amyl series; and as I carefully separated the facts from the speculations that were fairly to be founded on them, the Association expressed its satisfaction by requesting me to continue researches in the same direction but with a wider object. I was desired in the next Report to repeat what might require repetition, but specially to pay attention to the *ethyl*-compounds, with a view to determine, if that were possible, whether there was any analogy in physiological action between the analogous compounds of the two series.

SUMMARY OF PAST RESEARCHES.

Before I enter on new ground, it will be advisable for me to recall the main facts described in previous years and bearing on the amyl series.

1. It was shown that the *nitrite of amyl* when inhaled was the most powerful excitant of the circulation at the time known. It was demonstrated that during such inhalation the action of the heart was doubled in rapidity in thirty seconds, in men and warm-blooded animals: further, it was proved that this intense action was immediately followed by deep suffusion of the skin, by breathlessness like that produced by running, by a peculiar sensation of fulness and throbbing in the head, and ultimately by failure of muscular power of the extremest kind. It was also proved that there was no destruction of the nervous sensibility, that in animals there was an obvious expression of sensibility up to the moment of death. Lastly, it was shown that in cold-blooded animals, such as frogs, the nitrite of amyl suspended animation for hours, and even days,—and that, in young warm-blooded animals, after exposure to it until they seemed to be dead, the action of the heart continued for so long a period as eighteen hours.

2. In respect to *amylene*, it was shown that the vapour of it was antiseptic, even when freely admixed with air; physiologically tested on living animals, it is found to be capable of administration by being inhaled. It does not provoke local irritation, but it rapidly produces collapse and total insensibility to pain. At the same time it seems to interfere less with consciousness than other narcotic vapours. This fact is of peculiar interest, because the apparent consciousness exhibited by the subject is not shared in by himself, it is an objective, not a subjective phenomenon. The person under the influence of the vapour may perform acts which have all the semblance of conscious acts; but when he recovers he has no recollection of anything that has occurred. The state thus induced is very much like the phenomenon of somnambulism; and I ventured to suggest that in this experiment we had a key to the cause of the disease somnambulism, viz. that there was possibly formed in the body of the somnambulist, by a faulty digestion, a substance of similar action to an amyl-compound. Amylene I showed was a good anæsthetic, and many surgical operations have been performed under its in-

fluence, but it enters into no chemical combination with the tissues. This is due to its great insolubility in the blood and animal fluids. Amylene requires 9319 parts of water for its solution.

3. Of *amylic alcohol* it was shown that, like amylene, it was antiseptic. When the vapour of it is inhaled, it produces first irritation of the nostril, and next drowsiness and a kind of coma, but without insensibility to pain. In this comatose state there is developed a peculiar muscular action, a series of rigors which increase in force under any degree of excitement; but it is almost impossible to destroy life by its means. Animals brought to the verge of death and seeming past all recovery begin to rally so soon as they are placed in the open air.

4. The *acetate of amyl* was shown to produce the same kind of symptoms as those produced by amylic alcohol; it also preserves organic substances from putrefaction. It is used for flavouring-purposes under the name of essence of pears.

5. The action of the *iodide of amyl* was shown to be somewhat different from that of any of the other compounds. When inhaled it induces mixed symptoms, resembling in part those produced by the nitrite of amyl, and in part those produced by amylic alcohol. It causes excitement, great tremor of muscles, and during recovery a singular motion of the animal in a circle; it also excites salivation, and renders the extremities of the animal red and vascular during inhalation.

In the discussion which followed the reading of the papers named above, one special point attracted most attention. A question first was asked by Dr. Heaton, of Leeds, and afterwards by Professor Wanklyn:—Whether the differences of symptoms observed in dealing with different compounds of the amyl series turned actually on a change in the base itself, or on the combination of the base with a new compound. To take an illustration: was, for instance, the nitrite of amyl so peculiarly active simply because it was an amyl-compound, or because it was the *nitrite* of amyl?

This question is one of the chief (if not the chief) questions answered in the present Report. It was considered in the last Report in the following terms:—"The base amyl is, if I may use the expression, the keynote; but variations are introduced as new elements are added. The order of variation is most interesting. We take a simple hydrocarbon, the hydruret of amyl, and we have an almost negative body, acting not unlike nitrogen, and partly destroying motor force and consciousness, but no more. We introduce the element oxygen into the inquiry by using the hydrated oxide of amyl or the acetate, and there is added to the above-named phenomena violent and persistent tremor. We move from this to another compound, and bring iodine into the field, and the phenomena now embrace free elimination of fluid from the body, vascularity of the extreme parts, with increased action of the heart and of respiration. We change the combination once more to bring nitrogen and oxygen into operation with the base, and the vascular action is raised beyond what is seen from any other known substance, to be followed by a prostration so profound that the still living animal might for a time pass for dead."

NEW RESEARCHES.

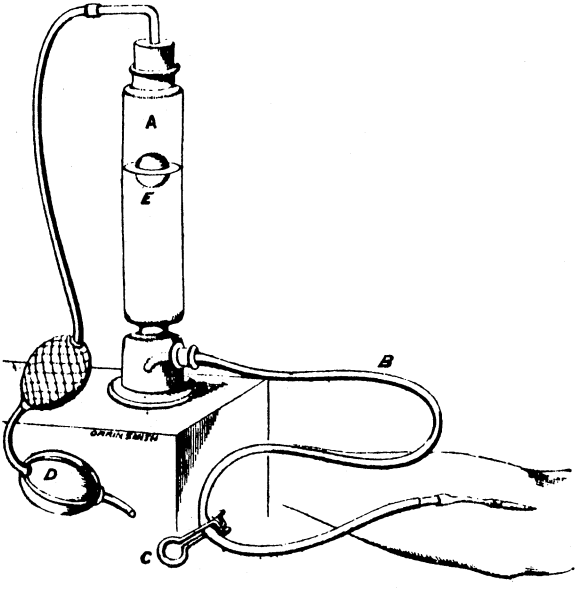
In the past year I have repeated the experiments conducted originally with the compounds of amyl, the compounds themselves being most accurately made. The result has been to confirm the facts previously observed, in all their integrity. In two directions I have extended these researches, with the

object of trying to make the substances under notice of practical utility to mankind.

NITRITE OF AMYL AS A REMEDY.

I first experimented to ascertain whether nitrite of amyl, which, as we have seen, exerts so decided an effect in quickening the action of the heart when it is inhaled by the living animal, might be turned to account as a means for stimulating the heart into action in cases where that organ has suddenly ceased to beat, as in cases of fatal fainting, in drowning, in sunstroke and lightning-stroke, in death by chloroform, and in suffocation from other narcotic vapours. To test this, the substance was introduced into the body in two ways—by artificial respiration, and by transfusion directly into the heart through the arteries. By neither of these methods could any decided effect be produced. By the first (the artificial respiration) a spasmodic action of the diaphragm and a peculiar action of the muscles of the nose are produced for a short time; but the effect is very transient. By the second, the effect seemed to be that the action of the heart was the more decidedly and rapidly paralysed. In one case, in connexion with my friend Mr. Gay, after repeating in the dissecting-room the experiment of the injection of a dead limb of the human subject with oxygenated blood, I introduced a free current of a blood containing one minim of the nitrite of amyl to the eight ounces. The muscles were by this means evenly and steadily injected, and the odour of the amyl-compound was distinctly perceived; but there was no sign of muscular action in response to the injection, and muscles laid bare and subjected to irritation were still quiescent.

For these experiments I invented a new instrument for transfusion, which works so simply and effectually that I may be excused, perhaps, if I diverge for a moment to describe it: the practical physiologist will find it of great value in many inquiries. This instrument, as shown in the diagram, con-



sists of a glass cylinder (A), with a flexible tube (B) running from its lower

part or chamber, for insertion, by means of a quill or hollow probe, into the vein to be injected: the upper part of the cylinder is provided with a stopper, through which a tube passes, connected with a small pair of hand bellows (D). Within the cylinder is a small hollow ball (E), or safety-valve regulator, which floats if there be fluid in the cylinder until the fluid allows it to descend to the constricted lower part of the cylinder, when all further passage of fluid is prevented. The flow of fluid along the escape-tube can be checked, or set at liberty at pleasure by the clip (C).

In using this instrument, first place the fluid to be injected in the cylinder (A) and let a little run through the escape-tube (B) to displace all the air; next close the escape-tube by means of the clip (C); then, having opened the vein or artery, while it is being pressed upon from above, insert and fix the quill or hollow probe at the end of the escape-tube, and, when all is ready for the fluid to flow, remove the clip and raise the cylinder two or three feet above the subject. The ordinary fluid-pressure will now usually suffice to carry the fluid into the body equably and gently; but if there be any obstruction, the merest pressure of the lower ball of the hand bellows will remove it. As the fluid descends, the hollow ball goes down with it to within three inches of the bottom of the cylinder, where it is opposed by the constricted neck, and where it effectually closes in all that is below it, so that no air can possibly get into the blood-vessel.

Reverting to the experiments related above, they, although negative as regards the particular object in view during their performance, teach an interesting and useful physiological lesson. They illustrate that when in the living body the nitrite of amyl, after its inhalation, excites the heart to such vigorous action, producing suffusion of the skin and the other extreme symptoms of excitation, the effect is conducted solely through the nervous system. I believe that the action of the nitrite, telling, at the moment of inhalation, upon the extreme filaments of the olfactory nerves, as well as on the pneumogastric tracts, communicates a peculiar and rapid motion, which traverses them and, without any indirect action on the blood, reaches the heart, giving to it impulse and vehemency of action.

The experience of every-day life tells us that the heart may be thrown into similar activity by impressions or influences communicated from the external world to the senses, and through them to the heart. The influences of sounds, harsh or melodious, of sights, appalling or fascinating, are well known, from the manner in which they come upon us. From their invisibility of action, if I may be allowed such an expression, we are prone to look on them as immaterial agents: they are not so; thoroughly understood they are as material as a physical blow, or the impress of a liquid or gaseous substance.

Nitrite of amyl is one of those substances which enable us to realize this connexion between the really material and the seemingly immaterial influences which surround us. We take an appreciable quantity of it, say, half a grain, and inhale it from paper, and at once we feel a quickened action of the circulation so decisively that we trace the effect immediately to the cause: we could, if we liked, quicken the heart to absolute silence by pushing the cause far enough. Here there is no mistake, no possibility of mistake. But we can modify the experiment and refine upon it. By admixing the vapour of ammonia with that of amyl, and diffusing the combined vapours through a large space of air confined by walls and closed windows, we can charge a room with a compound which the olfactory sense, as such, does not detect, but which tells with active and peculiar force upon the heart. In this way an invisible

and, as it would seem to the unlearned, an immaterial agency acts by known rules and in obedience to the human will*.

The day will soon come when we shall know the mode by which these agencies act upon the body through the nervous expanse: we shall follow out the living organism as so much matter moveable and transformable or transmutable, built in, and I had almost said upon, a refined medium, itself unchangeable, all-pervading, and establishing a bond of union between our own material parts, ourselves, our planet, our universe. We shall see how this fluid, itself physical, subjected to various influences, is disturbed, and how it communicates such disturbance to the grosser matters which it permeates; then a vast number of strange and, as they now appear to us, conflicting phenomena will resolve themselves into a single and simple law, and physiology, in its wholeness, the science of the sciences, will be the most useful and the most exact.

I have said that when the motion of the heart has once been stopped, the influence of the nitrite of amyl ceases; that the nitrite can quicken the living action, but cannot restore the lost action. These are the facts as they stand at the moment; but I must add as a qualification that the negative result may perchance be due to inadequacy of experiment, and that new and continuous experiment may change the argument.

The Amyls as Antiseptics.

The second new line of inquiry to which the amyl-compounds were subjected, was to determine whether they could be turned to account, practically, as antiseptics. I had already found that every one of the series is preservative, and I therefore took one (the acetate) and subjected it to special inquiry. The reason for taking the acetate (essence of pears) was that it is most easily obtainable, is comparatively innocuous, and is removed entirely from any organic substance by the process of cooking.

The experiments were made in the following manner:—

1. By placing organs of soft texture of dead animals, such as the spleen, kidneys, and liver, in lightly closed earthenware chambers, in which the acetate of amyl was also placed, in a small open dish, or in cloth or sawdust.

2. By painting over the substance to be preserved with a mixture of size and acetate of amyl.

3. By injecting the body of a rabbit through the arteries with a fluid consisting of glycerine, water, and acetate of amyl.

4. By subjecting the quarters of a sheep to a solution of acetate of amyl, and then burying the parts in melted fat or melted size.

The results of the experiments are as follow:—

By the first method, animal substances may be preserved fresh when the temperature is below 46° Fahr. for three weeks; and when the temperature is above 46° and under 65° for a week. When the temperature is over 65°, the effect of the acetate is very uncertain. The change that takes place in the meat when the effect of the acetate ceases, is a change differing from ordinary putrefaction; it is a process of white odourless softening.

The second method, that of painting over the surface with a gelatinous envelope containing acetate of amyl, was not successful.

The third method, that of injecting the tissues by the arteries, is a good method. The body keeps well, even when exposed to the air at 60°, for four-

* I could make every heart in a room rise ten beats, at least, within a minute without diffusing a detectable odour, as surely as I could vary the motion of a steam-engine by moving the lever.

teen days. I have no doubt that animals injected in this way might be transported wholesale, if enclosed in boxes, during a voyage of three weeks or a month.

The last method, that of bringing the structure into close contact with the amyl-compound, was not successful. I gathered from all these experiments that as antiseptics the amyls require to be so applied that they diffuse through the tissues, and that they continue to act until they are carried away.

ON THE PHYSIOLOGICAL ACTION OF SOME COMPOUNDS OF THE ETHYL SERIES.

Turning from these amyl-compounds, I have next to report on some of the bodies belonging to the ethyl series. For many centuries the ethers have been known and studied as substances possessing peculiar powers over animal bodies; and of late years their use as anæsthetic substances for general and local purposes has given to them additional interest.

The compounds of ethyl which I have specially studied are the oxide, the acetate, the nitrite, and hydrofluoric ether.

Oxide of Ethyl.

The first of these, commonly known as pure ether, rectified ether, or sulphuric ether, is a substance that has been of great interest to the modern physiologist, owing to the fact that it has been applied largely for producing general insensibility to pain by the process of inhalation, and more recently by the local process of evaporation.

Although largely demanded for the first of these processes, the oxide of ethyl that has been sold for the purposes of the medical physicist has been most imperfect. The absurd rule of the Pharmacopœia, which allowed a certain small admixture of alcohol with ether, was the loophole through which the most flagrant abuses were permitted to find way. In fact, when at the commencement of the present year I required oxide of ethyl on a large scale, I could not for many weeks obtain any pure specimen that was not specially made for me: there was no uniformity either in respect to specific gravity, boiling-point, or reaction. These facts fully account for the great diversity of the opinions that have been expressed relative to the action of ether on the bodies of men and animals. The process for obtaining a pure oxide of ethyl is nevertheless very simple, and demands only care, patience, and honesty. Since February last, two thousand pounds weight of absolute ether have been sent out from one London house alone, that of Robbins and Company of Oxford Street.

The pure substance is a colourless, almost inodorous fluid; its specific gravity is 0·716 to 0·720; and 88° Fahr. may be taken as its mean boiling-point.

With a pure and reliable oxide of ethyl, I have been enabled to study the physiological action of the substance with a precision not before attained.

To produce a decided effect on the body of a warm-blooded animal by means of ether, it is best to administer the substance in the form of vapour, charging the air with from twenty to twenty-five per cent., and sustaining the supply steadily. The sensations produced are from the first pleasurable; there is expansion of idea in relation to space and to objects, then confusion with a peculiar sensation of sweetness in the mouth, and at last oblivion. The ether being withdrawn, recovery is very rapid indeed, so rapid that there is scarcely any perceptible stage of recovery: it is a sudden awaking to complete consciousness. In this respect ether closely resembles amylene in its action.

If inferior animals be subjected to absolute ether, and the influence of the vapour on their lungs, heart, and blood be carefully observed, we find that the lungs undergo a slight congestion, that the heart is filled with blood on both its sides, and the venous blood in its transit through the pulmonic circuit ceases to become arterialized. At the same time there is no destruction of the parts of the blood, and the process of coagulation is unaltered. When death is induced by pure ether, the event occurs by arrest of respiratory power. It occurs much in the same way as in death by drowning or by suffocation in carbonic acid. It is a great point to state, and it is most strictly true, that absolute ether has no directly poisonous action upon the heart. I have seen good pulsation of both sides of the heart for forty-five minutes after what may be considered the death of the animal. For this reason the action of absolute ether contrasts most favourably with chloroform. Chloroform kills by its paralyzing action upon the heart; hence when chloroform becomes deadly, it is inevitably deadly because it becomes impossible to remove it from the parts on which it acts to destroy. Ether, on its side, when it begins to cause embarrassment, is acting simply upon the respiration; and it is only necessary to cease to administer it to ensure recovery.

On the whole, after a most careful comparison of the action of absolute oxide of ethyl with the action of other volatile substances possessing anæsthetic properties, I claim for it that it is the safest of all known anæsthetics, that any indifferent effects arising, in past times, from its employment were due to badness of the article, and that science, not less than regard for human life, bids us, when a general anæsthetic is absolutely necessary, go back to ether as the safest agent.

In order to ascertain what would be the effect of actually impregnating the whole body of an animal with absolute ether, I injected one ounce of it into the aorta of an animal (a rabbit) already rendered insensible by the vapour. The result was that the fluid injected began to boil rapidly in the tissues with a free escape of ether-vapour, followed by a sudden, almost instant stiffness affecting the muscles of the whole body. This effect was due to the rapid extrication of heat from the tissues. It was a kind of general freezing of the tissues.

Acetate of Ethyl and Hydrofluoric Ether.

The acetate of ethyl and hydrofluoric ether are chiefly remarkable for their powerful solvent action on all the tissues of animals. They can neither of them be safely administered by inhalation, but both of them may admit of being largely and usefully employed for the destruction and removal of morbid growths. Directed on the blood they break it up absolutely, destroying alike the corpuscles, the fibrine, and the albumen. In short, hydrofluoric ether may be looked on as a universal solvent of the animal tissues; nothing escapes its action except the gelatinous structures, and these not altogether.

Nitrite of Ethyl.

The nitrite, or more correctly the hyponitrite of ethyl, nitrous ether, is made in a similar manner to nitrite of amyl, the difference being that the nitrous fumes are passed through *ordinary* alcohol. The fluid when pure is of a light amber-colour; the specific gravity is 0·950, and the boiling-point 60° Fahr. The physiologist who would work with it, should mix it with absolute ether in fixed proportions—say, of ten, twenty-five, or fifty per cent. It is so volatile that without this precaution it cannot be readily employed.

The action of nitrite of ethyl, as Professor Wanklyn suggested last year,

is closely analogous to the action of nitrite of amyl. Inhaled in quantities of not less than a grain, it induces the same sensation of fulness of the head, rapid action of the heart, and some suffusion of the skin. Animals subjected to it in the proportion of fifteen minims diffused as vapour through a cubic foot of air, die almost instantaneously from sudden failure of the heart, but even up to the moment of death they retain their consciousness and sensibility. The nitrite, consequently, is in no sense to be regarded as an anæsthetic.

Precisely as the nitrite of amyl, nitrite of ethyl, when it kills, leaves the lungs entirely collapsed and so perfectly white that one could assume they had been carefully washed free of blood. This effect is due perhaps to the rapid contraction of the pulmonary capillaries. The blood is changed in colour, the arterial blood being rendered very dark, and the venous of a deep chocolate tint*; the muscles are also all left blanched, as if the death had occurred from loss of blood.

It will be remembered that, in describing the action of nitrite of amyl, I explained that in cold-blooded animals the substance suspended their animation, and that frogs that had been rendered powerless by it, and to common observation inanimate, would sometimes spontaneously recover even so long as nine days after the administration. This same phenomenon I have observed with nitrite of ethyl, together with another even more singular. It is this. If a young animal, say a kitten, be subjected so suddenly to the nitrite as to fall senseless and to appearance dead in or within the minute, it will remain in the same state for six or even ten minutes, yielding no evidence of life: it will not breathe, and the most delicate auscultation will fail to detect motion of the heart. But after a period varying from six to ten minutes it will spontaneously recommence to breathe, and with every movement of expiration a breath sufficient to dull a mirror will pass from the nostril. As the breathing recommences, the heart also begins its work, making a series of distinct intermittent strokes. This condition, looking like an actual return of life, will last so long as half an hour, and will then cease gradually, the animal lapsing again into a state of actual inertia or death.

In concluding this Report I would place the facts I have collected, in respect to the ethyl series, as follows:—

1. Oxide of ethyl, or pure rectified ether as it is commonly called, is the best of all known agents for the production of general anæsthesia by inhalation.

2. The peculiar difference of action between the oxide of ethyl and the nitrite of ethyl is due to the introduction of a new element, nitrogen, into the latter compound. This difference of composition makes the nitrite approach, in action, bodies of the alkaloidal class, strychnine and its analogues.

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* The coagulation of blood is not modified.

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FIBRILLAR CONTRACTION OF THE HEART.

By JOHN A. McWILLIAM, M.D., *Professor of the Institutes of Medicine in the University of Aberdeen.*

MANY years ago Ludwig and Hoffa[1] showed that the application of strong constant currents or faradic currents to the ventricles of the dog's heart causes an abolition of the normal beat. The ventricular muscle is thrown into a state of irregular arhythmic contraction, whilst there is a great fall in the arterial blood pressure. The ventricles become dilated with blood as the rapid quivering movement of their walls is insufficient to expel their contents; the muscular action partakes of the nature of a rapid incoordinated twitching of the muscular tissue. This condition persists for a very long time in the dog, and as Ludwig showed, it is possible to kill an animal in this way—by applying a faradic current to the ventricles. The auricles go on beating rhythmically; they do not participate in the irregular movement excited in the ventricles. These phenomena are familiar to all who have worked much with the mammalian heart; they have been designated by various names—Herz-delirium, Delirium cordis, Fibrillar contraction, Intervermiform movement, &c.

During the last two years I have performed a large number of experiments bearing upon this subject. My earlier investigations were pursued in the Physiological Laboratory of University College, London, and the more recent ones in the Physiological Laboratory of the University of Aberdeen. I have studied the phenomena in question in the hearts of the dog, cat, rabbit, rat, mouse, hedgehog and fowl; both in the young animal and in the adult.

The experiments were all conducted on completely anaesthetised animals; artificial respiration was carried on, a cannula being inserted in the trachea; the thorax was opened in many cases and the heart laid bare; the temperature of the animal was kept up by means of a warm pan.

[1] *Zeitschrift f. rat. Medicin*, 1850, vol. ix.

I shall briefly state the main facts in my investigation.

I. The state of arhythmic fibrillar contraction is essentially due to certain changes occurring within the ventricles themselves. It is not due to the passage of any abnormal nerve impulses to the ventricles from other parts, or to the interruption of any impulses normally transmitted to the ventricles and necessary for their normal co-ordinated action. The condition is not due to injury or irritation of the nerves that pass over the ventricles from the base of the heart.

The ventricles contain within themselves the entire mechanism necessary for the execution of regular co-ordinated beats. They are not dependent for this power on any nervous or mechanical connection with other parts. The continuity of the nerves that pass from the auricles to the ventricles is not at all essential for the execution of regular and effective beats by the ventricles; nor is the mechanical connection between those parts necessary. This is obvious from the fact that when a section is made through the auriculo-ventricular groove so as to separate the ventricles entirely from the auricles, the isolated ventricles can still exhibit their co-ordinated rhythmic contraction. Instead of cutting off the ventricles Wooldridge[1] and Tigerstedt[2] physiologically disconnected the ventricles from the auricles so as to destroy all vital connection between them while the parts were still kept *in situ* and the flow of blood through the cavities of the heart was allowed to go on; the ventricles went on beating in regular fashion though at a slower rate than before. I have frequently performed a similar experiment and have watched the ventricular action as it went on, strong and regular for prolonged periods. It is evident that neither the nervous, nor the mechanical connection between the auricles and the ventricles is necessary for the effective contraction of the latter. It is clear that a mere solution of the continuity of the nerves passing to the ventricles does not destroy the character of the ventricular beat; and it is plain, that such a solution of continuity cannot be the cause of a sudden replacement of the normal systole by the arhythmic fibrillar form of contraction.

Nor is the fibrillar contraction due to irritation of those ventricular nerve trunks. Many observers have noticed its occurrence when the nerve trunks on the surface of the ventricles were being stimulated. But such results appear to be due entirely to an escape of the exciting

[1] *Arch. f. Anat. u. Physiol.* 1883. [2] *Arch. f. Anat. u. Physiol.* 1884.

current to the underlying ventricular substance. For when the nerve-trunk is isolated for some little distance and precautions are taken to prevent an escape of the current, I have never found the nerve stimulation to have any effect at all in inducing the fibrillar contraction. Moreover, an interrupted current readily brings about the arhythmic fibrillar condition when applied to regions of the ventricles where there are no nerve-trunks, e.g. to the very apex of the heart. Even mechanical or thermal stimulation applied to this region may lead to the same result.

The arhythmic fibrillar contraction is undoubtedly a phenomenon depending on changes within the ventricular substance; it can occur quite independently of any mechanical relation of the ventricles to the rest of the heart, and of any nervous relation of the ventricles to the rest of the heart or to the extra-cardiac nerves. The isolated ventricles whether in the quiescent state or beating rhythmically, can by the application of faradic currents be readily thrown into the characteristic fibrillar state, just like the ventricles of an intact heart. And in the intact heart the fibrillar contraction appears to be entirely uninfluenced by nerve excitation of any kind; stimulation of the vagus or any other nerve appears to produce no effect whatever.

Further, the fibrillar contraction can be propagated from one part of the ventricular substance to another quite independently of the nerve-trunks. For if a number of overlapping incisions be made across the long diameter of the ventricles so as to leave the apex attached to the rest of the ventricles by a zig-zag isthmus of tissue, it often occurs that fibrillar movement excited by faradisation in the apex travels along the zig-zag isthmus of connecting substance, and so comes to pervade the whole of the ventricular tissue.

II. The arhythmic fibrillar contraction is not necessarily dependent on the destruction or paralysis of a co-ordinating centre located in any particular part of the ventricles.

Kronecker and Schmey[1] succeeded in throwing the ventricles of the dog's heart into the state of fibrillar movement by piercing with a needle a certain limited part of the ventricular septum near the junction of its upper and middle thirds. This result these investigators attributed to the destruction of a centre located in that region, and normally presiding over the co ordination of the ventricular muscle in the execution of its regular beat.

[1] *Sitzungsber. d. Berliner Acad.* 1881.

There is conclusive evidence that all cases of fibrillar contraction of the ventricles cannot be explained by such a hypothesis—the destruction of a co-ordinating centre localised as indicated above. The fact that recovery may take place—that the ventricles may resume their co-ordinated rhythm, controverts the idea of the actual destruction of a centre essential for co-ordination. Such recovery I have witnessed in several instances in the dog's heart, and in a very large number of instances in the hearts of other animals (cat, rabbit, rat, mouse, hedgehog and fowl). Recovery occurs with different degrees of facility in different animals and in different conditions in the same animal. In the dog, recovery occurs with much difficulty and only after the fibrillar contraction has lasted for a considerable space of time; indeed there very frequently is no recovery apparent—the ventricles may not recommence beating after the inco-ordinated quivering movement has ceased. At times however a number of regular beats are seen after the termination of the fibrillar contraction. A depression of the excitability of the ventricular tissue often appears to favour recovery.

In most mammals recovery commonly occurs. Very often it is possible to induce the fibrillar movement again and again, complete recovery occurring in the intervals, when the normal systoles are seen. In young mammals, fœtal or after birth, recovery appears to be the rule; the fibrillar movement is only a temporary condition, and soon gives place to normal beats.

In birds also I have frequently observed complete recovery. The fibrillar condition is readily induced by faradisation. The ventricles exhibit the characteristic quivering movement; they become dilated with blood. In consequence of the stagnation of blood in the ventricles the auricles also become gorged and may become so over-distended that they temporarily stop beating; asphyxial convulsions occur in the skeletal muscles. After a time however the fibrillar movement ceases, the ventricles remain quiescent for a little time, then give a regular co-ordinated beat and the action of the whole heart proceeds in the normal fashion. These phenomena can by the application of a current of the proper strength be induced again and again.

Further, in addition to the evidence afforded by the recovery of the ventricular beat, there is the fact that the arhythmic fibrillar movement may very readily be induced by means that are not capable of destroying a deep-seated co-ordinating centre e.g., faradic, mechanical, or thermal stimulation of the surface of the ventricles even at the very apex.

Since it is certain that the arhythmic fibrillar movement is not

necessarily due to the actual destruction of a co-ordinating centre, there next arises the question as to whether the fibrillar contraction may be due to the temporary paralysis of such a centre as that indicated by Kronecker—of the existence of which no histological evidence has, as far as I am aware, been advanced.

I shall at a later stage of this paper have to adduce some evidence regarding the action of certain poisons which when injected into the blood lead to the occurrence of fibrillar contraction of the ventricles. Such a result might be regarded as due to the paralysis of a hypothetical co-ordinating centre. And the fibrillar contraction caused by stimulation (electrical, mechanical &c.) of the ventricular surface might be explained in a somewhat similar fashion. For it is conceivable that such stimulation might give rise to strong abnormal afferent impulses with the result of deranging or paralysing the action of the co-ordinating centre; the paralysis might be a temporary one or might be permanent according to the particular circumstances in each case.

But there is strong evidence against the adoption of such a view—against the idea that the phenomena are due to the behaviour of a definite co-ordinating centre localised above the middle of the ventricular septum in the dog's heart. For the influence of such a centre does not appear to be at all essential for the production of co-ordinated and efficient beats. The amputated apex—the lower third or fourth of the ventricles—both in the dog and in all other mammals I have examined,—is capable of executing co-ordinated beats when it is entirely removed from all possible relation with any co-ordinating centre high up in the ventricular septum. This one can verify by the rough but conclusive experiment of tying the freshly removed apex of a vigorous heart upon a double cannula through which the cavity of the left ventricle can be filled with blood; the propulsion of fluid at each beat of the isolated apex can be readily observed. The visible character of the beat may also be noted, and the co-ordinated nature of the contraction causing a marked diminution of the cavity at each systole may be felt with the finger tip inserted into the cavity of the left ventricle. It is obvious then that the paralysis of a co-ordinating centre in the upper half of the ventricular septum would not necessarily cause a loss of co-ordination in the contraction of the whole of the ventricular muscle.

Further there is the fact that the apical portion of the ventricles—capable as it is of performing regular beats—can be thrown into a state of fibrillar contraction by the usual means, e.g. the application of a

faradic current. In the isolated apical part of the ventricles (in all the mammals I have examined) I have been able to excite the fibrillar contraction again and again, recovery occurring in the intervals, and co-ordinated beats being given in response to single stimuli applied during those intervals. It appears then that the behaviour of the intact ventricles and of the entire isolated ventricles both as regards co-ordinated single beats and as regards the fibrillar contraction can be reproduced in the isolated apical portion; and hence we may conclude that these phenomena are not necessarily dependent on the condition of any co-ordinating centre in the upper half of the ventricles.

III. The outstanding features of the arhythmic fibrillar contraction are:—

(1) The complexity of the movement.

(2) Its persistence.

(3) Its rapidity.

The complexity of the fibrillar movement appears to be in direct relation to the complex arrangement of the muscular fibres of the ventricular walls.

In the ventricles we have bundles of muscular fibres forming by their interlacement a texture of remarkable complexity. It appears that the complex quivering movement depends on the passage of rapidly repeated waves of contraction along the complexly arranged muscular bundles which are enclosed by connective tissue and joined to one another by cross-branches. It is readily conceivable that contractions simply conducted along the muscular fibres should be transmitted with unequal rapidity along the ventricular walls and should reach the same part of the ventricular wall at different points of time. Some bundles of fibres are in a state of contraction while neighbouring bundles are relaxed and so instead of a co-ordinated contraction causing a definite and (in the case of the left ventricle) concentric narrowing of the ventricular cavity, there occurs an irregular and complicated arhythmic oscillation of the ventricular walls which remain in a position of diastole.

That the complexity of the fibrillar movement in the grown animal depends on the character of the muscular structure is illustrated by the appearances presented by the corresponding movement in the hearts of foetal and young animals. In these as long as the structure of the ventricles is simple the rapid movement excited by faradization is of a simple character. And just as the complexity of the muscular structure

increases in the growing animal so does the complexity of the movement obtained. There can be observed a complete gradation from the simple movement excited by faradisation in the ventricles of the mammalian foetus or of the chick (a movement much resembling that seen in similar circumstances in the comparatively simple ventricles of cold blooded animals) to the very characteristic and striking complexity of the fibrillar contraction in the adult mammal or bird. It is obvious that the nature of the muscular structure is a cardinal feature, and it is not very evident why such should be the case if the condition is due to derangement of a nervous mechanism causing it to discharge irregularly; for a deranged nervous mechanism discharging irregularly might cause an equally irregular movement whether the muscular arrangement is simple or complex.

The simpler character of the movement excited by faradisation in the auricles of warm-blooded animals is probably due to the simpler histological structure of the auricular walls and the simpler mode of propagation of the normal contraction.

The persistence of the fibrillar contraction appears to depend on the high excitability of the ventricular tissue.

When the fibrillar contraction has been brought about by stimulation of the ventricles, the prolonged continuance of the movement, after the cessation of the exciting cause is a striking feature. It appears to be a result of the excitation of a highly excitable, and probably highly rhythmic tissue. The duration of the movement, varies in each instance with the excitability of the ventricular muscle. It can easily be shown, that in certain depressed conditions of the ventricular tissue, the duration of the fibrillar movement, induced by stimulation is much diminished, and when the ventricular excitability is very much lowered, (by gradual cooling, exhaustion etc.) it frequently occurs that the fibrillar contraction does not persist after the stimulating current is discontinued; it simply occurs during the passage of faradic current and passes off at the cessation of that current. Indeed, in some instances it may be found that the fibrillar contraction cannot be excited at all by faradisation, whilst the ventricles are still capable of executing single beats. A certain degree of excitability is necessary for the production of the fibrillar contraction in response to stimulation.

Similar facts with reference to the duration of movement, after the discontinuance of the exciting cause, may be seen in the hearts of cold-blooded animals. In the heart of the eel, for example, where there are a number of parts possessed of different degrees of excitability and

rhythmic power, very marked differences are to be observed in the behaviour of the several parts after a stimulating current has been temporarily applied. The sinus with the basal wall, and the canalis auricularis, the auricle and the ventricle, form a descending series as far as rhythmic power is concerned, and they present similar differences as regards the after effects of stimulation. In the ventricle a short period of moderate stimulation excites a movement, which usually terminates immediately or very soon after the end of the stimulation; the precise period at which the movement terminates, varies according to the strength of the exciting current and the excitability of the ventricle; in a very excitable ventricle (in situ with the normal circulation intact) the movement may persist for some little time after the stimulation has ended. In the auricle the movement usually persists longer, and in the sinus a great deal longer still. Indeed, in the sinus a single stimulation can often lead to a series of beats, whereas in the case of the auricle, and still more in the ventricle a single stimulation excites but a single contraction. Moderate heating of the tissue causing a rise in its excitability usually leads to a marked increase in the persistence of the movement excited by a short period of stimulation.

Similarly in the mammalian heart the duration of the fibrillar movement after the end of the period of excitation varies. In the fœtal heart it lasts but a short time, and in adult hearts that have been much depressed by exhaustion and by gradual cooling the fibrillar movement usually passes away very much earlier than it does in a more excitable heart.

The mechanism of the movement, as will be subsequently stated, appears to be such as to involve its continuance as long as the excitability of the ventricular tissue is sufficiently high.

The cause of the great rapidity of the series of contractions that course over the ventricular fibres during the state of fibrillar contraction will be considered later on.

IV. The arhythmic fibrillar contraction is in one class of cases a phenomenon of irritation induced by the action of various recognised stimulants.

The state of excitement generated in the muscular tissue appears to resemble in some respects the state of excitement obtaining in the nerve cells of the cortex cerebri during an attack of epileptiform convulsions induced by strong stimulation.

It has been stated that the duration of the fibrillar contraction

depends on the excitability of the ventricular tissue. In like manner the readiness with which the fibrillar contraction can be excited by stimulation, is in close relation with the ventricular irritability. In a depressed heart it is frequently very difficult to produce the phenomenon in question by stimulation; very powerful currents are necessary.

On the other hand when the excitability is heightened, it is easy to induce the fibrillar contraction. The occurrence of this phenomenon in response to stimulation is retarded and its duration shortened by conditions that depress the excitability of the cardiac muscle; its occurrence is favoured and its duration prolonged by causes that augment the cardiac irritability. In an exhausted heart it can frequently be seen that faradisation of the right ventricle leads to the occurrence of the fibrillar contraction in both ventricles, when such a result has ceased to be obtained by faradisation of the left ventricle. The difference in the behaviour of the ventricles, in this respect appears to be due to the greater persistence of the excitability in the right ventricle as compared with the left.

When the fibrillar contraction has been excited by stimulation it can often be arrested by the cautious application of depressant measures calculated to diminish the excitability of the ventricular tissue, e. g. deprivation of blood supply and cooling.

The readiness with which the ventricles are thrown into the fibrillar condition varies remarkably in different conditions of the cardiac tissues. In a normally-contracting and vigorous heart it usually requires a faradic current of considerable strength to produce the result in question. And it is not easy in these circumstances to induce the fibrillar contraction by mechanical or thermal stimulation. But in certain changed conditions of the organ it becomes extremely easy to throw the ventricles into the fibrillar movement. An exceedingly weak faradic current, a touch with a hot wire, a mere scratch with the point of a pin, slight friction of the ventricles against the cut end of a rib, or even slight pressure with the finger, are each of them sufficient at such times to excite the fibrillar contraction. The precise conditions in which there is such a remarkable sensitiveness to certain forms of stimulation are difficult to define; I have frequently observed such a sensitiveness when the action of the heart has been deranged or impaired by various causes—among others by a temporary arrest of the respiration or by a great fall in the blood-pressure leading to anaemia of the cardiac tissues &c.; the phase of increased sensitiveness seems to be a transitory one.

The frequent occurrence in the ventricles of such phases of extreme

readiness to assume the fibrillar form of contraction appears to me to be of great importance with regard to the question of electrical stimulation of the heart in man during sudden cardiac failure (syncope during the administration of anaesthetics, &c.). It is obvious that the use of faradic currents of any strength is attended with grave danger in such cases. For although Von Ziemssen and others have applied the induced current to the human heart without any serious results, the conditions were different in such cases. They experimented with normally-beating hearts, the tendency of which to assume the fibrillar form of contraction is strikingly less than what frequently obtains in hearts placed in abnormal circumstances—necessarily present in those cases where the faradic current is employed clinically.

But although the exposed heart in the opened thorax may be readily thrown into the arhythmic fibrillar contraction by faradisation, it may be urged that possibly the normally-beating heart in the intact thorax, is not similarly affected. I have on several occasions introduced a fine platinum wire electrode through the chest wall so as to come in contact with the ventricles, and have then faradised, the other electrode being applied to the outside of the chest wall; the fibrillar contraction was at once induced.

By the use of single induction shocks I have never seen the fibrillar contraction excited either when the shock is passed through the thoracic walls or when it is applied to the exposed heart. The single induction shock seems to be free from the dangers accompanying the use of the faradic current. Hence I have urged its superiority as a means of cardiac stimulation, in a paper to be read at the Ninth International Medical Congress at Washington.

The extreme readiness with which in certain circumstances the ventricles are thrown into the fibrillar contraction by any form of irritation, mechanical as well as electrical, renders it apparent that the experiment of puncturing the heart in order to destroy a certain part is attended with many difficulties. For very frequently the mere mechanical irritation would be amply sufficient to produce all the phenomena usually resulting from faradisation. And this condition of increased sensitiveness to irritation and increased tendency to assume the fibrillar mode of contraction appears to occur with special frequency and to a very marked degree in the heart of the dog.

V. In another class of cases the fibrillar contraction is induced by the more or less sudden action of certain influences of a depressing nature.

The injection of certain salts (e.g. bromide of potassium in strong solution) into the blood appears to induce the fibrillar condition in a very short space of time (frequently within one minute). A dose of about 0·1 gramme is sufficient in the hedgehog.

When such an injection is made (cat and hedgehog) there is almost immediately a marked change in the character of the systole. The origin and course of the contraction become very apparent both in the auricles and in the ventricles. In the former it passes forwards from the entrance of the great veins; in the latter it sweeps from the base of the heart towards the apex; on the front of the heart the contraction can be most distinctly seen beginning at the conus arteriosus and passing downwards. The ventricles become dilated with blood; the contractions are evidently unable to empty the cavities. When the heart is in a depressed state no further important change may be observed; the contractions gradually become weaker and slower until they cease altogether. But in the case of a vigorous heart there usually occurs a striking change—a short time after the injection of the bromide. The ventricles go into the state of fibrillar contraction with its usual features.

I have not as yet seen any complete recovery from the incoordinated condition produced in this way. The ventricles do not seem to recover their power of giving regular beats. Single contractions may occur after the rapid quivering movement has ceased but they appear to be fibrillar in their nature. And any contractions excited by single induction shocks in such circumstances appear to be of the same character.

After the injection of a solution of atropin I have observed somewhat similar phenomena; here however the fibrillar movement was arrested by the injection of pilocarpin, and complete recovery of the ventricular beat took place.

I have on some occasions observed phenomena of the same kind when an animal (cat) was suddenly and powerfully cooled by the application of a mixture of ice and salt to the surface of the skin and the insertion of an ice bag into the abdominal cavity. After the cooling had gone on for a time, the ventricles suddenly passed into the state of fibrillar contraction.

See and others have described the occurrence of a similar fibrillar movement in the dog's ventricles as one of the results of sudden occlusion of the coronary arteries.

VI. The arhythmic fibrillar contraction is fundamentally different from a rapid series of normal contractions. Its

genesis probably assumes in all cases one or other of two forms.

It is probable that the normally contracting ventricles possess within themselves certain co-ordinating arrangements in virtue of which the muscular contraction constituting a normal beat rapidly traverses the whole of the ventricular substances, causing a uniform or nearly uniform contraction of all the fibres of the ventricular walls thus leading to a concentric narrowing of the ventricular cavity and a consequent expulsion of its contents. The co-ordinating arrangements appear to exist in the lower portion of the ventricles as well as in the upper portion; for it has been seen that the apical part can execute co-ordinated beats when severed from the rest of the heart.

A normal co-ordinated contraction appears to be essentially different from the individual beats that may be seen after poisoning with bromide of potassium and occasionally in other conditions. In the latter case the contraction is obviously of a peristaltic nature; the contraction wave can be seen passing over the ventricular surface in definite directions. The contraction may be caused to start at any part in the ventricular substance by the application of a single direct stimulus; the contraction begins in the stimulated area and hence spreads over the rest of the ventricles; a phenomenon precisely similar to what one sees in the hearts of cold-blooded animals.

The peristaltic contraction evidently passes over the various interlacing bundles at different points of time, so that the whole thickness of the ventricular wall at any part is never uniformly contracted. Hence there is a wiry feel distinctly perceptible when the ventricles are held between the fingers as the peristaltic contraction is passing through its substance; certain fibres are hardened by the presence of contraction in them while neighbouring fibres are relaxed and soft. Such peristaltic contraction appears to be incapable of emptying the ventricular cavities of their contents; it appears to be essentially different from a co-ordinated beat however slow the latter may be. A co-ordinated beat never presents a wiry feel to the finger; it gives the sensation of a steady and uniform hardening of the muscle substance—of precisely the same nature as the hardening one feels in a skeletal muscle during its contraction. The contraction seeems to involve as a whole the complicated interlacement of fibres forming the ventricular wall.

It appears then that the ventricles are capable of executing two forms of beat. One is the co-ordinated contraction seen in the normal

heart and capable of being excited by artificial stimulation (e.g. by single induction shocks) either in an intact heart, or in the fresh and vigorous excised ventricles or ventricle-apex. The other form of beat is the inco-ordinated or simple peristaltic contraction, such as may be seen after poisoning with bromide of potassium and in certain other conditions.

VII. The state of arhythmic fibrillar contraction (delirium cordis &c.) appears to be constituted by a rapid succession of inco-ordinated peristaltic contractions—a condition that can be brought about either (1) by the influence of certain depressing or paralysing agents upon the ventricular tissue, or (2) by the application of certain forms of stimulation to the ventricular tissue.

In the first class of cases the depressing influences alluded to probably throw out of gear the co-ordinating arrangements while they leave the muscular irritability intact—or it may be even augmented largely. Then the excitable (and probably highly rhythmic) muscle contracts, but its excitation instead of assuming the form of a normal beat becomes a peristaltic contraction wave along the complexly arranged and inter-communicating muscular bundles. And if the ventricular muscle is in an excitable state there would naturally occur a rapid series of such inco-ordinated peristaltic contractions. For apart from the possibility of rapid spontaneous discharges of energy by the muscular fibres, there seems to be another probable cause of continued and rapid movement. The peristaltic contraction travelling along such a structure as that of the ventricular wall must reach adjacent muscle bundles at different points of time, and since these bundles are connected with one another by anastomosing branches the contraction would naturally be propagated from one contracting fibre to another over which the contraction wave had already passed. Hence if the fibres are sufficiently excitable and ready to respond to contraction waves reaching them there would evidently be a more or less rapid series of contractions in each muscular bundle in consequence of the successive contraction waves reaching that bundle from different directions along its fibres of anastomosis with other bundles. Hence the movement would tend to go on until the excitability of the muscular tissue had been lowered, so that it failed to respond with a rapid series of contractions. Then there might be some isolated peristaltic contractions, such as I have often seen after the cessation of the fibrillar movement.

In the second class of cases—when the fibrillar contraction is excited by stimulation (e. g. faradisation of the surface of the ventricles) there appears to be a condition of violent excitement set up in the muscular tissue. The excitation of the muscular fibres travels peristaltically producing the characteristic movement; the inco-ordinated contraction of the various fibres may be most distinctly realised when the ventricles are held between the forefinger and thumb; there is a sort of wriggling sensation to be felt as the individual muscular bundles become hard and wiry while the contraction is passing over them in succession. The co-ordinating arrangements of the ventricles are powerless to regulate and guide the contractions; those co-ordinating arrangements are very possibly not paralysed nor rendered incapable of action, but they are temporarily superseded and rendered inoperative by the excessive state of excitement which pervades the muscular fibres—just as the cerebro-spinal co-ordinating mechanism might be rendered impotent by strong local stimulation of the skeletal muscles. When the fibrillar movement having become less rapid has at length stopped its duration depending on the excitability of the muscle—there ensues a pause.

Then there may be a recovery of the normal co-ordinated beat provided the fibrillar condition (and consequent blood stasis) has not lasted so long as to involve a paralysis or death of the co-ordinating mechanism.

When the last mentioned change has taken place, any beats that may occur are of the fibrillar character.

VIII. The phenomena resulting from faradic stimulation of the auricles differ in various respects from those seen in the ventricles.

The application of the current sets the auricles into a rapid flutter, the rapidity of which largely depends upon the excitability of the auricular tissue and the strength of current employed. The movements are regular; they seem to consist of a series of contractions originating in the stimulated area and thence spreading over the rest of the tissue. The movement does not show any distinct sign of inco-ordination; it looks like a rapid series of contraction waves passing over the auricular walls. The difference between this appearance and that seen in the ventricles probably depends on the simpler structure and arrangements obtaining in the auricles.

The persistence of the movement after the discontinuance of the stimulating current varies according to the excitability of the auricular tissue and strength of current employed. In very excitable conditions

the rapid movement lasts for a considerable time; in depressed states the movement ceases almost immediately after the stimulation has ended. The persistence after the use of a strong current is, *cæteris paribus*, usually very much greater than when a weak current has been employed to excite the fluttering action.

IX. The movements excited by faradisation in the auricles and ventricles differ very markedly in their relation to the inhibitory influence of the vagus nerve. The fibrillar movement in the ventricles appears to be entirely unaffected by vagus stimulation; the fluttering movement of the auricles can be checked or arrested by the influence of the vagus.

Sometimes, when the auricles are very excitable the fluttering movement is entirely suspended during vagus stimulation only to reappear when the inhibitory influence has passed away. The vagus influence appears to act by weakening the individual contractions to the point of invisibility. At other times the contractions are markedly weakened without being rendered invisible. Often the movement is entirely arrested and does not recur; the normal action of the auricles goes on after the period of inhibition has passed.

The relation of the vagus nerve to the auricular muscle seems to be entirely different from the relation of that nerve to the ventricular muscle.

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MDCCCLXXXIX.

cases has any evil resulted from the treatment; and previously to the present case I have never heard patients complain of headache during its continuance. I have consequently never before had occasion to give bromide of potassium in combination with the chloral. This patient, however, had suffered much from headache, as well as pains in other parts of the body, for a long time before the treatment was commenced, so that the pain could not be ascribed to the chloral, and she is now, indeed, comparatively free from it, suffering only at intervals. In one other respect, also, my treatment of this case has been different from others which have preceded it. During the second period she was kept asleep for three weeks, though I had never previously allowed the time to exceed two weeks. I was tempted to prolong the period in this case, because the movements were distinctly diminishing, and the patient was taking her food well and complaining less of headache. Perhaps, however, it would have been safer had she not been kept this extra week under the influence of the chloral, even though it might have involved another two weeks' sleep after an interval for the cure of the chorea. Certainly, on awaking (although the choreic movements had nearly disappeared) she lapsed for a time into a very unsatisfactory condition mentally. She became extremely emotional and full of fancies, one might almost say delusions; but then it must be recollected that she was a very weak and unstable subject, who had probably dropped into much the same sort of condition after the accident to the child, when for many days she was, as she said, "light-headed," not knowing what she did. During part of this period she menstruated, after an interval of nearly eight months.

In the course of a few days, under the influence of treatment and careful management, she passed out of this state, assumed a cheerful and natural mental condition, and began to improve in all ways. It is worthy of note moreover, that while under our care she never had a single one of the "fainting" attacks, or fits, from which she had been suffering for the previous three years. During the whole period of the treatment the patient's general nutrition was well maintained, and the careful records which were kept of the temperature, pulse, and respiration, showed that the great vital functions were in no way affected unfavourably. On a few occasions for a short time her temperature dropped to rather a low point, but on the whole it was well maintained. During the time of actual sleep, also, the unnatural frequency of the pulse and respiration which had previously existed was kept in check. There is nothing to show, therefore, that any harmful effect was exercised upon the patient by the large quantities of chloral which she took in order to maintain sleep during these two periods of two and three weeks respectively.

But now let me say a word or two as to the kind of cases for which I consider such a mode of treatment advisable. In all ordinary cases of chorea I never think of having recourse to it. With rest and very various kinds of treatment, in the course of six to twelve weeks such cases recover. Then, again, in the most acute and severe cases of chorea, in which the temperature is raised, and the movements are violent and continuous, with or without delirium or maniacal symptoms, I have never yet tried this mode of treatment, and should not recommend its adoption. It is, I think, especially applicable to a class of cases in which there is no fever and no heart disease, but where the movements are usually severe and continuous, and have so continued for months or years without abatement. These are the cases which I consider most suitable for such a method of treatment, and it is not the less applicable should there be, as in the present instance, a possible hysteric element about the case, provided always that the movements cease absolutely during sleep. For you must not forget that the essential object of the treatment is to ensure the prolonged cessation of the unnatural movements by producing sleep. I attach little importance to any supposed curative influence of chloral itself over the chorea, except through the intervention of the sleep which it induces. This drug has been used simply because it was originally recommended for the purpose, I think, by Bouchut, and because no evil effects have followed its use. Paraldehyde, which might otherwise be suitable, has too nauseous a taste to be employed. Sulphonal might prove, however, to be quite as efficacious in procuring continuous sleep as chloral. The difficulty we have here to contend with is its great insolubility and slower action, which would probably involve a distinct lengthening of the interval of wakefulness on each repetition of the drug. Whichever medicine be used, however, the great object should be to give no more than is absolutely needed to maintain the continuous sleep, and therefore all accessory means, such as quietude, slightly darkening the room, the expeditious administration of fluid nourishment five or six times a day whenever the patient awakes, and the use of the bedpan, should be had recourse to. The period in which the patient is awake should, as far as possible, not exceed half an hour at a time.

There is another advantage attaching to this method of treating hospital patients which is worthy of mention. You will recollect that it is mentioned in the history of our patient that she was under treatment for four months in the Edinburgh Infirmary, and that for nine weeks of this time she was kept in an isolation ward. Those of you who saw the patient when she was first admitted to this hospital will recollect how greatly the movements were aggravated whenever we came to stop at her bedside to inquire into her condition. The frequent repetition of this process would certainly have been most adverse to her recovery, and had I not intended to treat her by prolonged sleep, after carefully observing her condition for a few days, I too should certainly have kept her under comparative isolation, so that she might be free from the perturbing effects of frequently seeing a number of students round her bed. By the method I have detailed to you, however, even the worst of such cases may be successfully treated in the general wards of a hospital; and I recommend it to you also as an occasional method which you may find hereafter of great use in private practice, when the aid of skilled nurses can be obtained, in the treatment of protracted and aggravated cases of chorea. Without such aid this method of treatment should never be attempted.

ABSTRACT OF

The Croonian Lectures

ON THE

RELATIONSHIP BETWEEN CHEMICAL STRUCTURE AND PHYSIOLOGICAL ACTION.

Delivered at the Royal College of Physicians of London, June, 1889,

BY T. LAUDER BRUNTON, M.D., F.R.S.,

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LECTURE III.

WE now pass from the prevention of disease to its control and cure. The power which many antiseptics possess of reducing temperature and relieving pain renders them of immense value in treatment; and the association supplies a natural link by which to pass directly to the consideration of antipyretics. Many new facts have been ascertained concerning the effects of members of the aromatic series upon the functions of protoplasm. Isolated cells, such as leucocytes, exhibit during life contraction and extension of protoplasm, which result either in locomotion and diapedesis, or are concerned in their nutrition and the manifestation of vital phenomena. Kühne showed that isolated cells have the power of absorbing oxygen, by observing under the micro-spectroscope their action upon a solution of hæmoglobin; and Pflüger by his investigations on the gases of the blood demonstrated the occurrence of oxidation and reduction in the tissues, similar results being obtained in living men by Pettenkofer and Voit; and it was found by Harley that the absorption of oxygen and elimination of carbonic acid by blood could be altered by admixture with various poisons. With these observations is associated the discovery of Binz, that quinine has the power to lessen such processes, and by so doing reduces the body temperature. Substances differ in the degree of affinity which they have for oxygen, it being greater in some and less in others. Thus it happens that we might draw up a scale containing a number of bodies, each of which would have a greater affinity for

oxygen than the one above and less than the one below it. Each one would therefore abstract oxygen from the one above it, and act as a reducing agent towards it; while it would give up oxygen to the one below it, and thus act as an oxidising agent. This affinity for oxygen is greatly altered by the reaction of the fluid in which it is exercised, so that a body having a powerful reducing action in an alkaline solution may have none at all in one which is acidulated. Processes of oxidation or reduction may also be originated by electric currents, and are particularly effective when either of the poles are composed of an oxidisable or reducible material, the process also being reversed with reversal of the current. By means of alternating currents of this sort, Drechsel has succeeded in converting carbonate of ammonia into urea, and has rendered it probable that alternate oxidation and reduction are constantly occurring within the tissues of the living body, though the exact place and manner in which they take place have still to be made out. By the introduction of various aniline compounds into the circulation Ehrlich has been able both to show that these processes go on, and that they do so with very different intensity in the different organs and tissues, occurring most rapidly in those whose functional activity is great, as in the heart, brain and muscles. The power which living cells exert in this direction is almost incredible; alizarin blue, which can only be reduced by the most powerful agents outside the body, such as by boiling with caustic potash and grape sugar, is completely reduced by the liver and cortical substance of the kidney during life, and by these organs and the muscular substance after death; the alteration being marked by more or less complete loss of colour, a change from blue to white. When first injected, alizarin blue circulates in the blue state, and colours even the serum and fluid of the anterior chamber of the eye. Most of the organs of the animals injected have a blue colour, with the exception of those just mentioned, showing that the reducing power necessary to change it from blue into white is greater than most of the tissues possess. By using indophenol blue, which is more easily reduced, Ehrlich found that reduction occurred in almost all the tissues; so that the reducing power of the cells lies between the limits fixed by these two substances. The occurrence of reduction in the tissues indicates that they are not saturated with oxygen, though they possess a sufficient amount to enable them to carry on their functions. In this respect they resemble a damped furnace, which permits slow combustion, but may at any time be excited to more vigorous action. The supply of oxygen must be very free in the heart and brain, since they do not reduce alizarin blue during life, but do so after death or under electrical stimulation. In the living protoplasm of a cell Ehrlich supposes there are three zones: one in which it is saturated with oxygen; another, functionally active, in which the degree of saturation varies; and a third, which is always unoxidised, and exerts an attraction for the oxygen of the blood or lymph. The affinity of protoplasm for oxygen may well be supposed to vary, as that of indophenol white does, according to the reaction of the surrounding fluid. This affinity is strongest in an alkaline solution, becomes much weaker in a neutral one, and in an acid is completely destroyed, so that reducing agents quickly convert the blue into white, though in an alkaline medium they have no such effect. The association of varying reaction in cells with these changes in colour of the indophenol was demonstrated by Ehrlich, by introducing another aniline colour with a delicate reaction to acidity, the reduction of the indophenol blue always occurring when an indication of acid reaction was given by the other. The process of combustion in a cell is, then, diminished or arrested by the formation of acid, though oxidation begins again as soon as the circulating fluids have restored the alkalinity. A sort of self-acting mechanism is thus exerted by the cell, inasmuch as the products of its activity are acid, so that functional exercise sets a limit to itself. A further regulating principle is afforded by the paraplasm or cell juice which surrounds the protoplasm and shuts off the latter, when contracted, from the surrounding oxygen of the blood; the supply of oxygen being reduced according as the protoplasm is contracted to a small bulk and the surrounding layer of paraplasm is thicker. If we suppose that stimulation of the thermal centres causes contraction of the protoplasm in muscle and gland cells, so that its attracting surface to oxygen would be diminished, and the resistance to the passage of oxygen through the paraplasm increased in the manner alluded to, we can see that oxidation would probably be greatly lessened and the temperature correspondingly reduced.

From the experiments of Binz upon quinine two very striking facts resulted: one, that the drug had the power to lower temperature in febrile conditions not due to malaria; the other, that quinine had an extraordinary power of arresting the movement of leucocytes, causing them to draw in their pseudopodia and contract into a sphere. That this will diminish the surface exposed to oxidation in the blood stream is obvious, though the change can hardly interpose any obstacle between the protoplasm and the oxygen contained in the surrounding serum. The case, however, is different, if we take such a structure as the pigment cell of the frog. Here the protoplasm does not always completely fill the cell; occasionally it stretches out into all the ramifications of the branches, allowing a large surface for oxidation, and being separated by a very thin layer of paraplasm from the nourishing fluid. When the protoplasm contracts, it forms a rounded mass in the centre, presenting a minimum surface for oxidation, and simultaneously a maximum thickness of paraplasm between it and the cell wall. If we suppose quinine produces a similar effect upon the cells composing the tissues of the body, we can at once see how it will lessen oxidation and act as an antipyretic; and this whether it acts directly or through the thermal centres. This hypothesis also enables us to explain the fact that antipyretics have comparatively little action upon the temperature of the healthy body, for in this state the cell protoplasm is believed to be in a state of chronic contraction, and already reduced nearly within its narrowest limits.

The variation in colour produced by contraction of pigment corpuscles in the frog has been alluded to by Edward Jenner in connexion with the occurrence of rheumatism, as well as with the swelling of dry wood under the influence of an atmosphere laden with moisture. In his poem on the signs of rain he says—

> "Hark! how the chairs and tables crack;
> Old Betty's joints are on the rack;
> The frog has lost his yellow vest,
> And in a russet coat is dressed."

The darker colour is due to the extension of protoplasm containing dark-coloured granules throughout the cell, while the yellow colour results from contraction of the protoplasm drawing the granules together into a compact clump, and allowing the yellow colour of the subjacent cells to appear. In some experiments recently made with Dr. Cash, contraction of the pigment cells was a prominent feature in poisoning by some members of the aromatic series.

The power of producing anæsthesia and abolishing reflex action is common to most of the substances of the fatty or alcoholic series, and was first noticed in connexion with ethylic alcohol, for Solomon makes the drunkard say, "They have beaten me, and I felt it not"; and apparently he determines to use it deliberately to prevent pain, for he says, "I will seek it [strong drink] yet again." The power, however, is greatly influenced by two circumstances: (1) the position of the radical in the fatty or aromatic group, and (2) the nature of the element or alkyl with which the radical is combined.

To revert here to the illustration employed in the first lecture, let us imagine a knife fastened to the end of a fishing-rod. The rod represents the radical and the number of joints indicates its position in the series. Every addition of carbon with hydrogen makes the substance heavier and more cumbrous. Petroleum ether, which is a mixture of pentane C_5H_{12} and hexane C_6H_{14}, is a light mobile fluid; higher members of the series form the soft paraffin or vaseline, while those that are higher still form hard paraffin. The instrument consisting of a fishing-rod and a pocket-knife can be altered by changing the knife as well as by altering the number of joints in the rod. So in the case of the alkyls, their action differs according as they are combined with hydrogen in the hydrides, with hydroxyl in the alcohols, or with oxygen and hydroxyl in the acids. Moreover, both the physical condition and physiological action may be changed by replacing hydrogen by other elements. Thus, if we replace the atoms of hydrogen in marsh gas, CH_4, by chlorine, with an atomic weight of 35·5, that of hydrogen being only 1, we convert the light gas with a molecular weight of 16, into the heavy liquid chloroform,

with a molecular weight of 119·5. If in place of chlorine we introduce three atoms of iodine, with a weight of 127, the molecular weight of the whole compound becomes 394, and in place of a gas or heavy fluid we get a solid, like iodoform. The physical condition of the substance may be influenced also by the number of atoms of hydrogen so replaced, intermediate substances being formed; thus monochlormethane is a gas at ordinary temperature, but can be condensed to a liquid, boiling at 22°. Dichlormethane is a heavy liquid, boiling at 41°, and trichlormethane or chloroform is still heavier, and boils at 61°. The anæsthetic, then, can be rendered denser and its molecular weight increased by replacing more and more atoms of hydrogen with heavier ones of chlorine or iodine.

All substances belonging to the alcoholic series possess the power of abolishing the excitability of the nerve centres within the body, affecting them in the inverse order of their development, destroying first the functional activity of the highest ideational and volitional centres in the cerebrum, those centres which are the latest to be developed, and which not only raise men above the animals, but raise individual men above their fellows; whilst the lowest, most simple, and at the same time most automatic centres are affected last. The perceptive and motor ganglia, the reflex centres of the cord, the vasomotor and respiratory centres, and the heart, all become eventually paralysed. They are not all rendered inactive in the same order by each member of the group. Some members, with a heavy molecule and a slight prolonged action, are useful as hypnotics; others, with a light molecule, acting rapidly and powerfully, and being quickly eliminated, are adapted for anæsthetics. The theories of their action are—(1) that they alter the blood in such a way as to render it incapable of maintaining the functional activity of the nerve cells; (2) that they alter the circulation; and (3) that they affect the nervous tissue itself. Some—such as nitrogen, nitrous oxide, and marsh gas—act by excluding oxygen from the lungs, anæsthesia occurring when the blood is quite venous. That the anæsthetic action is produced by alteration in the circulation is disproved by narcotising a frog, in which saline solution has been substituted for the blood, and in which therefore changes in the local circulation could have no effect. Changes in the circulation are, however, important in hypnotics, and anæsthesia has been induced by suddenly checking the circulation in the brain. That a frog in whose vessels salt solution is circulating can be anæsthetised shows conclusively that the condition is due to the direct effect of the anæsthetic on the nerve centres themselves, the change being supposed to be one of "transient fixation" of the albuminous molecules in the nerve elements—a change comparable to that which occurs in tetanic contraction of muscle. In connexion with this it may be stated that, while the direct application of the lower alcohols coagulates albumen immediately, the higher ones do not do so at all.

The changes produced by anæsthetics and hypnotics appear to be due to an affinity existing between the members of the alcoholic series and the nerve structures, causing the protoplasm of the ganglion cells to contract, and lessening their affinity for oxygen. The accumulation of acid also tends to reduce the activity of the protoplasm, and the presence of the halogens materially increases the anæsthetic action of the alcoholic radicals, as it also emphasises their action upon muscle. The introduction of these bodies therefore increases the risk of cardiac paralysis, whilst it increases the anæsthetic power. The choice of anæsthetics is limited to a great extent by consideration of convenience, safety, inflammability, and bulk, besides the desirability of employing a substance which is not disagreeable to smell and which does not injure the skin. In spite of their deficiency in some of these properties, chloroform and ether are practically the most useful anæsthetics we possess. Hypnotics are substances which merely cause natural sleep, from which the person can be readily awakened by external stimuli. In healthy sleep the person becomes unconscious to the external world, voluntary action ceases, and even the automatic centres for the respiration and circulation act less energetically, so that the breathing becomes slow, the pulse quiet, and the vessels tend to dilate. This dilatation may be so well marked that it causes the feet to swell, and renders a pair of well-fitting boots too tight. At the same time, it makes one more liable to be chilled by exposure to external cold. The two principal theories to explain sleep are: first, that it depends upon anæmia of the brain; and, secondly, that it is due to an exhausted or inactive condition of the brain cells. The latter is most probably true, though the condition of the cells is much influenced by the state of the circulation. Arterial blood neutralises the acid resulting from functional activity, and gives off oxygen to the brain cells. Thus, in some conditions of the brain simple increase in the supply of arterial blood will restore functional activity and produce wakefulness, while diminished supply will produce sleep. The effect of position has been shown by Friedländer in a research on the hypnotic properties of isopropyl alcohol. If the animal experimented upon were held up by the legs, so as to increase the blood-supply to the head, it at once awoke; but when held up by the ears it fell asleep. The same effect of the circulation is seen in debilitated subjects, who tend to fall asleep standing, or especially sitting down, and yet are very wakeful in the horizontal position. The influence of disturbance of the circulation is also seen after taking food, many people tending to fall asleep after a hearty meal, owing to the dilatation of the gastric and intestinal vessels drawing away blood from the brain. External cold also, unless very intense, acts in the contrary direction, and, by contracting the vessels in the skin and even in the intestines, drives the blood to the brain and prevents sleep. In high blood tension, as in Bright's disease, we often find troublesome insomnia, whilst in cases of debility with low tension there is often persistent drowsiness. The condition of the circulation is, therefore, a most important factor in the production of sleep, but it will by itself no more explain completely the insensibility of sleep than it will that of anæsthesia. As Ehrlich has shown, the acid products of functional activity tend to lessen the power of the cells to absorb oxygen; but it is highly probable that other products of tissue change, whether arising in the brain or in other parts of the body, have a similar power upon the brain cells. At all events, Bouchard has found that the toxic substances excreted in the urine during the day have a soporific action, while those excreted during the night have a stimulating action. It would thus appear that there is a sort of self-regulating mechanism in the body by which sleeping and waking are made to alternate. Now Voit found that during the waking hours more carbonic acid is given off, while during sleep the reverse is the case, and more oxygen is absorbed than carbonic acid eliminated. It is therefore evident that during waking the organism as a whole is an oxidising agent, while during sleep it is acting as a reducing agent. The stimulating action of such substances as cocoa, tea, and coffee would lead us to regard them as belonging to the class of products formed during sleep. In the early part of the day we might reasonably expect that the substances formed in the body would have no narcotic action, whereas later on the more completely oxidised products of waste would gradually assume a more and more soporific character. And this being so, we might naturally expect that by oxidation of some of the stimulant substances mentioned we might obtain products having a narcotic action. This is the case, at least, with caffeine, for in hydroxy-caffeine the stimulant action is less powerful. Caffeine-methyl-hydroxide is neither a stimulant nor narcotic, whilst ethoxy-caffeine acts altogether as a soporific. It will be noticed that the last mentioned, ethoxy-caffeine, is a compound of a radical belonging to the alcoholic series with one in which ammonia plays a prominent part. These two constituents are examples of two classes of soporifics: 1. Substances belonging to the alcoholic group. 2. Substances allied to urea or uric acid.

Hypnotics may probably lessen the functional activity of the brain cells—(1) by causing their protoplasm to contract, and so interposing a barrier of paraplasm between it and the oxygen of the blood; and (2) by lessening the affinity of the cells for oxygen by diminishing their alkalinity or by acting in direct combination with them, and so altering their chemical relationships. The products of brain-waste appear to be of an acid nature, and therefore lessen oxidation; but lactic acid, resulting from muscular exertion, may equally find its way into the circulation and have a similar effect. Another and final product of tissue-waste is carbonic acid, and this likewise has a soporific and anæsthetic action. The convulsions which occur in asphyxia are more truly referred to absence of oxygen than to the presence of carbonic acid, the deprivation in cases of suffocation producing in a few minutes intense stimulation of the

nerve centres, while the lessened oxidation occurring in sleep has a similar but much slighter effect in the course of several hours. It is probable that, in both cases, the stimulation—which gives rise in the one case to waking, and in the other to convulsions—is immediately caused by products of tissue-waste. The drowsiness which results from sitting in close rooms and churches, though partly referable to external warmth, is, in large measure, due to the presence of carbonic acid and volatile poisons from the lungs and skin.

The narcotic power of the alcohols increases as we ascend the series, as does also the number of possible isomeric compounds. There are three divisions of alcohols: (1) Primary, (2) Secondary, and (3) Tertiary, according as the carbon atom to which the hydroxyl is attached is united to one, two, or three radicals. Tertiary amyl alcohol, amylene hydrate, was recommended as a hypnotic by Schmiedeberg, and has been introduced into practice by von Mering. It is said to be intermediate between chloral and paraldehyde, safer than either, and not disturbing to the digestion. The next member of the series, hexyl, may yield thirty-eight alcohols, and thirteen of these are actually known, so that the possible field for the introduction of new hypnotics is very large. The ethers, for the most part, are too volatile and their effects too transient to be of much service as hypnotics. Sulphonal: Diethyl-sulphon-dimethyl-methane appears to be one of the most effective of all the newly introduced hypnotics, and although it does not, like morphine, compel sleep, it induces sleep in a pleasant manner, and has few disagreeable after-effects, and little or no danger. Paraldehyde: Ethylic aldehyde unites with itself, their molecules combined forming paraldehyde. A greater number in combination form metaldehyde. Though simple aldehydes are intensely irritating to the mucous membranes, these polymeric forms are much less so, and paraldehyde forms a useful hypnotic, which does not depress the heart's action or give rise to subsequent discomfort. The chief objection is its unpleasant smell, which remains about the patient for many hours. Ketones: In these the group CO is the connecting link between two radicals. When both radicals are methyl we have acetone, which has been found in the blood of diabetics, and has been supposed to give rise to diabetic coma. By substituting other radicals for methyl, numerous other ketones are produced, which form a long series of hypnotics. The other class of hypnotics, allied to urea, in which nitrogen may be said to form the basis, is obtained by uniting carbamic acid ($CO\,NH_2\,HO$) to an alkyl, so that the stimulating effect of ammonia is associated with the narcotic action of the alkyl. The ethyl compound, called urethane, is a useful hypnotic, though not so powerful as chloral. Unfortunately the higher members of this series are not sufficiently soluble to be active medicines.

Local Anæsthetics.—It is often convenient to annul pain in some particular region, without producing general anæsthesia. For some time the effect of cold has been utilised, either by the use of ice and salt, or, more conveniently, by the evaporation of a volatile spray, such as that of anhydrous ether, or, better still, a gas liquefied by cold and pressure, such as chloride of methyl. Another plan is to employ some drug which possesses the power of producing anæsthesia, such as carbolic acid or the allied substance, paracresol. From one of the decomposition products of cocaine, ecgonine, which has no anæsthetic action, cocaine itself can be built up by combination with benzoyl and methyl. In a similar way a compound of tropine, itself destitute of anæsthetic power, with benzol produces the local anæsthetic homatropine. Filehne, suspecting that the anæsthetic property resided in the benzoyl, has found that the benzoyl derivatives of several substances have a marked anæsthetic action. Unfortunately, however, many of them produce a primary irritant action, which renders them inadmissible as local anæsthetics. The same is true of most of the cardiac poisons, like digitalis, which has a similar local action.

MATER MISERICORDIÆ HOSPITAL, DUBLIN.—The following have been awarded prizes:—Leonard Prizes—First Medical Gold Medal: Matthew B. Savage. Second Medical Silver Medal: John McNamara. First Surgical Gold Medal: Not awarded. Second Surgical Silver Medal: Matthew B. Savage. A special prize (Silver Medal) was awarded to Richard Smyth for the high marks obtained by him in Medicine.

SURGERY AS PRACTISED IN TURIN.[1]

BY PROFESSOR HUMPHRY.

SURGERY in Turin, as represented by Signor Carle at the Ospedale Mauriziano, Signor Caponotto at the Ospedale S. Giovanni, and Signor Raymond at the Ospedale Ottalmico, is of very high order.

The Mauriziano Hospital, on the outside of the town, has been recently built, at a cost of £120,000, with the effort to present all modern improvements. It contains 200 beds, equally divided between medical and surgical patients, who are disposed in four long wards, two for men and two for women; and there are several smaller wards for patients of rather higher class, who pay a certain sum, and are attended by the same medical and surgical officers as the other patients. Each of the surgical wards has at the end, shut-off by folding doors from the rest of the ward, a spacious and abundantly lighted room, in which the dressing of the wounds is conducted. The bedsteads, upon castors or placed on tressels, are wheeled in and out of this room, and the wards are thus freed from the impurities attendant upon the dressing of wounds. There is also ample ward space, windows on the two sides, and the beds, each between two windows, are placed at a distance of several feet from the walls. The floors of the wards, however, are of pine, not very good or well laid, and already show much staining. The waterclosets and urinals, in projections from near the middles of the wards, admit of improvement. Professor Carle is the chief surgeon, having all the surgical patients under his charge, and, with a good staff of assistants, performs operations of all kinds. One patient was recovering from supra-pubic lithotomy, and another from rhinoplasty (the nose having been formed from the forehead); one from removal of the vertebral arches at the seat of fracture, which had been attended with some benefit; others from osteotomy, amputation of the mamma, other amputations, &c. The operations on women are, however, those which most interest the Professor. One woman was recovering from supra-pubic removal of the uterus and ovaries, the pedicle, transfixed and girt by elastic ligature, being external; two were recovering from removal of sarcoma of the ovary. He told me that he had removed the uterus by the vagina for cancer eighteen times, with only two deaths. I saw this operation, the details of which give a good idea of the method pursued in conducting the operations here. Professor Carle and his assistants, dressed in long linen coats, occupied themselves at least a quarter of an hour in making their toilette, washing the hands many times with hot water and soap, cutting and cleaning the nails, and soaking them in sublimate fluid (1 in 5000). The chamber was heated to about 80° by hot air. The woman, already washed, was brought in quite naked, under chloroform, and subjected to thorough washing and injection of the vagina and surroundings with the sublimate. She was then taken into an adjoining room, in which operations are performed upon suppurating and septic cases. Here the carcinomatous disease of the os uteri was scraped away with Volkmann's spoons and other instruments; and, after syringing and drying, Paquelin's cautery was freely applied, the object of this being to ensure an antiseptic condition of the part. The woman, still under chloroform, was taken into the third room, a spacious and well-lighted room, where cases primarily antiseptic—for ovariotomy, laparotomy, &c.—are operated on. After renewed sublimate washing of the surgeon's hands and patient's vagina, the os uteri having been drawn down with vulsellum forceps, an incision was carefully made into the peritoneal cavity between the bladder and uterus, a sublimated sponge in locked forceps pushed in, the fundus of the uterus pulled out with the finger and vulsellum, the lateral connecting structures ligatured piecemeal with silk passed by means of curved needles in porte-aiguilles, and divided with scissors; and, finally, the structures between the uterus and rectum being divided also with scissors, the uterus was removed. The parts having been thoroughly washed with the sublimate solution and sponged, the peritoneal surfaces were sutured by means of the curved needles and the porte-aiguilles, which seemed to be the most tedious and

[1] Paper read at a recent meeting of the Cambridge Medical Society.

With The authors' kind regards.

A REPORT

ON THE

PHYSIOLOGICAL ACTION OF CHLOROFORM

WITH A

CRITICISM OF THE SECOND HYDERABAD CHLOROFORM COMMISSION.

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THE PHYSIOLOGICAL ACTION OF CHLOROFORM,

WITH A CRITICISM OF THE SECOND HYDERABAD CHLOROFORM COMMISSION.

Introductory Observations.

In the summer of 1890, when Surgeon-Lieutenant-Colonel Lawrie was in England, he asked one of us (Gaskell) to look over the curves of the Second Hyderabad Chloroform Commission, and make a report on them, supplementing that report with experimental investigation, if necessary.

At the very outset it was evident that the Commission did not supply any answer to the most important question connected with the action of chloroform—namely, What is the reason of the fall of blood pressure which always occurs when a large dose of chloroform is administered? Before, therefore, it was possible to report on the curves of the Commission, it was necessary to make up our minds upon the meaning of this fall of blood pressure. For that purpose, we have carried out a number of experiments, and propose in this paper to give the results of those experiments, as well as a criticism of some of the conclusions of the Hyderabad Commission. The funds for this research were most generously provided by H.H. the Nizam, upon the application of Surgeon-Lieutenant-Colonel Lawrie; and we beg here to thank them for their aid in carrying out this investigation.

As far as the physiological action of chloroform is concerned, the controversy which has raged so long about the safety of its administration resolves itself into the question of its relative action upon the central nervous system and the peripheral organs. On the one side, we find the evidence given by Lawrie and the Hyderabad Commission, that chloroform acts essentially, if not entirely, as a paralyser of the central nervous system, but does not act directly upon any of the peripheral organs; while, on the other hand, the evidence of Snow, and in recent years of the Glasgow Commission, of Wood, and of McWilliam, is to the effect that chloroform acts directly as a paralyser of the heart, as well as on the nervous system.

So much has been written and spoken about chloroform of late years, that it is hardly necessary to write out the history of its experimental investigation; but it is perhaps advisable to mention some of the original observations and conclusions of Snow in 1858, seeing that at the present time the older observations are apt to be overlooked.

Snow's experiments on animals were performed without the graphic methods of modern days, and were largely directed towards the investigation of the relative effects upon the heart and respiration of air containing chloroform to a varying amount. His experiments show that if the air breathed contains 3 to 6 per cent. of chloroform vapour then respirations cease while the heart sounds are very distinct; but if the air contains 8 to 10 per cent. of chloroform vapour then the action of the heart is always extremely feeble, even if it does not actually cease before the arrest of the respiration; and on page 89 he observes with respect to the danger of concentration of the chloroform vapour, "If the air the patient breathes never contains more than 5 per cent. of chloroform vapour the pulse can never be seriously affected by the direct action of chloroform, and the state of the breathing affords the best warning against continuing the inhalation too long a time."

He further says that the pulse sometimes becomes intermittent or irregular during the administration of chloroform, but adds that he has never seen any danger in this condition. Also, page 90, "the patient sometimes holds the breath after he is unconscious and before he is insensible; in other cases, in the third stage of narcosis, where there is rigidity of muscles. In neither case is there danger in this condition *per se*." He points out that after the cessation of inhalation the symptoms of poisoning may increase owing to the absorption of chloroform still in the lungs. Also struggling and rigidity with holding of breath, which usually occurs when the patient has nearly absorbed the necessary amount, requires careful looking after, owing to the excessive inspirations which follow and may lead to the intake of a large amount of chloroform unless precautions are taken.

After the advent of graphic methods of registration we have the evidence of the Glasgow Commission in which special prominence was given to sudden stoppage of the heart and to capricious effects of chloroform. Such effects are seen mainly at the beginning of chloroform administration, and are clearly free from danger, as asserted by Snow, being simply Nature's safeguard against an irritant vapour, as pointed out by the Hyderabad Commission. Such effects are: (1) stoppage of respiration reflexly through the trigeminus and other nerves; (2) slowing or stoppage of the heart through the vagus nerve—both reflex actions for the purpose of preventing access of the vapour to the blood and so to the nervous system. In this of itself there is no danger; the only danger is in the after-effect, as maintained by the Hyderabad Commission; namely, in the likelihood of too large a dose being taken in owing to the excessive inspirations.

It is agreed on all sides that the effect of a large dose of chloroform is to cause insensibility, diminution of reflexes, a marked lowering of blood pressure, and finally slowing and cessation of respiration.

The Hyderabad Commission does not attempt to explain the reason of the fall of blood pressure, though it is evident, from the following remarks of Lawrie, that he at all events is inclined to attribute it to the action of the drug upon the vasomotor centre. He says:[1] "The Commission has given no opinion as to the cause of the fall produced by diluted chloroform alone. It is obvious from all their experiments that the effects of chloroform are first exerted upon the nervous tissues, the vasomotor centre is very soon involved, the respiratory centre becomes paralysed, then the muscular tissues become affected, and last of all the heart."

So also the Glasgow Commission and Wood regard the paralysis of the vasomotor centre as a possible factor in producing the fall of blood pressure, but do not attempt to distinguish between its share and that of the heart.

Even McWilliam,[2] who makes so much of the dilatation of the heart by chloroform, says: (Par. 17) "The fall of blood pressure is in its earlier stages due mainly to the depressing effect of the anæsthetic on the vasomotor centre, preceded often by a slight stimulation; the later stages are associated with failure of the heart as well as of the vasomotor centre." In fact, the fall of blood pressure is looked upon by most observers as largely due to paralysis of the vasomotor centre, and yet, as far as we can find out, this conclusion is not based upon any direct experimental evidence. Further, seeing that the initial part of the blood pressure fall is that part which is especially attributed to the paralysis of the vasomotor centre, and also that the fall of blood pressure is an early symptom in chloroform administration, it follows that experimental evidence ought not only to show a paralysis of the vasomotor centre by the action of chloroform, but also that centre ought to be more susceptible to the paralysing action of the drug than the neighbouring respiratory and cardio-inhibitory centres, seeing that the fall of blood pressure begins before the respiration shows any signs of paralysis and vagus effects upon the heart can still be produced after the blood pressure has commenced to fall.

Plan of Our Experiments.

In considering the relative share played by the heart and the vasomotor centre in the production of this blood pressure fall there are two possibilities: 1. The fall of blood pressure

[1] *Hyd. Com. Report*, p. 244.

[2] British Medical Journal, October 18th, October 25th, and November 1st, 1890.

may be due in the first instance to failure of the vasomotor centre, the heart not being affected until a very excessive dose has been given. 2. The fall of blood pressure may be due from the very first to a weakening of the heart's action, the vasomotor centre not being affected until a very excessive dose has been given.

The object of our investigation then was to determine (1) the primary effect of chloroform, and (2) the ultimate effect of a large dose on the vasomotor centre and on the heart respectively. Our object was to separate, as far as possible, the application of the drug to the medulla oblongata and to the heart, and for this purpose we made, in the first instance, the following experiments:

1. Direct application of chloroform to the exposed fourth ventricle.
2. Injection of chloroform into the jugular vein.
3. Injection of chloroform into the internal carotid artery.
4. Injection of chloroform into the vertebral artery.

In this set of experiments we found, as will appear below, a decided difference of effect according as the chloroform was injected heartwards or brainwards. We felt, however, that a legitimate objection might be taken to drawing any conclusions from these experiments as to the behaviour of chloroform when administered by inhalation, because it did not necessarily follow that the injection of chloroform into a blood vessel was strictly comparable in its effects with chloroform vapour in the blood. We therefore determined to supplement these experiments by another set, the object of which was to administer chloroform by inhalation, and, at the same time, to isolate the brain in such a way that it alone might be subject to the action of the chloroform, or, on the other hand, so that it alone might be exempt from that action. In order to do this we have used in each experiment two animals so arranged that the brain of the one (called the *fed*) was supplied by the blood of the other (called the *feeder*), and was therefore isolated from its own heart; chloroform could be administered to either animal after the cross circulation was established, with the result naturally, as far as the fed animal was concerned, of conveying chloroformed blood to the brain only, or to the heart and all other organs with the exception of the brain. The necessary procedure for the successful carrying out of these experiments was, as can be imagined, long and laborious, but the results amply repaid the trouble, as will, we hope, be evident from the detailed description of these experiments.

Both sets of experiments point to the same conclusion, namely, *the fall of blood pressure caused by administration of chloroform is due primarily to a weakening of the heart's action, and not to a paralysis of the vasomotor centre.* On the contrary, the primary effect of blood containing chloroform vapour on the vasomotor centre is an excitation, causing thereby a marked rise of blood pressure, and it is only after an excessive dose has been given that there is any evidence of any paralysis of this centre.

In our investigations we have used rabbits and dogs. Most of the experiments were made on rabbits, because we desired to register the movements of respiration as well as the condition of the blood pressure, and, in our opinion, no better method exists for the registration of the movements of respiration, both as regards rate and nature of muscular contraction, than that introduced by Head,[3] a method which is only applicable to the rabbit, and consists of the direct registration of the contractions of an isolated strip of the diaphragm muscle itself. In all cases a dose of chloral hydrate was given to the rabbit before the experiment commenced, and, in the case of dogs, they were always under the influence of acetate of morphine before the chloroform was administered.

The blood pressure, taken either from the carotid or femoral artery, was measured by a mercury manometer, recording in the ordinary way on Ludwig's kymograph.

For artificial respiration we used the very efficient apparatus designed by the Cambridge Scientific Instrument Company. By this apparatus an active withdrawal of air from the lungs, as well as an active supply of air, is secured. The rate, depth, and character of the respiration, that is, the relative duration of the inspiratory and expiratory phases, could be regulated with great nicety and maintained with accuracy.

[3] *Journ of Physiol.*, vol. x, p. 1.

Comparison of the Injection of Chloroform into the Jugular Vein and into the Brain Arteries: Injection into Jugular.

The Hyderabad Commission assert that in Experiment 92 repeated injections of 20 minims of chloroform were made into the jugular vein, and its effect was not to paralyse the heart, but to produce anæsthesia and a gradual fall of blood pressure exactly as if the chloroform had been inhaled. The amount of chloroform injected into the circulation in this experiment was 180 minims, given in 20-minim doses at varying intervals of time during 46 minutes. In other words, this large amount of liquid chloroform was said to have been sent into the circulation, and it was clear from its anæsthetic action on the brain and its effect on respiration that it circulated over the whole vascular system, and yet it produced exactly the same effects as if the chloroform had been inhaled.

Our experiments agree with those of the Hyderabad Commission as to the nature of the effect produced when chloroform is injected into the jugular vein; we do not, however, interpret these effects in the same way.

When a small amount of chloroform is injected into the jugular of a rabbit it always causes a fall of blood pressure, during which (1) the excursions due to the heart beats are diminished in size, and (2) the respiratory curves on the blood-pressure tracing are very much smaller, and may, indeed, almost vanish. During this fall of blood pressure the respiration is not necessarily altered either in rate or force; the blood pressure then recovers either entirely or partially, the pulse and respiratory excursions of the blood-pressure curve become again more conspicuous, and with the rising pressure the respiration may be affected, and the anæsthesia become more profound. Repeated small injections depress the blood pressure more and more, the pulse excursions become less and less visible until, when the pressure is very low, they vanish altogether; the respirations, after having continued vigorously for a long time, gradually slow off with diminishing force of contraction, and finally cease at a time when the heart beats have long ceased to be visible on the blood-pressure tracing.

Such a sequence of events is clearly to be explained by the gradual weakening of the heart's contractions in consequence of the injection, with the final result of a gradual cessation of respiration; and it is noteworthy how the heart is capable of recovering itself after each injection, for some considerable time at all events.

In such a case as this it may be said, without fear of contradiction, that death is due to failure of the heart's action, even although it may be found, on opening the chest, that the heart is very feebly beating after the respiration has stopped. The type of this effect of the injection of chloroform into the jugular vein is given in the following table taken from an experiment on December 11th, 1890, and is illustrated by the tracings in Fig. 1.

It is impossible to reproduce the whole length of the tracing from which this table was compiled, so we have endeavoured, in this case and in others, to give the general effect of the experiment by the publication of portions of the original tracing taken at the times indicated in the corresponding table.

In all the figures, with the exception of Figs. 6, 7, 8, 9, 10, the upper tracing records the contractions of the slip of diaphragm, the upstroke corresponding to the contraction of the muscle, and therefore to a movement of inspiration. The lower tracing is that of the blood pressure, and is recorded from the carotid artery, except in Figs. 6, 7, 8, 9, 10. The points in these two tracings which correspond as regard time may be seen by the two short vertical lines drawn on each figure. The base line, or line of zero pressure, was carefully determined at the end of each experiment, and its position is shown in each figure. In all cases a record of time in seconds was taken, an example of which is reproduced in Fig. 2 upon the base line. An electric signal marker was also attached to the kymograph by means of which the moment of application of chloroform or other important event was registered. The tracings all read from right to left.

Injection of chloroform into the jugular vein frequently causes a fatal result in quite a different manner, death occurring through failure of the respiration, and not through

FIG. 1.—*December 11th, 1890. Rabbit. Injection of Chloroform into Jugular Vein.*

Time.	Blood Pressure in mm.	Respiration Rate per min.	Amount of Chloroform Injected.	Remarks.
H. M. S.				
1 33 0	70	23	—	*a* in Fig. 1 represents a portion of tracing at this time.
1 34 8	70	23	1 m	
1 34 38	45	—	—	*b* in Fig. 1 shows disappearance of respiratory curves.
1 36 0	62	32	—	*c* in Fig. 1 shows recovery of blood pressure.
1 36 27	62	32	1 m	
1 37 0	40	—	—	Respiratory curves nearly disappeared, and did not return throughout experiment.
1 38 0	56	—	—	*d* in Fig. 1.
1 38 22	56	—	1 m	
1 38 46	40	32	—	Pressure did not recover before next injection.
1 40 21	39	32	1 m	
1 41 0	38	32	—	*e* in Fig. 1.
1 42 0	38	—	—	
1 43 0	38	—	—	
1 44 0	38	—	—	
1 45 0	38	—	—	
1 45 32	38	—	1 m	
1 47 0	36	—	—	
1 48 12	36	—	2 m	
1 49 30	34	—	—	
1 51 23	34	—	2 m	
1 52 30	32	34	—	*f* in Fig. 1; pulsations barely visible.
1 53 30	30	—	—	
1 55 0	29	33	—	*g* in Fig. 1.
1 57 0	28	—	—	Pulsations still visible.
1 58 0	24	—	—	Pulsations not visible.
1 59 0	23	22	—	
1 59 22	23	—	2 m	
1 59 52	23	—	—	Last respiration, *h* in Fig. 1.
2 15 0	—	—	—	Artificial respiration was put on and continued until 2.52, when it was stopped, as animal was quite dead. Heart examined at 3.3 and was found to be cold, still, and dilated.

FIG. 2.—*December 10th, 1890. Rabbit. Injection of Chloroform into Jugular Vein.*

Time.	Blood Pressure in mm.	Respiration Rate per min.	Amount of Chloroform Injected.	Remarks.
H. M. S.				
4 20 30	86	42	—	Respiratory curves of blood pressure well marked.
4 21 50	88	42	1 m	
4 22 2	50	51	—	Temporary quickening of respiration. Respiratory curves diminished during the fall of blood pressure.
4 22 30	60	44	—	
4 23 30	78	42	—	
4 25 0	88	42	—	The blood pressure had entirely recovered from the effects of the previous injection.
4 25 30	88	42	1 m	The effect of this injection is shown in Tracing *a*.
4 25 45	42	48	—	Temporary quickening of respiration.
4 27 0	86	41	—	
4 28 30	80	41	1 m	
4 28 45	29	—	—	Active expirations alternating with inspirations. Marked diminution of size of respiratory curves of blood pressure and of pulse excursion.
4 30 0	52	35	—	Respiratory curves of blood pressure and pulse excursions recovered.
4 31 0	51	27	—	Respiration markedly slowing. Strip of diaphragm muscle elongating.
4 32 0	50	12	—	Pulse excursions and respiratory curves of blood pressure very prominent, as seen in the beginning of Tracing *b*.
4 33 0	12	—	—	
4 34 0	4	—	—	Immediately afterwards a few gasping respirations, and then absolute cessation of respiration as shown in end of Tracing *b*. Heart at the time beating well. After cessation of respiration blood pressure fell quickly, and at 4.39, on examining heart, auricles and ventricles were still and inexcitable, the right ventricle being much dilated, and the left slightly.

failure of the heart. In these cases the blood pressure recovers after every injection, and finally the respiration ceases at a time when the blood pressure is fairly high, and the heart is beating well. An example of this effect is given in the preceding table, taken from an experiment on December 10th, 1890, and is illustrated by the tracings in Fig. 2.

In other cases the respiration fails with perhaps the very first injection, simultaneously with the fall of blood pressure. Such an experiment as that of December 10th shows that the heart has managed to rid itself of the chloroform after each successive injection, and consequently the blood pressure recovers either entirely or partially; the chloroform thus got rid of by the heart has then passed to the medulla oblongata in amount sufficient to hinder, and finally to paralyse, the action of the respiratory centre. Further it suggests that this chloroform in the medulla oblongata does not paralyse the vasomotor centre simultaneously with the respiratory; for at the time of cessation of respiration the blood pressure was rising rather than falling.

When the respiration ceases with the very first injection, simultaneously with the fall of blood pressure, this means that in these cases some of the chloroform has managed to pass into the medulla oblongata with the very first beats of the heart.

Injection into Brain Arteries.

Upon the assumption that the injection of chloroform into the vascular system acts in the same way as inhalation, it follows that injection of chloroform into the brain arteries and so directly to the vasomotor centre ought most markedly to produce a fall of blood pressure due to the paralysis of the vasomotor centre, if the inhalation of chloroform causes a fall of blood pressure mainly because it paralyses the vasomotor centre. On the contrary, if in reality the injection of chloroform into the jugular vein causes a fall of blood pressure by the weakening of the heart's beat, then naturally such a fall would not occur upon injection into the carotid or vertebral arteries until an amount of chloroform sufficient to affect the heart had passed through the brain region.

We have injected chloroform in small amounts into one of the carotid arteries (in all cases the external carotid was first ligatured) or into one of the vertebrals, and have found that in both cases the effect of the injection is to cause a rise of blood pressure, and not a fall; in both cases the respiration ceases when the blood pressure is still high; in both cases the conjunctival reflex is abolished, although naturally more quickly when the injection is made into the carotis. The contrast between the injection into one of the brain arteries and into the jugular vein is most marked; in both cases the production of anæsthesia and the cessation of respiration is brought about by the action of the drug very much in the same way as in ordinary inhalation; in both cases the injection is not necessarily associated with signs of strong irritant action upon the nervous system. Occasionally upon the first injection into the carotis a certain amount of contraction of various muscles takes place; but not only is there no such sign upon subsequent injections, but also the injections of normal saline solution may produce the same effects.

Chloroform injected into the vertebral artery does not produce quite the same effects as when injected into the carotis; such differences are of considerable interest from a physiological point of view, although they do not affect the main argument as to the action of chloroform. These effects may all be summed up by the statement that chloroform first excites, then paralyses, the different centres in the medulla oblongata.

Contraction of various muscles and excessive rapid respiratory movements usually take place when chloroform is first injected into the carotis; subsequent injections, however, show less and less sign of any primary excitation of muscles, and at the same time the conjunctival reflex is abolished, so that the primary excitation effects upon the muscular system of the body appear to be connected rather with the injection of the chloroform into the higher parts of the brain than into the medulla oblongata. In confirmation of this supposition it is found that muscular movements are much less likely to be produced when the chloroform is injected into the vertebral than when it is injected into the carotis.

Injections into the carotis or into the vertebral both kill the animal invariably by causing cessation of the respiration.

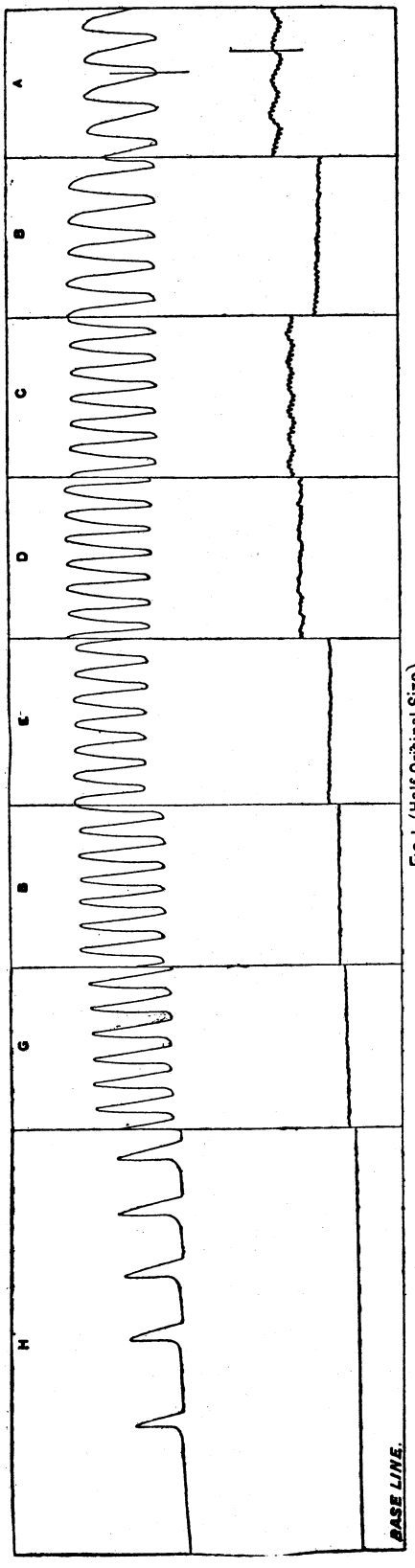

Fig 1. (Half Original Size.)

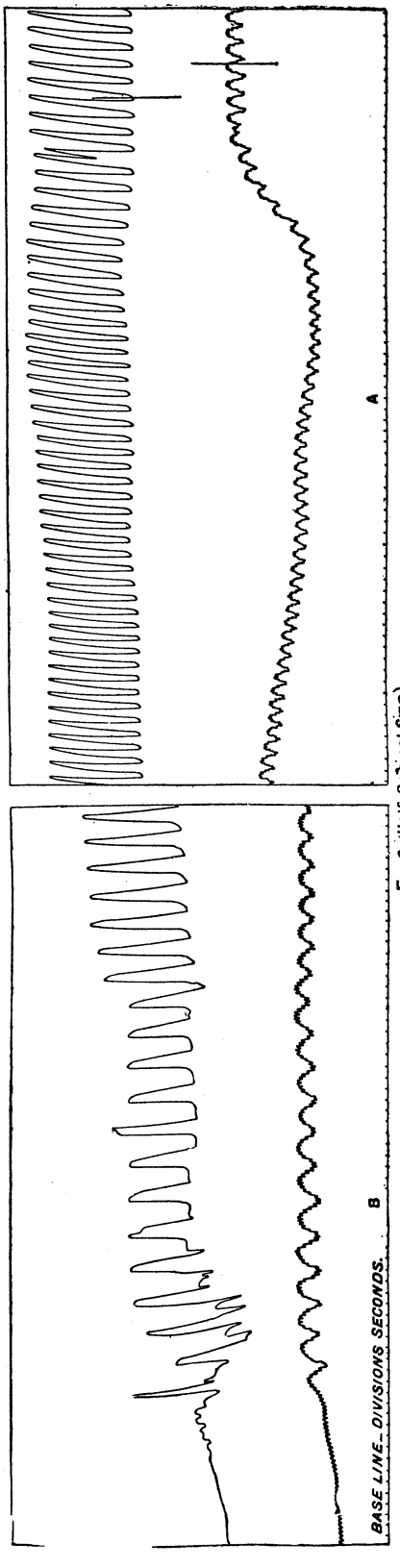

Fig 2. (Half Original Size.)

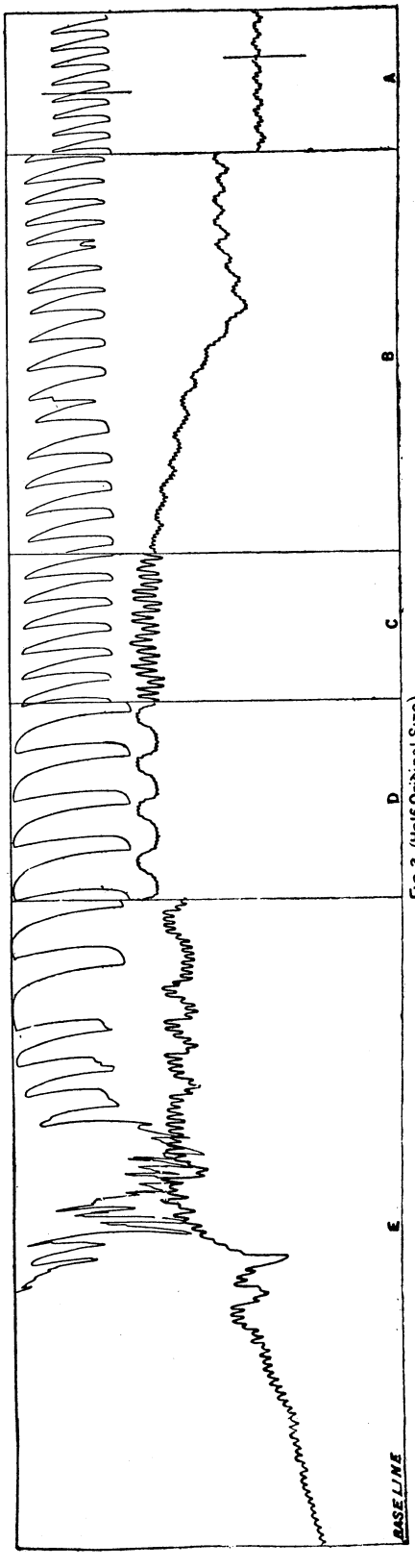

Fig 3. (Half Original Size.)

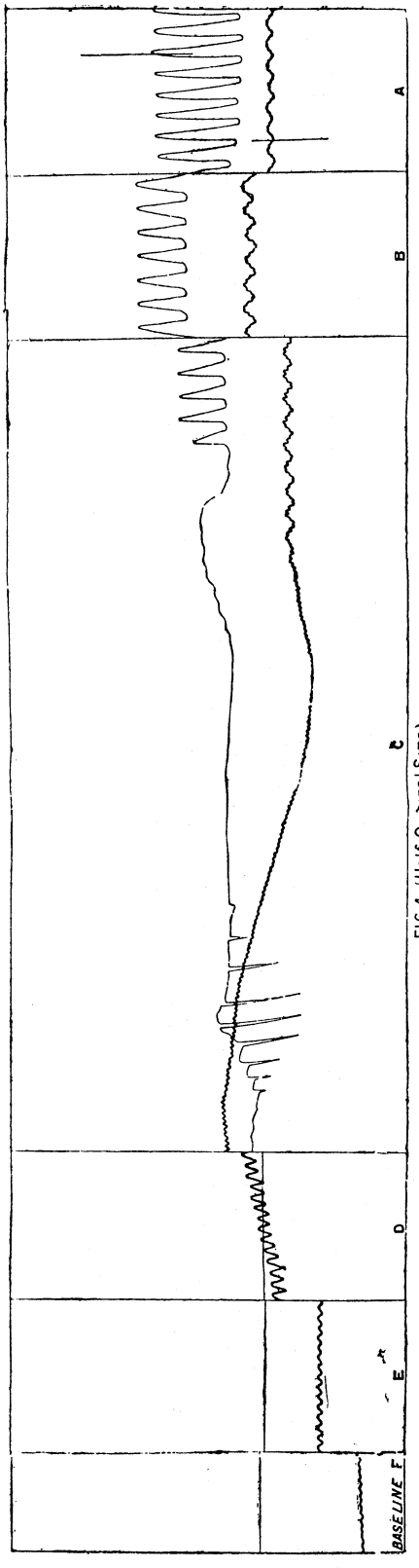

FIG 4 (Half Original Size)

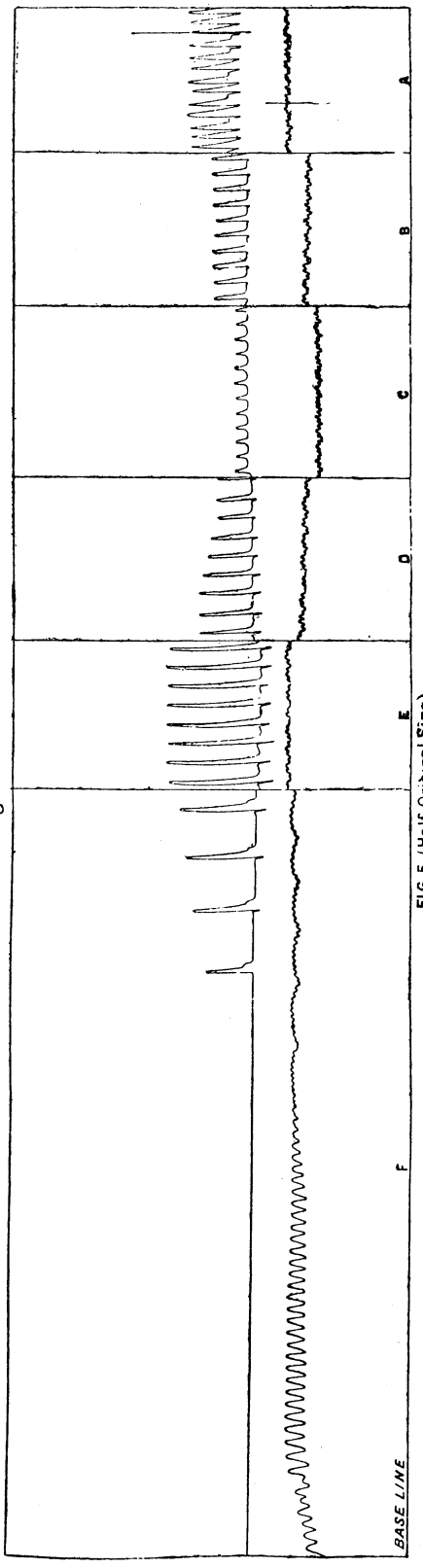

FIG 5. (Half Original Size)

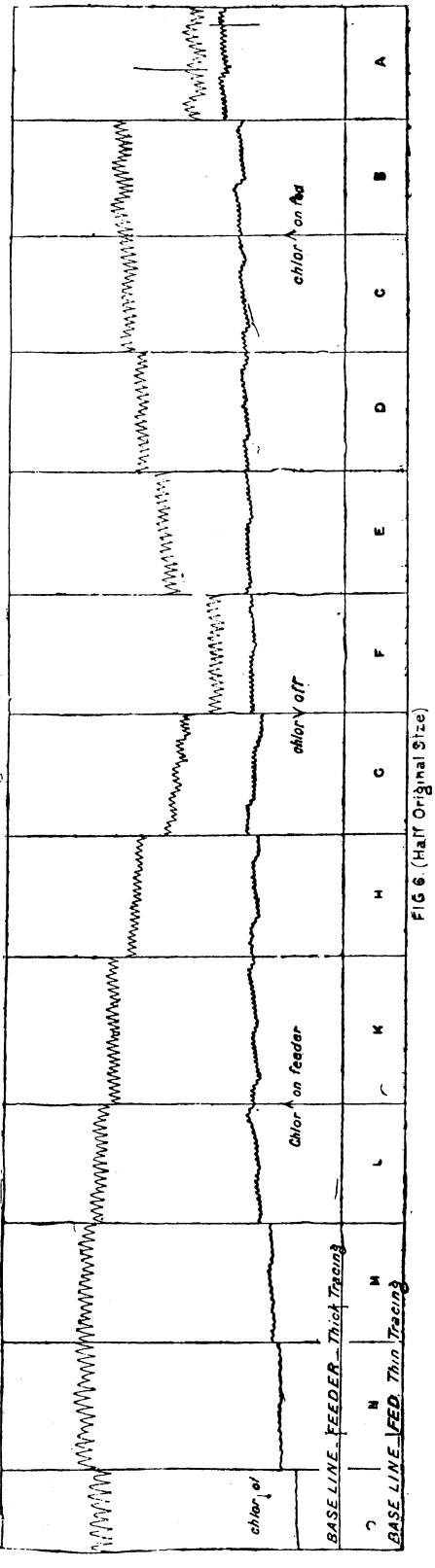

FIG 6. (Half Original Size)

B

In both cases the respiration becomes markedly slower before it ceases, and, as a rule, the final stoppage takes place with great suddenness. We see, however, a very marked difference between the carotis and vertebral injections as far as each individual contraction of the diaphragm is concerned. Carotis injections not only slow, but produce also a remarkable lengthening of each individual contraction, as is seen in Fig. 3, *d*, so as to produce a type of respiration called by

FIG. 3.—*December 11th, 1890. Rabbit. Injection of Chloroform into Internal Carotis.*

Time.	Blood Pressure in mm.	Respiration Rate per min.	Amount of Chloroform Injected.	Remarks.
H. M. S.				
4 57 0	76	48	—	Tracing *a*.
4 57 17	—	—	—	Left vagus cut.
4 57 25	—	—	—	Right vagus cut, leading to rise of blood pressure.
4 58 0	102	32	—	—
4 58 30	100	34	—	—
4 59 30	102	38	1 m	1 m injected into external carotid, and so to internal carotid. Tracing *b*.
5 0 0	144	35	—	Sudden slowing of ventricular beat to half previous rate; this lasted 1 min. 20 sec.
5 0 30	144	36	—	Tracing *c*.
5 1 20	—	—	—	Contractions of abdominal and limb muscles.
5 6 30	142	18	—	Tracing *d*.
5 7 50	128	—	—	Inspiratory movements suddenly ceased 8 min. 20 sec. after injection. Tracing *e*.
5 9 0	24	—	—	—
5 10 0	12	—	—	After this heart beats no longer visible on tracing.
5 40 0	—	—	—	Chest opened, heart still, not dilated.

FIG. 4.—*July 7th, 1891. Rabbit. Injection of Chloroform in Distal End of Subclavian, and so to Vertebral Artery.*

Time.	Blood Pressure in mm.	Respiration Rate per min.	Amount of Chloroform Injected.	Remarks.
H. M. S.				
11 47 0	78	49	—	Tracing *a*. Vagus nerves not cut.
11 47 7	—	—	1 m	Contractions of abdominal and limb muscles, in consequence of which the respiration lever became shifted in position and required readjustment, so that levels of respiratory tracing before and after injection do not correspond.
11 48 30	90	42	—	Tracing *b*.
11 49 30	72	42	—	—
11 50 36	67	42	1 m	The last respiration occurred at 11 h. 50 m. 41 s., as shown in Tracing *c*.
11 51 30	102	—	—	Pressure falling; Tracing *d*.
11 52 0	—	—	—	—
11 53 30	50	—	—	—
11 54 30	47	—	—	Tracing *e*.
11 55 30	38	—	—	—
11 56 30	25	—	—	Heart beats very regular and conspicuous; Tracing *f*.

Marckwald[4] inspiratory spasms; this type of respiration is frequently associated with a steady shortening of the muscle strip, as though the tonic contraction of the diaphragm was increased by the injection of chloroform into the carotis. On the other hand, chloroform. when injected into the vertebral, causes a slowing, with a diminishing strength of contraction, and a relaxation of the diaphragm strip; there is here no sign of any lengthening of each contraction, but, on the contrary, the contractions diminish steadily in extent (see Figs. 4 and 5, *a*, *b*, *c*). At a later stage of the injection into the vertebral, it frequently happens that the relaxed condition of the diaphragm muscle gives way to a condition of tonic contraction, just as though the chloroform had, upon the first injection, reached and affected some part of the nervous centre concerned with inhibition of the respiratory contractions, and, later on, had reached some higher part, so as to affect respiration in the same way as injection into the carotis.

A very similar difference in action is seen on the blood pressure tracings when chloroform is injected into the vertebral and carotid arteries respectively; in both cases the main result is a marked rise of blood pressure, but, in the case of vertebral injections, that rise is often preceded by a preliminary fall of slight extent, a good deal resembling the fall of pressure which can be obtained by stimulation of the depressor nerve (see Fig. 5, *a*, *b*, *c*).

Another difference in the blood-pressure curve consists in the frequency of occurrence of well-marked periodic undulations, resembling Traube-Hering curves, after injection into the vertebral, in comparison with their rarity after carotis injections. The effects produced by injection into the carotis and vertebral arteries respectively are illustrated by the tables and tracings of December 11th, 1890 (Fig. 3), July 7th, 1891 (Fig. 4), and July 9th, 1891 (Fig. 5).

FIG. 5.—*July 9th, 1891. Rabbit. Injection of Chloroform into the Vertebral Artery by means of a Cannula placed in the Subclavian distal to the Vertebral; Vagi Intact.*

Time.	Blood Pressure in mm.	Respiration Rate per min.	Amount of Chloroform Injected.	Remarks.
H. M. S.				
1 38 0	70	82	—	Tracing *a*.
1 38 30	70	82	0.25 m	No movement whatever.
1 39 30	57	62	—	Tracing *b*.
1 40 0	54	62	—	Marked diminution in strength of contractions of the diaphragm slip, coincident with the slowing.
1 40 30	52	62	—	Tracing *c*. From this point the blood pressure began to rise, and was accompanied by a steady increase of the size of the diaphragm contractions.
1 41 0	53 5	62	—	—
1 41 30	59	52	—	Tracing *d*.
1 42 0	70	52	—	Tracing *e*. The contractions of diaphragm had now reached the maximum.
1 42 30	74	36	—	—
1 43 30	68	25	—	—
1 43 43	64	—	—	Tracing *f*, showing the last respiration. The mean blood pressure continued at 64 for half a minute after the last respiration, and then began to fall.

In one case of injection into the carotis, the first injection caused a marked primary fall of blood pressure, the respiratory contractions were not lengthened, and the Traube-Hering curves were well marked; in fact, in this instance the chloroform seems to have reached mainly that part of the central nervous system which is supplied by the vertebral artery.

In whichever artery the chloroform is injected, the rise of blood pressure is ultimately followed by a fall; this fall takes place in both cases after the respiration has ceased, the difference between them being that, when the injection is made into the carotis, the fall of blood pressure usually occurs suddenly, and is absolutely coincident with the cessation of respiration, as in Fig. 3, while, in the case of injections into the vertebral, the pressure may continue high for some little time after the cessation of respiration, and then gradually sink, as in Figs. 4 and 5.

This fall of pressure in carotis injections coincident with a sudden cessation of respiration appears to be due to the chloroform paralysing the vasomotor centre at the same time as the respiratory centre ceases to act, for, in the first place, there is never an asphyxial rise of blood pressure after the respiration has stopped such as is always observed if the vasomotor centre is intact, and, in the second place, stimulation of a sensory nerve is unable to cause the pressure to rise. On the other hand, the characteristic of injections into the vertebral is an asphyxial rise of pressure after respiration has ceased (see Fig. 4 *c*), and the vasomotor centre is found to be susceptible to the action of such a nerve as the depressor. Again, cessation of respiration is caused by a very much smaller amount of chloroform when injected into the vertebral artery than when injected into the carotis;

[4] *Movements of Respiration*, trans. by McKendrick.

thus, a single injection of as small an amount as ½ m has sometimes proved sufficient in the former case (for example, Fig. 5), while in the latter from 1 to 2 m are necessary to produce any effect, and usually three or four injections of 1 m each must be given before the animal ceases to breathe. It is worthy of notice that the primary fall of blood pressure which occurs in many cases upon injection into the vertebral is seen only when the amount injected is small, such as ¼ m; with larger doses, such as 2 m, the blood pressure rises immediately after the injection.

In many cases when the injection is made into the carotis, a well-marked slowing of the heart occurs soon after the injection, and it is striking to see how these slow beats of the heart are unable to lower the blood pressure, owing to the simultaneous stimulation of the vasomotor centre, as is well shown in Fig. 3 *c*. In this case the slowing of the heart observed cannot be attributed to stimulation of the vagus nerves, for both vagi were cut before the chloroform was injected into the carotis. In other instances where well-marked slowing was obtained in consequence of chloroform administration, such slowing was undoubtedly due to vagus stimulation, for the effect was dependent on the integrity of the vagi. We have, however, observed in the course of our experiments many instances similar to the one quoted, where undoubtedly, owing to the fact of previous section of the vagi, some other explanation must be found; and careful measurement has shown us that in the majority of such cases of slowing, the rate of beat was diminished to exactly half the immediately preceding rate, as in the instance quoted. This suggests very strongly that the slowing in question is an indication of a partial block between auricle and ventricle, in consequence of which the ventricle responds only to every second auricular contraction, a phenomenon which is well known to occur in the hearts of both cold- and warm-blooded animals. We have observed this peculiar form of slowing under many different circumstances, but have not yet been able to make up our minds as to the paramount condition for its occurrence; in some cases it has appeared to be associated with an asphyxial condition of the blood; it certainly is not necessarily dependent on the presence of chloroform in the blood, for we have never observed it after the injection of chloroform into the jugular. It is not advisable to discuss the question further in this place, but we hope to be able to throw further light upon the causation of such a dropping of beats upon a subsequent occasion.

Chloroform applied to Fourth Ventricle.

Finally, to finish up with the effects produced by the direct action of chloroform on the nervous centres, we have found that the respiration can be easily stopped by the direct application of one or more drops of chloroform to the fourth ventricle of the brain. We have not as yet made a sufficient number of such experiments to enable us to discuss the differences observed in connection with the differences of effect of the carotis and vertebral injections.

It is remarkable how small an effect is produced on the anæsthetised animal by the opening of the atlo-occipital membrane; a large amount of cerebro-spinal fluid runs out as a rule, yet neither the respiration or the blood pressure is appreciably affected; when the chloroform is first applied muscular movements often occur and the respirations are increased in depth and frequency. Upon the application of a second drop no movements of the animal take place as a rule, but the respiration is temporarily quickened and increased. The cessation of respiration takes place gradually, not suddenly; the diaphragm contractions become weaker and weaker, and finally cease. At the commencement of this weakening each contraction for some time is apt to be lengthened as in the case of carotis injections. The paralysing effect on the respiration of the chloroform, when applied to the fourth ventricle, is its most striking effect, and is in marked contrast to the action of such a stimulant as nitrate of silver, which, according to Gad,[5] does not stop respirations when applied to the fourth ventricle.

The effect on the blood pressure is not well pronounced, as far as can be judged from the few experiments we have made; in some cases there is a slight primary fall followed by a slight rise; in others a rise only, without any preliminary fall. The respiratory blood pressure curves are apt to be very well pronounced, and the gradual fall which takes place with the gradual cessation of respiration is not broken by an asphyxial rise. Periodic undulations resembling Traube-Hering curves were not observed as the result of the application of chloroform to the fourth ventricle.

From these experiments we may draw the conclusion that chloroform, whether injected into the cerebral arteries, or applied directly to the medulla oblongata, first stimulates, then paralyses the parts of the brain with which it comes in contact: thus the stimulation of the respiratory centre is shown by increased frequency and force of the contractions of the diaphragm strip; these last but a very short time and then the respiratory movements become slower and weaker or slower and longer up to complete cessation, or cease somewhat suddenly. The stimulation of the cardio-inhibitory centre may be shown by the occurrence of heart slowing dependent upon the integrity of the vagus nerves; this effect also is seen only for a short time after injection. The stimulation of the vasomotor centre is shown by the marked rise of blood pressure, which continues for a long time and gives way ultimately to a paralysis, as shown by the absence of any asphyxial rise of pressure after respiration has ceased, and also by the absence of any reflex rise of pressure upon stimulation of a sensory nerve. Perhaps also the presence of the periodic undulations resembling Traube-Hering curves indicates the action of a strong stimulus upon a less excitable centre, as seems to be the case in many instances of periodic rhythmical activity of the central nervous system.

Comparison of Chloroform Injection and Chloroform Inhalation.

These experiments point directly to the conclusion that chloroform causes a fall of blood pressure by the weakening of the heart's contractions and not by a paralysis of the vasomotor centre; when, however, we attempt to explain the effects of chloroform inhalation by the experience thus gained we must always remember that liquid chloroform possesses a much more powerful irritant action upon the tissues than the vapour of chloroform. This is naturally only a question of degree, for the stimulating action of strong chloroform vapour is shown most markedly by the reflex effects produced upon the nasal and pharyngeal membranes. Although, then, we should expect for this reason that injection of chloroform into the vascular system should produce stronger signs of irritant action than its inhalation, yet there can be no doubt that these experiments show that such injections of chloroform, whether brainwards or heartwards, do produce also anæsthesia and paralysis of respiration resembling in effect the symptoms seen upon inhalation of the drug. We are therefore, it seems to us, justified in concluding that although these experiments are not of themselves absolute proof of the action of chloroform when inhaled, yet they support rather than oppose the view that chloroform when inhaled differs in its action from chloroform when injected in degree rather than in kind, and afford therefore valuable evidence of the action of chloroform if they prove to be in accordance with the evidence given by other experiments in which chloroform was brought into the blood by direct inhalation. Another possibility must be borne in mind when discussing the value of these experiments, namely, the possibility that fluid chloroform when injected into an artery may cut off the blood supply from one or more vascular areas supplied by that artery, either because the fluid itself obstructs some of the small arterioles owing to its cohesive power and immiscibility, or because its irritant action causes capillary stasis, and so blocks the flow through the area in question. In either case the effect produced in any experiment would depend upon the position of the small vessels which were blocked rather than upon the specific action of the drug.

Undoubtedly the effects produced by chloroform when injected into the cerebral arteries resemble in many respects those produced by a blocking or ligature of those arteries. Thus the characteristic lengthening of each contraction of the diaphragm when chloroform is injected into the carotis recalls forcibly to mind the respiratory spasms described by Marckwald when the higher brain paths connected with respiration as well as the vagi nerves were cut, and Marck-

[5] *Verhandl. der physiol. Gesellsch.*, 27th June, 1890.

wald[6] has shown that the same kind of elongated spasmodic respiration can be obtained by the injection of wax into the carotis so as to block the arteries supplying the posterior corpora quadrigemina, if at the same time the vagi nerves are cut. Further, Marckwald has shown that such elongated respiratory spasms can be cut short so that the type of respiration more nearly resembles the normal by the stimulation of such inhibitory nerves as the superior laryngeal or trigeminal. Our experiments have shown us that the lengthened diaphragm contractions produced by injection of chloroform into the carotis can also be cut short with a consequent quickening of the rate of respiration when a stimulating vapour, such as ammonia or chloroform, is applied to the nose.

In Marckwald's wax injection experiments the spasmodic type of respiration was caused by the complete removal of the regulating influence of the lungs on the respiration in combination with a partial removal of the regulation from the higher brain regions. In our experiments, when the vagi nerves were intact, it was easy to show that their regulating influence was not impaired to any very great extent, for every inflation or suction was still able to produce the well-known Hering-Breuer effects described by Head,[7] so that if the prolonged respiratory spasms caused by wax injection and ours caused by chloroform injection have any common ground of origin, that common cause must be sought for in the paralysis of higher brain paths combined with a possible diminution of the regulating power of the vagi nerves.

Comparison of Chloroform Injection and Ligature of Brain Arteries.

Again, it is interesting to compare the effect of ligature of the four brain arteries with the effect of injection of chloroform into them. We have made a number of experiments for the purpose of observing the sequence of events which follows ligature of the four brain arteries. In most cases the two subclavian arteries were tied proximal to the vertebrals, as well as the vertebrals and carotids. In order to estimate the extent of the circulation in the brain after ligature of these vessels, we placed a cannula in the peripheral end of the carotis as well as the ordinary blood-pressure cannula in the end connected with the heart, and tied the external carotis and auricular arteries as well as the superior thyroid. In this way the only communication with the cannula is by way of the internal carotis, and the blood pressure measured is that in the circle of Willis. This method was used by Hürthle.[8] It gives a rough-and-ready test of the amount of diminution of the blood in the circle of Willis, and also of the efficacy of the ligatures round the vertebrals and carotids. With the ligature of each vessel the circle of Willis pressure falls, while the ordinary blood pressure rises, and, finally, when all four vessels are ligatured, the pressure in the circle of Willis is very low, and then falls very slowly, nearly to zero—that is to 3 to 5 mm. Hg, while at the same time the ordinary pressure is very high. Further, it is clear that such a proceeding as stoppage of the heart by vagus stimulation must produce a fall in both blood-pressure curves as long as the brain arteries are open, while naturally it would produce a fall in only the systemic blood-pressure curve if the closure of the four brain arteries has been efficiently performed. This control we found to be quite satisfactory; as long as one vessel was unclamped or unligatured then both blood pressures responded to the peripheral end of the vagus nerve. When they were all clamped no sign of a fall was to be seen in the circle of Willis pressure curve, although naturally the fall in the systemic blood-pressure curve was as great as ever.

Further, the efficiency of the ligatures was seen by opening the atlo-occipital membrane after death, when it was found that no cerebro-spinal fluid ran out, and that the fourth ventricle looked white and bloodless. As a rule the last artery to be closed was the carotis on the left side, the two ends of the carotis on the right side having been previously fixed in connection with the two mercury manometers. A respiratory tracing was not taken, but the condition of the respiration was noted occasionally. It was found, as is well known, that the ligature or clamping of the last artery caused considerable struggling, the well known Kussmaul-Tenner convulsions, and violent respirations; if, however, the clamp was immediately taken off these ceased very quickly. By putting on and taking off the clamp at frequent intervals, taking it off whenever the animal commenced to struggle, we were enabled finally to leave the clamp permanently on without any struggling, and we always found that complete closure in this way was followed by a very marked rise of blood pressure in the cannula connected with the heart, and an equally marked fall of pressure in the cannula connected with the circle of Willis; stimulation of the peripheral end of the vagus then produced no effect on this latter pressure. In no case have we seen any attempt at a spontaneous recovery of blood pressure in the circle of Willis, much less an increase of that pressure above its original height, as mentioned by Corin,[9] provided that the subclavians were ligatured proximal to the vertebrals; in fact, our experiments agree closely with Hürthle's, and we conclude, as he does,[10] that there is no evidence of the establishment of any efficient collateral circulation after the ligature of the four brain arteries. It is, however difficult to believe that no blood whatever reaches the medulla oblongata, seeing that, as will be explained later, chloroform still appears able to produce an effect upon respiration. The effect of this cutting off of the circulation to the brain is in all cases death by failure of respiration, and it is remarkable how long a time the animal is able to continue to breathe with the blood supply to the medulla oblongata cut off. In our experiments respiration has continued for a length of time, varying between eight minutes to thirty minutes after the closure of the last blood vessel. In all cases the rate of respiration becomes slower and slower, so that the stoppage is a gradual one. Throughout the whole time during which the respiration lasts the aortic blood pressure, which had become very high, immediately after the ligature of the last artery remains high, the amount of fall being very slight, and the height at the time of cessation of respiration is greatly above the normal blood pressure as seen before the brain arteries were ligatured. The blood pressure does not fall to any extent until after the respiration has ceased. This long continued high blood pressure is further characterised by the presence of regular periodic undulations, which are in many cases remarkably regular, and resemble those seen when chloroform is injected into the vertebral artery. Finally, the ligature of the brain arteries produces a complete anæsthesia, as shown by the absence of any corneal or conjunctival reflex before the respiration ceases, so that in this case, as in the case of injection of chloroform into the brain arteries, paralysis of the higher centres occurs first, then paralysis of the respiratory centre, and finally paralysis of the vasomotor centre. Primary excitation of the cardio-inhibitory centre, as evidenced by a slowing of heart rate soon after the complete closure of the brain vessels, is clearly indicated on some of the curves. We see then that an insufficient supply of blood to the medulla oblongata causes an excitation, followed by paralysis, of the various centres situated there, and that, just as in the case of chloroform injection, the excitation of the vasomotor centre lasts so much longer than that of the respiratory centre as to keep the blood pressure high during the time the respiration is failing, and even up to the time of its stoppage. In both cases the vasomotor centre is ultimately paralysed, for it is impossible in either instance by means of artificial respiration to prevent the blood pressure from falling after the cessation of natural respiration.

Comparison of Action of Chloroform and of Other Agents on the Medullary Centres.

The resemblance in the sequence of events connected with the respiratory and vasomotor centres when the brain arteries are ligatured, and when chloroform is injected into those arteries, emphasises one most important conclusion, namely, that it is not necessary or even probable that a paralysing agent should paralyse these two neighbouring centres simultaneously, the evidence is rather in the direction that the excitation of the vasomotor centre will outlast both the excitation and subsequent paralysis of the respiratory centre whenever an agent which first excites and then paralyses is applied to the medulla oblongata.

[6] *Zeits. f. Biol.*, xxvi, 259.
[7] *Loc. cit.*
[8] *Pflüger's Archiv*, vol. xliv, p. 574.
[9] Quoted by Hürthle.
[10] *Loc. cit.*, p. 601.

This conclusion is in complete accord with other evidence, such as the action of amyl nitrite when injected into the carotis, and the effect of pressure applied to the fourth ventricle. Cash and Dunstan,[11] in a recent paper, have shown that the injection of amyl nitrite into the brain arteries produces a marked rise of blood pressure which lasts even after the respiration shows signs of failure. So also Horsley and Spencer,[12] in their paper "On the Changes produced in the Circulation and Respiration by Increase of Intracranial Pressure," show that if the vagi nerves are cut so as to abolish the action on the heart an increase of intracranial pressure causes a marked rise of blood pressure with a failure of respiration; indeed the respiratory and vasomotor centres are so related to each other that, when the respiration has ceased owing to a moderate increase in the intracranial pressure, then a further increase of that pressure causes a still greater rise of blood pressure with the result of restarting the respirations. The paralysis of the vasomotor centre, in consequence of long-continued increase of intracranial pressure, only occurs long after natural respiration has been abolished, and artificial respiration has been employed for some time. In fact, so far from the same influence producing simultaneously similar effects upon the two neighbouring centres of respiration and vasomotor action, we see rather that the vasomotor centre is subordinate to the much more important respiratory centre, Nature's safeguard action being to keep up the blood pressure as long and as high as possible for the purpose of recovering the failing respiratory centre by supplying it with a large supply of blood. A larger supply of blood is brought to the brain region with the rise of blood pressure, because the evidence of physiology in recent years points to the conclusion that the vessels of the abdominal area and of the brain are not simultaneously constricted when the vasomotor centre is stimulated, but rather that the brain vessels behave like the vessels of the skin, and are dilated when the vessels of the abdominal area are constricted.

These experiments upon the effect of injection of chloroform into the brain arteries on the one hand, and into the jugular vein on the other, point strongly to the conclusion that the fall of blood pressure observed when chloroform is inhaled is due to a weakening of the heart's action, and not to a primary paralysis of the vasomotor centre; still, however, as already mentioned, they cannot be regarded as a conclusive proof that such is the action of chloroform when inhaled. We require, therefore, as a supplement to these experiments, some method by which chloroform can be inhaled in the usual manner, and the blood containing chloroform thus inhaled can be sent either to the heart alone or the brain alone at will. As already mentioned, we have devised the method of cross circulation between two animals in order to test this point.

Cross Circulation Experiments.

1. *Method of Performing the Experiment and the Effects of Establishing the Cross Circulation.*—In order that chloroform, when inhaled in the ordinary way, could be carried to the brain only or to the heart only, the circulation through the brain was separated from the general circulation, and a supply of blood for the brain obtained from another animal. The exact way in which this was accomplished varied in different experiments, for one reason because the relative sizes of the animals selected determined to some extent the number of vessels which it was considered necessary to connect from one animal to another to obtain an adequate cross circulation.

In general, the plan adopted was to connect the cerebral ends of one or both carotids of the animal, whose cerebral and general circulatory systems were to be separated—and this animal we will speak of as the *fed*—to the cardiac ends of one or both carotids of the other animal, which we will call the *feeder*. When the remaining brain arteries of the fed animal were ligatured, the brain was supplied by blood reaching it by the internal carotids, and derived directly from the common carotids of the feeder. One external jugular vein of the fed animal was similarly cross connected to the cardiac end of one external jugular of the feeder, and the other external and the two internal jugulars of the fed animal were ligatured, so that the blood from the brain was very largely conducted back to the feeder, and was not allowed to reach the general circulation of the fed. In an experiment where a large bulldog of 17 kilogrammes supplied the brain of a small terrier of 5 kilogrammes, one carotid of the large dog was connected by a Y-piece to both carotids of the small dog, and the brain of the latter was wholly supplied by this one carotid.

The larger animal was, when possible, always selected for the feeder; but when rabbits were used, as there was no considerable difference in size of the animals, it was considered necessary to connect as many cross channels as possible from one rabbit to the other, so that an adequate supply of blood might be secured. In one such experiment both carotids and one subclavian of the feeder were connected severally to the two carotids and one subclavian of the fed, all the branches of the latter vessel, except the vertebral and the vessel itself on the cardiac side of the vertebral, being ligatured. In this case, therefore, blood was derived from the feeder by three channels, namely, the two carotids and one vertebral. The other vertebral of the fed animal was ligatured, and a return of blood was secured by one pair of cross connected jugular veins, the other external jugular vein of the fed animal being ligatured. In most cases the external carotids of the fed animal were ligatured, so that the internal carotids received all the blood derived by cross connection with the common carotids of the feeder.

In all cases an adequate supply of blood was left to the brain of the feeder, for in no case were its vertebral arteries interfered with, and in some experiments one carotid was left as well. The blood pressure in the general circulatory system of both animals was registered from the femoral arteries. In order to reduce the tendency to the clotting of the blood the connecting cannulæ were made as short as possible by dissecting out a considerable length of the vessels and by bringing their ends very close together. It was found convenient to suture together the reflected skin of the neck of one animal to that of the other, and so to form a bed on which the connected vessels could rest. It was, however, found necessary to diminish the clotting power of the blood by an injection of extract of leech or of peptone. The amount of these substances used was small, so that the blood pressure should be depressed as little as possible. Moreover, the injection was made some considerable time before the cross circulation was established; the immediate effect of the injection upon the blood pressure had then to some extent passed off. It will, however, be noticed, on reference to the protocols or the tracings, that the blood pressures, especially of the feeders, are small.

In the experiment made on February 18th (Fig. 6), referred to above, the feeder, a dog of 17 kilos., received an injection of 7 grm. of peptone (0.4 per kilo), and two hours later, immediately before the cross circulation was established, the blood pressure in the femoral artery was 68 mm. (Fig. 6, Tracing *a*). This is decidedly low for so large an animal, so that in this case the depression caused by the injection of peptone had not been fully recovered from. In the fed animal, in the same experiment the femoral blood pressure immediately before the cross circulation was established, which was two hours and a-half after the injection of 2¼ grm. of peptone, was 122 mm. (Fig. 6, Tracing *a*). The much higher blood pressure in this case is not due to recovery from the depression, caused by the injection being more complete in this animal than in the large one, but to the fact that at this moment many arteries in the neck of the small dog are occluded. The ascending cervical artery on the right side was ligatured, and the two carotids, which had been connected to the left carotid of the feeder, were still clamped. The left vertebral and the left subclavian were also tied, the ligature of the latter vessel, which was even placed proximal to the origin of the vertebral, being to prevent any possibility of blood passing by the ascending cervical arteries from reaching, by anastomoses, the upper part of the vertebral. Thus the right vertebral was the only vessel left for the supply of blood to the brain. Such an extensive closure of vessels accounts at once for the higher blood pressure in the fed animal as compared with the feeder. The right vertebral was tied as nearly as possible at the same moment as the clamps were removed from the carotids and the jugular

[11] *Proceed. Roy. Soc.*, vol. xlix, p. 314.
[12] *Phil. Trans.*, 1891, B., p. 201.

veins (the right external jugular of the fed being connected with the left of the feeder), and the cross circulation in this way established, so that at no time was the brain of the fed deprived of a supply of blood.

We are assured of this, because in no case in our experiments has there been at this moment any struggling or marked change in the respiration of either animal, except in one case, where the last brain artery was by mistake tied before the clamps on the connected vessels were removed, as will be mentioned later in the description of the experiment on February 20th. When the cross circulation was established, the blood pressure in the fed animal rose still higher. In one minute and a-half it had risen to 160 mm., and this was the maximum it attained, while that in the feeder had fallen slightly to 58 mm. (Fig. 6 *b*). The rise of pressure in the fed animal shows that there is a supply of blood from the feeder, and probably that the complete return of blood from the brain of the fed back to the feeder is not secured. In this particular experiment, where the right external jugular of the fed was connected to the left external jugular of the feeder, only the left external jugular of the fed was ligatured, so that there still remained the two internal jugulars, by which some portion of the blood would no doubt pass into the general circulation of the fed animal. The slight fall of pressure in the feeder probably also indicated that there was some bleeding of one animal into the other going on, but this fall would undoubtedly have been much greater if a large proportion of the blood had not been returned by the cross-connected jugulars.

This fall of pressure in the feeder does not always occur. In another experiment the left carotis of a dog of 12 kilos. was connected to the right carotis only of the fed animal, a dog of 5 kilos. Both vertebrals of the fed were ligatured and the last brain artery, the left carotis, was clamped at the moment the cross circulation was established. The right jugular of the fed was in connection with the left jugular of the feeder, and the left external jugular of the fed was ligatured. In this case, also, peptone had been injected. The small dog had received 2.5 grm. peptone (0.5 per kilo) one hour and a-half, and the large dog 4.5 grm. peptone (0.3 per kilo) half an hour before the cross circulation was established. Just before this was done, the femoral pressure of the feeder was 65 mm., the low pressure being due to the peptone having been injected only half an hour previously. The femoral pressure of the fed at the same time was 132 mm. When the cross circulation was established, this slowly rose, and in one minute was 164 mm., and that of the feeder did not in this case fall, but, on the contrary, rose slightly to 70 mm.

In the experiments with rabbits, where the cross supply of blood was derived by three channels, there is a more marked loss of blood by the feeder.

In the experiment on February 23rd (Fig. 9), one hour and a-half after the injection of leech extract, the femoral pressure of the fed animal was 70 mm. At this time the left vertebral was the only artery supplying the brain. The subclavian on the right side had been ligatured on the cardiac side of the vertebral, and all the other branches of the subclavian tied, so that the vertebral could by means of the distal portion of the subclavian be connected with the left subclavian of the feeder; and the two carotids were at this moment also clamped and connected to the two carotids of the other animal. The pressure in the feeder at this moment was 84 mm. (Fig. 9, Tracing *a*). The two carotids and the left subclavian of this animal were then clamped. The return of blood was secured by the connection of the right jugular of the fed with the left of the feeder, the other external jugular of the fed being ligatured.

When the cross circulation was established, and the last brain artery of the fed tied, the pressure in this animal rose, and in one minute and a-half was 94 mm., while that of the feeder fell to 44 mm. (Fig. 9, Tracing *b*). This considerable fall of pressure of the feeder may be partly accounted for by hæmorrhage into the fed, which must undoubtedly take place at first into the relatively empty vessels of the brain of that animal, but that this does not continue to any extent is probably shown by the fact that the pressure did not continue to fall, but, on the contrary, rose slightly, and three minutes after the circulation was established was 53 mm. Again, the mere effect of closure of both carotids and of one subclavian is to drive the blood pressure abnormally high, and, if this is due to mechanical causes and not to increased activity of the vasomotor centre consequent on the diminished supply of blood to the brain, the pressure in the feeder would fall when these vessels are again opened.

The rise of blood pressure in the fed animal reaches its maximum rather quickly, and then remains fairly constant, as is seen clearly in the experiments with dogs. This rise cannot be looked upon as due to an escape of blood from its brain into its general circulation. Such escape would need to be very large to produce the considerable rise observed, if, indeed, it could produce the effect at all. The explanation is rather one in accordance with the observations of Horsley and Spencer, who found that an increase of intracranial pressure led to a rise of blood pressure by increased activity of the vasomotor centre.

Eight cross-circulation experiments were made, three with two dogs, three with two rabbits, and two where the attempt was made to supply the brain of a rabbit with blood from a dog. This last procedure was unsuccessful, as the rabbit in both cases died very soon after the cross circulation was established.

2. *The Effect on the Fed of Chloroform Administered to the Feeder.*—In no experiment did we allow this condition of cross circulation to continue uninfluenced for any length of time, so that we cannot say how long the brain would continue to be supplied with blood adequate to maintain respiration in the fed animal. In all cases as soon as the immediate effects of establishment of the cross circulation had passed off and the blood pressures of both animals were fairly constant chloroform was administered either to the feeder or to the fed. As chloroform given to the feeder is carried to the brain of the fed the experiment corresponds to the injection of the drug into the carotis or vertebral and so shall be considered before the administration to the fed, which, in so far as the drug has free access to the heart but is excluded from the brain, corresponds to the injection into the jugular.

In the experiment on March 19th (Fig. 7) when the pressures in both dogs were constant, that of the feeder being 100 mm. and that of the fed 160 mm. (Fig 7, Tracing *d*), the tube in the trachea of the feeder was connected with a chloroform bottle and in a few seconds the blood pressure in this animal began to fall in the usual way and complete absence of the conjunctival reflex was produced in 1 min. 20 secs. The blood pressure of the fed animal, whose brain was receiving the same chloroform-carrying blood as that of the feeder, began after 20 secs. not to fall, but on the contrary to rise, and rose slowly and steadily as that of the feeder fell. (Fig. 7, Tracings *e*, *f*, *g*, *h*). When the chloroform had been administered for 1 min. 30 secs. and the pressure of the feeder reduced from 100 mm. to 62 mm. that of the fed had risen from 160 mm. to 195 mm., and then remained high, and when the chloroform was removed 33 secs. later, was still 195 mm. (Fig. 7, Tracing *k*). The pressure of the feeder was then 60 mm.

As the feeder recovered from the chloroform its pressure of course rose, and in 1 min. 30 secs. was 88 mm., while that of the fed fell to 186 mm., which is still higher than it was before the chloroform was given. (Fig. 7, Tracing *n*). An examination of the tracing shows that the rise of pressure of the fed was rather a quick one and then that it remained high. The vasomotor centre was stimulated by the chloroform and the excitation persisted and only very gradually passed off when the chloroform was removed.

Again, in another experiment, with a pressure of 68 mm. in the feeder and 164 mm. in the fed, chloroform was applied on a cloth to the nostrils of the feeder, and in 1 min. 30 secs., its pressure fell to 40 mm., while that of the fed rose

slightly to 170 mm.; and again, later in the same experiments with a pressure of the feeder of 78 mm., chloroform inhaled directly through a tube in the trachea caused, in fifty seconds, a fall of pressure to 46 mm., while the pressure of the fed rose from 210 mm. to 213 mm. The same effect is seen in the experiment on February 18th (Fig. 6, Tracing *l*, *m*, *n*), when chloroform was given to the feeder till its respiration stopped and its blood pressure was reduced from 50 mm. to 20 mm.; the pressure in the fed at the same time rose from 162mm. to 180 mm., and remained high, and was 178 mm. when the respiration of the feeder stopped, four minutes after the chloroform was put on.

That chloroform-carrying blood passes to the brain of the fed is moreover indicated by the abolition of the conjunctival reflex. This was clearly shown in the last experiment referred to. Immediately before chloroform was given to the feeder, the eye of the fed gave the conjunctival reflex; but 1 min. 35 secs. later the reflex was less pronounced, and 1 min. 36 secs. later still had quite disappeared.

These experiments conclusively show that chloroform taken up by the blood in the lungs in the ordinary way, and carried to the brain only, leads to a rise, and not to a fall of blood pressure. This rise can only be due to a direct or indirect action on the vasomotor centre. It cannot be due to increased intracranial pressure which might be caused by more blood coming from the feeder, because it takes place at a time when the blood pressure of that animal is tending to fall. Again, it cannot be considered as merely dependent on a diminished supply of blood to the brain, a relative anæmia, due to the fall of the blood pressure of the feeder, because the rise of pressure of the fed is usually established before the fall in the feeder takes place. Again, the latter is, except late in the administration of the chloroform, only small in extent, while from observations we have made on the effect of ligature of the brain arteries successively, it appears that a large diminution of the blood supply of the brain needs to be made to lead to a marked and lasting rise of pressure.

The rise of pressure observed in these experiments must then be due, largely at any rate, to a specific action of the chloroform.

Tracings of the respiration were not taken in these experiments, so that the effects produced on the respiration of the fed when chloroform was given to the feeder, can only be inferred from the respiratory undulations on the blood pressure tracing, and from such direct observations of the animal as were made at the time.

The few of these from which any inference can be drawn only show that the respiration of the fed usually becomes slower one or two minutes after chloroform is given to the feeder. Thus in one experiment with two dogs, when the respiration of the fed was 14 per minute, the administration of chloroform to the feeder led in one minute to a reduction of rate to 11 per minute; and later on, in the same experiment, led in one minute to a reduction of rate from 16 per minute to 12 per minute. Again, in the experiment with two dogs on February 18th, the rate of respiration was reduced in one minute from 29 per minute to 20 per minute. In one experiment, however—namely, that on March 19th, a quickening of respiration was in the same time produced, namely, from 15 per minute to 18 per minute.

3. *The Effect on the Fed of Chloroform Administered to the Fed.*—On the other hand, when chloroform is inhaled by the fed animal, and is carried to the heart and all other organs except the brain, a marked fall of blood pressure is always produced. In the experiment on February 18th (Fig. 6), where the blood pressure of the fed dog one minute after the cross circulation was established was 160 mm. (Fig. 6, Tracing *b*), the tube in its trachea was connected to the chloroform bottle. After the lapse of half a minute the pressure began to fall at first slowly, and during the next minute and a-half was reduced to 136 mm. (Fig. 6, Tracings *c*, *d*, *e*), it was then falling rapidly, and in eleven seconds more—that is two minutes eleven seconds after the chloroform was put on, the tracheal tube was removed from the chloroform bottle, the blood pressure being 120 mm. It however continued to fall for twenty seconds more to 104 mm. (Fig. 6, Tracing *f*), and then began to rise, and in less than a minute and a-half had regained its original height of 162 mm. (Fig. 6, Tracings *g*, *h*, *k*). The chloroform was prevented by the ligature of the brain arteries from reaching the brain; and that it did not do so is shown by the fact that the conjunctival reflex was not abolished, which it undoubtedly would have been in an intact animal supplying its own brain with blood had so extensive a fall of pressure occurred in consequence of the administration of chloroform. Again, in the experiment on March 19th, five and a-half minutes after the cross circulation was established, when the blood pressure of the fed animal was 186 mm. (Fig. 8, Tracing *a*), its trachea was connected to the chloroform bottle, and in one minute the pressure had fallen to 176 mm., in two minutes to 150 mm., and in three minutes to 138 mm. (Fig. 8, Tracings *b*, *c*, *d*, *e*, *f*. *g*.) The chloroform, however, was not removed till four minutes later; the pressure was then 132 mm. On the withdrawal of the chloroform the pressure began to recover, and in 43 seconds was 140 mm. (Fig. 8, Tracing *m*), and in one minute more had reached 152 mm. (Fig. 8, Tracing *n*). In the rabbit the fall of pressure was usually more rapid, and the contractions of the heart were, as far as could be judged from the blood-pressure tracing, extremely weakened so as to be quite imperceptible. This is well seen in the experiment on February 23rd (Fig. 9), when chloroform given to the fed animal when its blood pressure was 105 mm. led to a rapid fall in one minute to 66 mm., in two minutes to 54 mm., and in three minutes to 24 mm.; and twenty seconds later, when the chloroform was taken off, the pressure was only 20 mm. (Fig. 9, Tracings *c*, *d*, *e*). No indication of the beat of the heart could be seen on the tracing before this stage, and there was no recovery of the blood pressure after the chloroform was removed, for it continued to fall still further, and in five minutes more was 7 mm. Except for a pause in the respiration for about twenty seconds immediately after the chloroform was removed, the animal continued to breathe for the whole of this time, its brain being of course supplied with blood from the feeder. After the natural respiration had ceased, artificial respiration was put on for four minutes, but there was no recovery in the blood pressure, and a needle placed in the heart showed no sign of movement.

Again, in the experiment on February 20th, when the blood pressure was 131 mm., the trachea of the fed animal was connected with the chloroform bottle, and in one minute the pressure had fallen to 107 mm. (Fig. 10, Tracing *b*), and when the chloroform was taken off thirty seconds later was 84 mm.; the pressure was then falling rapidly (Fig. 10, Tracing *c*), and thirty seconds later the pressure had sunk to 36 mm., and there were no longer indications on the tracing of heart beats. The respiration continued for three minutes and a-half after the indication of heart beat was lost. The heart was not permanently arrested, as, after an apparent cessation of beat for about two minutes, it commenced to beat again, and continued to beat slowly for about three minutes, and then gradually stopped.

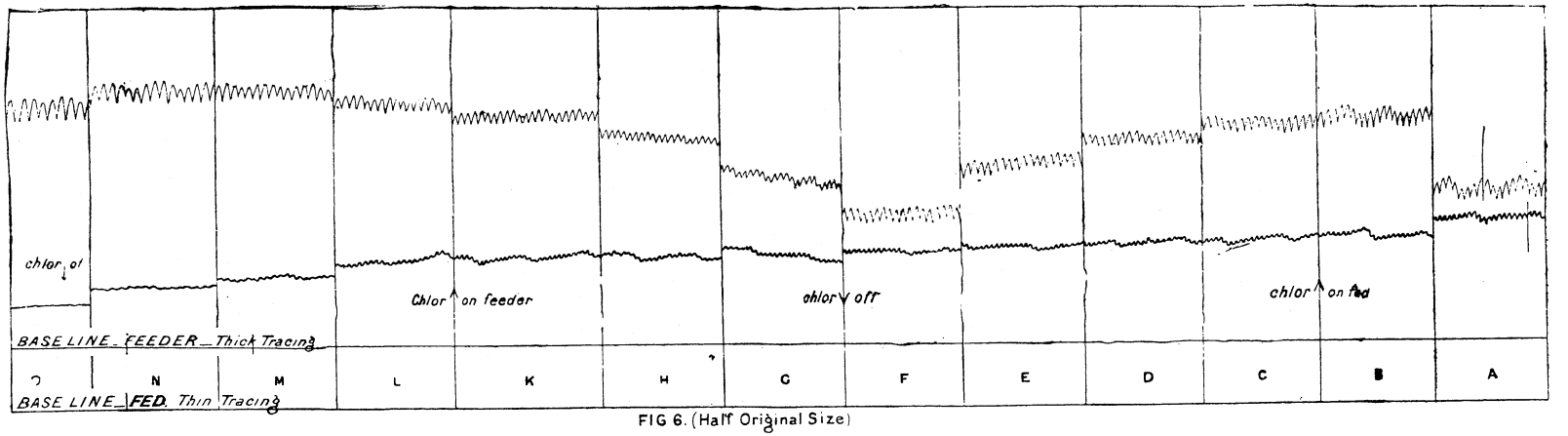

FIG 6. (Half Original Size)

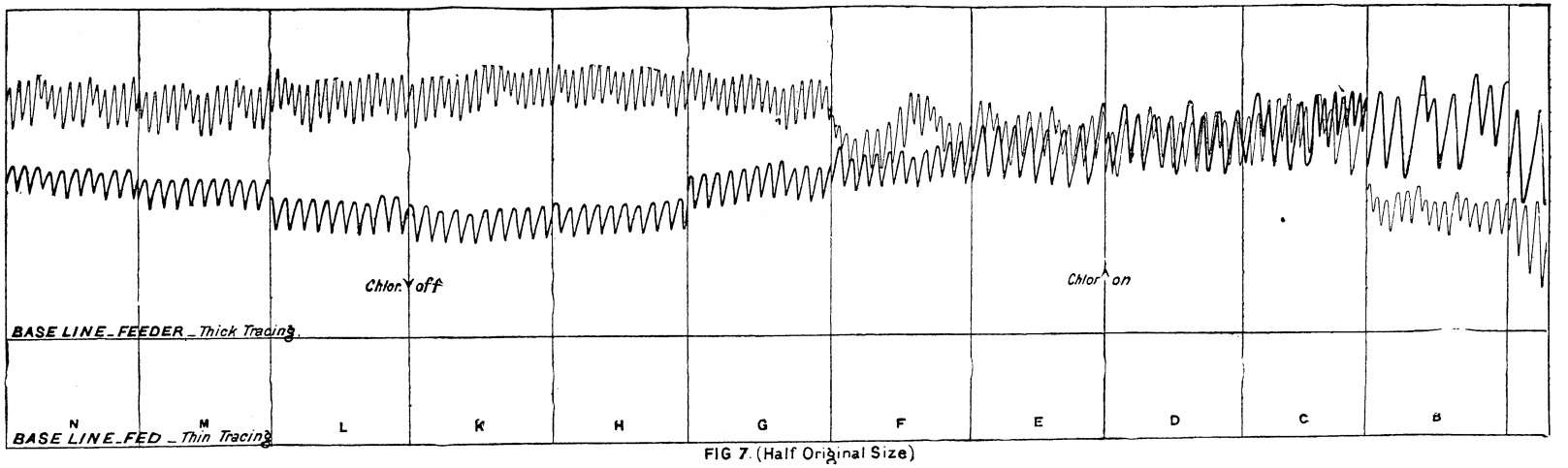

FIG 7. (Half Original Size)

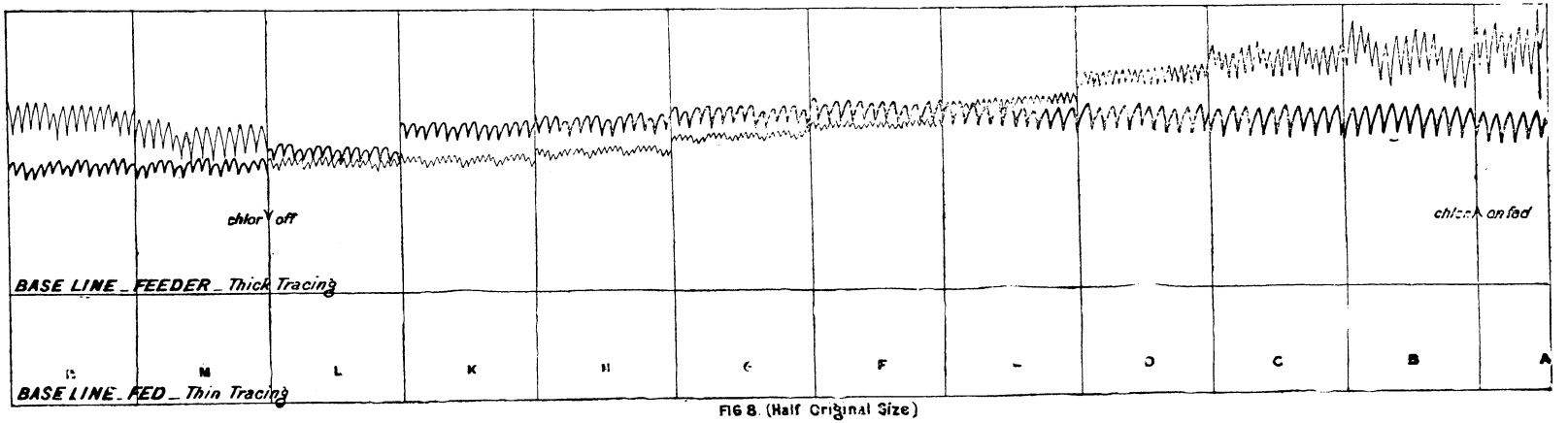

FIG 8. (Half Original Size)

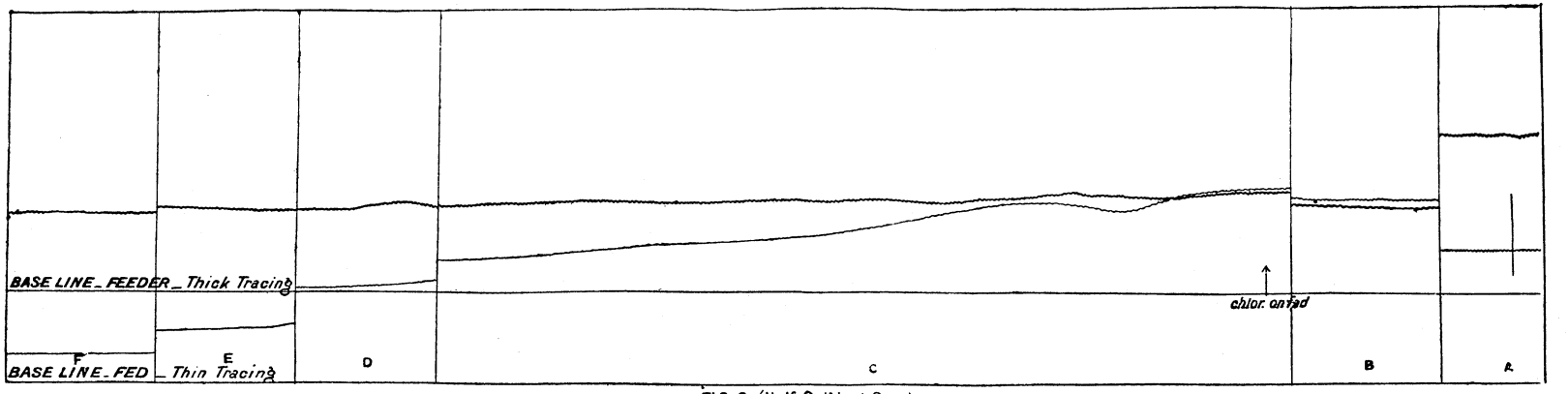

FIG 9 (Half Original Size)

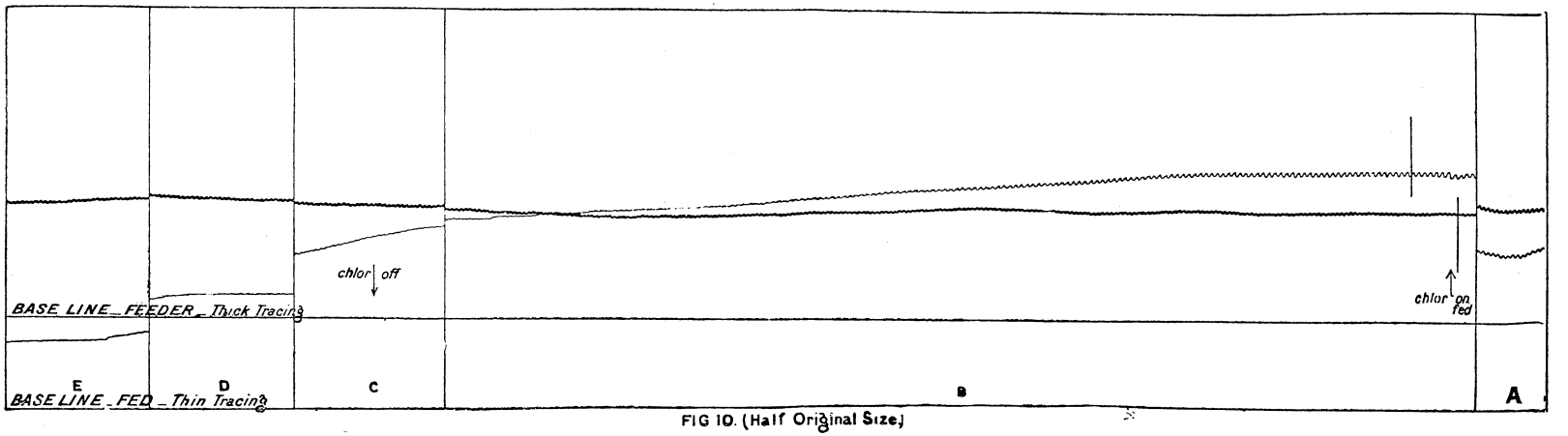

FIG 10. (Half Original Size)

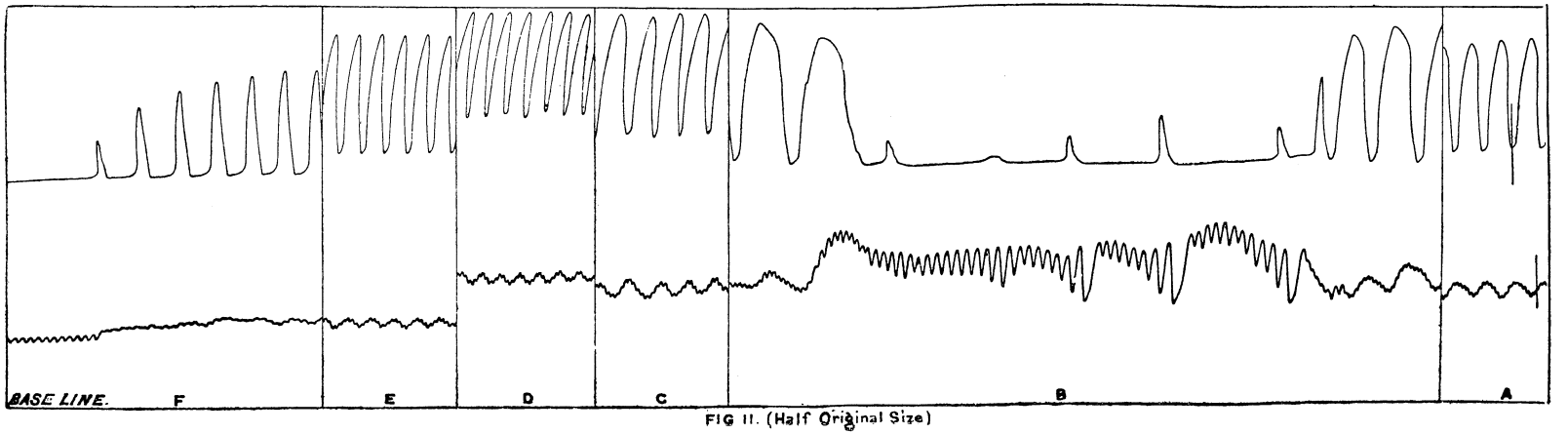

FIG 11. (Half Original Size)

FIG. 6.—*February 18th, 1891. Cross Circulation. Dogs. Peptone Injected.*

Feeder.—Left carotid connected to both carotids of fed; left jugular to right jugular of fed.

Fed.—Left subclavian proximal to vertebral tied; right ascending cervical tied; both carotids connected to left carotid of feeder; right jugular to left jugular of feeder; left external jugular tied; left vagus cut.

Time.	Mean Blood Pressure of Feeder in mm.	Mean Blood Pressure of Fed in mm.	Chloroform.	Remarks.
H. M. S.				
3 2 20	68	122	—	Tracing *a*.
3 2 30	—	—	—	Right vertebral of fed tied and cross circulation established.
3 4 0	58	160	Chloroform on to fed	Tracing *b*.
3 5 0	56	156	—	Tracing *c*.
3 5 30	54	144	—	Tracing *d*.
3 6 0	54	136	—	Tracing *e*.
3 6 11	54	120	Chloroform off	—
3 6 30	52	104	—	Tracing *f*.
3 7 0	52	126	—	Tracing *g*.
3 7 30	50	146	—	Tracing *h*; eye of fed gave conjunctival reflex.
3 7 55	50	162	Chloroform to feeder	Tracing *k*; chloroform to feeder.
3 8 15	46	167	—	Tracing *l*.
3 8 30	38	174	—	Tracing *m*.
3 9 30	32	180	—	Tracing *n*; conjunctival reflex of fed less pronounced
3 11 6	24	168	Chloroform off	Tracing *o*; no conjunctival reflex in fed.

FIG. 7.—*March 19th, 1891. Cross Circulation; Dogs; Chloroform to Feeder. (Leech Extract.)*

Feeder.—Left carotid connected to both carotids of fed. Left jugular connected to right jugular of fed.

Fed.—Right vertebral, right and left ascending cervical ligatured. Both carotids connected to left carotid of feeder. Left jugular ligatured. Right jugular connected to left of feeder.

Time.	Mean Blood Pressure of Feeder in mm.	Mean Blood Pressure of Fed in mm.	Chloroform to Feeder.	Chloroform to Fed.	Remarks.
H. M. S.					
3 23 0	100	110	—	—	Tracing *a*.
Pause of 32	—	—	—	—	During which the above connections were made.
4 9 0	112	128	—	—	Tracing *b*. At 4 h. 9 m. 30 s. connections between carotids opened. Connections between jugulars opened. At 4 h. 10 m. 50 s. left vertebral of fed clamped, and so isolation of brain circulation and cross circulation fully established.
4 11 0	100	168	—	—	Tracing *c*.
4 12 0	100	160	—	—	Tracing *d*.
4 12 27	—	—	Chloroform on	—	—
4 12 30	98	166	—	—	Tracing *e*.
4 13 0	94	173	—	—	Tracing *f*.
4 13 30	82	188	—	—	Tracing *g*.
4 14 0	62	197	—	—	Tracing *h*.
4 14 30	60	195	Chloroform off	—	Tracing *k*.
4 15 0	66	190	—	—	Tracing *l*.
4 15 30	79	188	—	—	Tracing *m*.
4 16 0	88	186	—	—	Tracing *n*.

FIG. 8.—*March 19th, 1891. Cross Circulation; Dogs; Chloroform to Fed. (Continuation of the Experiment illustrated by Fig. 7.)*

Time.	Mean Blood Pressure of Feeder in mm.	Mean Blood Pressure of Fed in mm.	Chloroform to Fed.	Remarks.
H. M. S.				
4 16 5	88	188	—	Tracing *a*.
4 16 20	—	—	Chloroform on	—
4 16 30	90	184	—	Tracing *b*.
4 17 0	90	180	—	Tracing *c*.
4 17 30	90	174	—	Tracing *d*.
4 18 0	93	156	—	Tracing *e*.
4 18 39	93	148	—	Tracing *f*.
4 19 0	94	144	—	Tracing *g*.
4 19 30	90	136	—	Tracing *h*.
4 20 0	88	131	—	Tracing *k*.
4 20 30	86	130	—	—
4 21 0	84	130	—	—
4 21 30	82	130	—	—
4 22 0	76	130	—	Tracing *l*.
4 22 30	72	132	—	—
4 23 0	72	132	—	—
4 23 17	—	—	Chloroform off	—
4 23 30	70	135	—	—
4 24 0	70	140	—	Tracing *m*.
4 24 30	68	146	—	—
4 25 0	68	152	—	Tracing *n*.

FIG. 9.—*February 23rd, 1891. Cross Circulation. Two Rabbits. (Leech Extract.)*

Feeder.—Carotids connected to carotids of fed respectively. Left subclavian to right subclavian of fed. Left jugular to right jugular of fed.

Fed.—Carotids to carotids of feeder respectively. Right subclavian tied proximal to vertebral, and with all branches except vertebral ligatured, connected to left subclavian of feeder. Right jugular to left jugular of feeder.

Time.	Blood Pressure of Feeder in mm.	Blood Pressure of Fed in mm.	Chloroform to Fed.	Remarks.
H. M. S.				
4 39 40	84	70	—	Tracing *a*.
4 40 0	—	—	—	Left vertebral and left jugular of fed tied, and cross circulation established by the three arterial channels and one venous channel.
4 41 0				
4 42 0	48	90	—	—
4 43 0	45	98	—	Tracing *b*.
4 44 0	53	105	Chloroform to fed.	—
4 44 30	47	86	—	Tracing *c*.
4 45 0	45	66	—	—
4 46 0	44	54	—	Chloroform with more air. No longer indication of heart beats on the pressure tracing. Tracing *d*.
4 46 40	44	28	—	Chloroform quite strong. Tracing *e*.
4 47 20	—	20	Chloroform off	—
4 48 0	44	15	—	Respiration continued at the slow rate of five per minute. Tracing *f*.
4 49 0	—	10	—	—
4 50 0	45	8	—	—
4 51 0	—	7	—	—
4 52 0	—	7	—	—
4 52 20	52	7	—	Last respiration of fed.

FIG. 10.—*February 20th, 1891. Cross Circulation between Two Rabbits. (Leech Extract Injected into Jugular Vein of Fed at 1 p.m.; of Feeder at 1.20 p.m.)*

In fed rabbit right carotis, right vertebral, and left subclavian were ligatured, so that animal only had left carotis open to supply the brain region.

In feeder the carotids on both sides were prepared, but not tied.

Time.	Mean Blood Pressure in Feeder.	Mean Blood Pressure in Fed.	Chloroform to Fed.	Remarks.
H. M. S.				
2 0 0	60	87	—	Leech extract injected into feeder. Pressure in both animals remained very constant, with heart beats showing plainly on both tracings. Leech extract injected into fed at 2 h. 7 m. 30 s. This injection produced no effect on the tracing.
2 8 0	62	87	—	Tracing *a*. The cross circulation was now begun to be established, but by mistake the connection between the left carotis of the fed and the right carotis of the feeder was begun first; in consequence, immediately upon the ligature of the left carotis of the fed the brain of the latter was for the moment deprived of all blood, with the result of causing Kussmaul-Tenner convulsions and a threatening of cessation of respiration. Artificial respiration was at once put on, and the cross circulation as quickly as possible established by connecting together the right carotis of the fed with the left carotis of the feeder and the right jugular vein of the fed to the left jugular of the feeder. When the cross circulation was well established the artificial respiration was removed, and the fed animal was found to be breathing spontaneously without any sign of convulsions. The effects produced by this accidental ligature of the only remaining brain artery of the fed is very instructive, as it demonstrates in the clearest way the efficiency of the cross circulation; without cross circulation ligature of the four brain arteries produces convulsions and quickly cessation of respiration; with cross circulation ligature of the four brain arteries causes no convulsions, no threatening of cessation of respiration.
2 33 30	—	—	—	Artificial respiration off.
2 34 30	60	131	Chloroform to fed	The pressure on fed had been constant for half a minute before the chloroform was given, and heart beats were very visible on the tracing.
2 35 30	58	107	—	Tracing *b*.
2 36 0	60	84	Chloroform off	Tracing *c*. Heart beats difficult to see in tracing of fed, pressure falling very rapidly.
2 36 15	61	62	—	Tracing *d*.
2 36 30	62	36	—	Tracing *e*. Heart beats quite imperceptible in tracing of fed.
2 37 30	62	34	—	Respirations of fed. 14 per minute. The respirations of the fed animal became shallower and shallower, and finally ceased at 3.40, that is, four minutes after the end of the chloroform administration. Before the respirations had ceased the slowened heart beats of the fed animal reappeared on the tracing for a time and caused the mean blood pressure to rise to 56 mm. at 3.39.

These cross-circulation experiments confirm absolutely the previous experiments in which chloroform was injected directly into the circulation. In both cases the blood containing chloroform excites the vasomotor centre and raises the blood pressure when it reaches the medulla oblongata, while it depresses the heart's action and lowers the blood pressure when it reaches the heart.

It is, then, clearly proved that the primary fall of blood pressure seen during chloroform administration is not due to paralysis of the vasomotor centre. We must, then, look beyond the central nervous system for an explanation of this fall—that is, to a direct paralysing action of the drug upon the vascular system—a direct action, therefore, upon the heart and blood vessels.

CRITICISM OF THE PROOFS OF THE COMMISSION THAT THE FALL OF PRESSURE IS NOT DUE TO WEAKENING OF HEART.

We have already, in the beginning of this paper, referred to the conflict of opinion upon the question whether, and in what way, chloroform affects the heart directly, and, seeing that the chief papers of late years have been collected together and published by Lawrie in the Report of the Hyderabad Commission, it is unnecessary to do more than refer to the evidence in that book as to the present state of the question. On the one hand, a large array of observers look upon it as proved that chloroform weakens the force of the contractions of the heart by its direct action upon the heart; on the other hand the Hyderabad Commission, as represented by Brunton, considers that chloroform only affects the heart in combination with an asphyxial condition of the blood, and, as represented by Lawrie, denies *in toto* any direct action of the drug upon the heart under any circumstances. To our minds it is perfectly clear that the weakening effect of chloroform on the heart is the chief, if not the only, cause of the fall of blood pressure seen upon administration of the drug, and it is difficult to understand how the Hyderabad Commission could have arrived at the conclusions they have published, for their experiments and their large number of curves confirm again and again the observations of others, and point directly to heart failure as the cause of the fall of blood pressure.

The report of the second Hyderabad Commission consists of five parts, in Part v of which all the manometer experiments are described in detail, and remarks made upon a large number of the individual experiments. This description of experiments and the remarks upon them, together with the tracings, form the most valuable part of the report, for they give the facts upon which the conclusions of the Commission are based. In their report the Hyderabad Commission do not state what is the reason of the fall of blood pressure so characteristic of chloroform poisoning; they imply, however, that such fall is not due to any direct action on the heart, but to the paralysis of the vasomotor centre through the drug. The reasons for such a belief are given on p. 137 in the discussion which follows Experiment 178.

"Experiment 178 is very like Experiment 162, in which the heart's action was temporarily arrested every time the respiratory centre was paralysed. As in 162, there was no further fall of blood pressure during the arrest, and the beats on each side of the stop were ample and strong. The most remarkable instance of this is seen at Fig. 13. For more than two minutes there were only 17 very slight pulsations recorded, and for over a minute of this tracing there was no pulsation at all. There was no fall of pressure during the arrest, and the Ludwig tracing shows how strong the beats on each side of it were. No better proof could be afforded than is to be found in these two experiments that direct weakening of the heart is not the cause of the fall of the blood pressure, which is inseparable from chloroform narcosis.

"Experiments 64, 65, 162, 178, and 186 prove three important points:—1. A general fall of blood pressure, whether sudden or gradual, is not in itself dangerous. 2. The fall of blood pressure, which occurs in chloroformisation with regular breathing, is due solely to narcosis of the vaso-

motor system, and is, if not a safeguard, absolutely harmless. 3. The fall of the blood pressure under chloroform is not due to weakening of the heart. The heart has nothing to do with producing it, unless the vagus is stimulated, or unless its nutrition fails either from imperfect oxygenation of the blood due to abnormal breathing, or from stoppage of the respiration from overdosing."

Turning to Experiment 162, we find again the same argument as in 178, and then follow the words:

"If direct weakening of the heart were the cause of the fall of blood pressure in chloroform administration, we ought to find the heart beats getting smaller and smaller up to the time when the pressure reaches its lowest, and gradually growing bigger and bigger again on the other side as the effect of the chloroform wears off."

According then to this argument the presumption is that if the beats of the heart do get smaller and smaller up to the time when the pressure reaches its lowest, and do gradually get bigger and bigger as the effect of the chloroform wears off, then at all events we must not exclude the weakening of the heart as a factor.

In the first of the conclusions of the Hyderabad Commission, *cf. Report*, p. 17,[13] the events typical of chloroform inhalation are described and illustrated by tracings from Experiments 168, 169, and 170; in every one of these curves we see that the excursions due to the heart beat as measured on the Fick manometer, do in the most typical manner get smaller and smaller as the pressure falls.

Such curves abound throughout the tracings of the Commission, and are, as they truly say, typical of the fall of pressure under chloroform. Everyone who has worked at the action of chloroform always obtains such curves, and everyone would agree with the Commission that they are of the typical kind which would be produced, if direct weakening of the heart were the cause of the fall of blood pressure in chloroform administration.

It is somewhat surprising that the Commission should have laid such stress upon Experiments 64, 65, 162, 178, and 186, as to assert that these tracings proved that the fall of blood pressure under chloroform is not due to weakening of the heart, when they make statements just before, which, applied to their typical curves, show that these are of the kind that would necessarily occur if the chloroform did cause a fall of blood pressure through weakening of the heart. It is natural to suppose that the evidence in these cases must be very strong before the Commission would allow it to have sufficient weight to overpower the evidence of what they style their typical cases. As a matter of fact these cases afford no proof whatever that the heart's action is unimpaired by the action of chloroform. In all the cases quoted the tracings afford simple illustrations of a peculiarity of blood-pressure tracings, which is well known.

Proof from Size of Pulse Excursions on the Pressure Tracings.

The size of the excursions on the blood-pressure curve, however taken, due to the beats of the heart, depend upon the amount of blood thrown into the aorta at each beat and upon the extent of fulness of the aorta at the time when the contraction of the heart takes place. Further, the amount of blood thrown into the aorta depends upon the force of the contraction of the left ventricle and upon the amount of blood coming to that ventricle, which again depends upon the condition of the pulmonary and systemic blood vessels, and the extent of fulness of the aorta at the time depends upon the rate of heart beat, as well as its strength, and upon the amount of resistance to the flow of blood through the peripheral organs. We have then the following factors to consider:

1. Strength of contraction.
2. Rate of contractions.
3. Condition of peripheral resistance.

Both in the natural circulation and in the artificial scheme it is found that if 2 and 3 are kept constant and, 1, the strength of the contractions diminish, then the mean blood pressure falls and the excursions on it due to the heart beat are diminished in size. In fact curves are obtained precisely similar to those which the Commission recognises as typical.

[13] See also *Lancet*, June 21st, 1890, where several of the tracings referred to are reproduced.

If 1 and 3 are constant, and, 2, the rate of beat is diminished then it is evident that the pulse excursions on the blood-pressure curve are increased in size, even to a very great extent, with a lowered blood pressure, for clearly the throwing in of the same amount of blood into the aorta, the walls of which are less tense owing to the greater length of time between each beat, must produce a greater excursion than when the walls are more tense. This effect of slowing of rate is very clearly seen when the vagus is stimulated. The large pulse excursions seen on the blood-pressure curve so characteristic of vagus stimulation do not in the least indicate any increase in the strength of the heart contracting, for, indeed, it is very probable that the contractions during stimulation of the vagus are slightly weaker than before the stimulation.

If 1 and 2 are constant and 3 diminished, then the size of the excursions on the blood-pressure curve tend to increase slightly and show no sign of diminution, until the diminution of the peripheral resistance has reached such an extent as to diminish the amount of blood flowing into the heart.

If 3 is constant and the strength of the contractions is diminished, then with the diminished blood pressure the pulse excursions will be increased in size if the rate is slower, because more blood is able to accumulate in the heart between the contractions.

If 1 is constant and 3 is diminished to such an extent as to diminish the amount of blood flowing into the heart, then with a slower rate the pulse excursions will be increased, because there is a longer time for the blood to accumulate between the contractions, and therefore more blood is thrown out with each beat.

We see then that in trying to interpret the meaning of any alteration in the size of the pulse excursions of any curve we must always take into account any variation of *rate*, and especially must we bear in mind the likelihood of any increase in the height of the pulse excursions being due to a slower rate of beat.

If now we turn to Experiments 64, 65, etc., it is at once clear that their importance is greatly over-estimated by the Commission, and that the so-called proof that chloroform does not affect the heart, which is afforded by them, is in every case an instance of a slight increase of the size of the pulse excursions due to a slowing of the heart's rate.

The first instance given is Experiment 64, and the argument is given as follows in paragraph 1 of the observations on the experiment, page 55:—

"9h. 14m. 20s.—Electrical irritation of peripheral ends of both vagi, causing an immediate fall of the blood pressure almost to zero. Chloroform administration was pushed during complete inhibition of the heart's action at 9h. 14m. 30s. There was entire absence of pulse tracing for more than one and a-half minute, the blood pressure remained nearly at zero, and the breathing became slow. The irritation and the administration of chloroform were both stopped at 9h. 16m. 0s. The blood pressure rose immediately to nearly its former height. It then gradually fell, exactly as it does in chloroform administration with normal breathing, and rose again spontaneously at the end of one minute. The fall of pressure after the cessation of vagus stimulation constitutes the most interesting phenomenon in this observation. From 9h. 14m. 20s. to 9h. 16m. 0s. cardiac inhibition, with sudden and prolonged fall of blood pressure, was caused by stimulation of the vagi. The arrest of the circulation, due to stoppage of the heart, prevented the chloroform, which from 9h. 14m. 30s. was saturating the air deep down in the lungs, from getting into the blood. But when the circulation was resumed at 9h. 16m 0s. the chloroform was forthwith taken up by the blood, and the respiration was no longer a factor in the process, except to eliminate it from the lungs. The effect of the uncontrollable absorption of chloroform into the blood was, not to give rise to any paralysis or weakening of the heart, but simply to produce the ordinary regular and gradual fall of the blood pressure, which is associated with narcosis of the nerve centres in the medulla, in normal chloroform inhalation."

It is impossible to test the assertion in the last paragraph of this quotation, because, unfortunately, no Fick tracing during the slight after-fall of pressure is given. Fick 16 is a sample taken before the stimulation of the vagi. Fick 17 shows the stoppage of the heart during the stimulation of the

vagi, and Fick 18 is taken six minutes after the end of the stimulation of the vagi. During the after-fall of pressure in question a pause in the Ludwig tracing occurs, as though a Fick tracing had been taken, but it is not numbered, and there is no sign of it among the Fick curves. On the other hand the series Fick 12, 13, 14, 15, and 16, afford a good instance of the typical recovery in the size of the pulse excursions after an excessive fall of pressure due to chloroform.

Experiment 65 is a fairly good instance of the effect of change of rate upon the magnitude of the pulse excursions. Thus Fick 4 in the series Fick 3, 4, 5, 6, gives larger excursions than Fick 6, owing to the much slower rate, although the mean pressure is higher in the latter curve. So also in Fick 8, 9, 10, the slowing of the heart produced by stimulation of the central end of the right vagus produces a larger pulse excursion.

Finally, the series Fick 12, 13, 14, 15, 16, 17, 18, 19 show most clearly the dependence of the size of the pulse excursions upon the rate, and also the manner in which the excursions of the pulse are diminished by chloroform. It is specially instructive to compare Fick 14, 15 with Fick 16, 17.

Experiment 162. In the observations on this experiment, p. 126, the Commission say: "If direct weakening of the heart were the cause of the fall of blood pressure in chloroform administration, we ought to find the heart beats getting smaller and smaller up to the time when the pressure reaches its lowest, and gradually growing bigger and bigger again on the other side as the effect of the chloroform wears off. Instead of this, Experiment 162 shows that there were ample pulsations on both sides of the temporary pauses. If Fick 9, with the Ludwig tracings on either side, is carefully studied, it will be seen that up to the time the heart beats ceased, the pulsations recorded in the Ludwig were ample and strong. There was then a temporary arrest of pulsation for 6 seconds (*vide* Fick 9). Immediately after Fick 9 the pulsation returned for 5 seconds (*vide* the Ludwig between 3h. 28m. 0s. and 3h. 29m. 0s.). Afterwards there was a long pause of 20 seconds without any pulsations at all. This pause was so marked that Dr. Bomford thought a clot had formed in the tube, and at 3h. 29m. 10s. he wrote on the Ludwig tracing '? clot.' Artificial respiration was just about to be commenced when the animal gave two spontaneous gasps; vigorous pulsations followed, and the pressure was raised in 5 seconds to the height it was at before chloroform was administered in Observation C."

Now the Commission, at the instance of Dr. Lauder Brunton, arranged purposely so that a mercury manometer tracing should be taken on a very slowly-running drum, for the purpose of seeing at a glance a record of a long blood pressure; in order at the same time to obtain a record of the pulsations, they arranged so as to connect up at will with a Fick manometer, which should register on a quickly-moving drum; and naturally all their conclusions as to size of heart contractions are drawn from the Fick tracings, while their conclusions as to fall of blood pressure are drawn from the Ludwig tracings. Whenever it was thought advisable during the Ludwig tracing to obtain a record of the pulse excursions, the Ludwig tracing was interrupted for a short time, and a tracing made with the Fick. This was done also in Experiment 162, with the result that the Fick tracings show in this instance, as in others, a diminution of the pulse excursions during the chloroform administration even to invisibility. These Fick tracings, 6, 9, 12, are taken in the ordinary way as samples, when the blood pressure has fallen very low, at a time when, according to the report, the Ludwig tracing showed that the heart was beating well and regularly, without any indication of any stoppage, and yet the sample taken with the Fick shows stoppage of the heart according to the Commission, in all three instances. We must say that any physiologist ought to have been very chary of drawing conclusions from an experiment in which the mere shifting of the tracing from the Ludwig to the Fick kymograph, and *vice versâ*, causes the contractions of the heart to disappear and reappear again respectively. As far as the heart pulsations are concerned, the Fick manometer is the guide to which the Commission has trusted throughout (except in this instance and in Experiment 178) and in Fick 6, it is clear that the pulsations are still visible, and even in Fick 9 the line is not perfectly even; very faint indications of pulsations are visible on it. As to the movements recorded in the Ludwig tracing on each side of Fick 9, upon which the Commission lays so much stress, even if they were due to contractions of the heart, they would not overweigh the positive evidence of the Fick tracing. There is no need, however, to suppose that they are evidence of heart contractions only; it is quite possible that they are due partly to heart beats and partly to respiratory movements so feeble as not to have been noticed by the observers who recorded cessation of respiration 55 secs. before Fick 9 was taken. If this were so, the true cessation of respiration would be signalled by the pause of 20 secs., which Dr. Bomford thought showed a possible clot in the cannula. Further, when artificial respiration was just about to be commenced the animal gave two spontaneous gasps, etc., showing that the respiratory centre was able to recover of itself, and was therefore not so very deeply affected by the chloroform. It is, however, impossible to argue about the excursions on a blood-pressure tracing, taken with a mercury manometer on a very slow-moving drum, without the simultaneous graphic record of the respiratory movements.

It is sufficient to point out that Experiment 162 gives no scientific evidence whatever that direct weakening of the heart is not the cause of the fall of blood pressure in chloroform administration, but, on the contrary, it confirms the other tracings of the Commission, that such weakening of the heart is, in all probability, the cause of the blood pressure fall.

The observations of the Commission on Experiment 178 have been already quoted. Here again we see, as in Experiment 162, that the Commission disregards the evidence of the Fick tracings, and places reliance upon the Ludwig tracings as to the strength of the heart beats, and yet the Fick tracings in this experiment throughout give the most typical curves of the steady diminution in the pulse excursions as the pressure falls; this is especially well seen in the series, Fick 14, 15, 16, 17, 18, 19, and also 20, 21, 22, 23, 24, 25, 26, 27. The series 4, 5, 6, 7, 8, 9 illustrate the effect of a slower rate on the size of the excursions; so also do the series 10, 11, 12, 13, in which the combined effect of the weakening of the strength and the slowing of the rate of the contractions is well shown. In Experiment 186 no Fick tracings are given, and the Ludwig tracing on the slow drum gives no possibility of coming to any conclusion as to the condition of the heart.

It is perfectly clear, then, that this part of the so-called proof given by the Hyderabad Commission of the absence of any direct effect upon the heart when chloroform causes a fall of pressure is no proof at all; but, on the other hand, all their curves yield evidence to the exact contrary.

Proof from Injection into Jugular.

So also the second part of their proof, as given in paragraph 19 of their conclusions, namely:[14] "On the other hand, it seems clear from Experiment 92 that the direct action of chloroform on the heart's substance is not the cause of the fall of pressure that occurs when it is inhaled," is equally inadequate. Experiment 92 is one of a series of experiments in which chloroform was injected into the jugular vein and so directly to the heart. In this experiment the jugular vein *was tied*, and then injections of chloroform were made into it as follows: 20 m at 8 h. 0 mins.; 20 m at 8 h. 2 mins. 30 secs.; 20 m at 8 h. 3 mins. 45 secs.; 20 m at 8 h. 5 mins. 45 secs. At 8 h. 5 mins. it was noticed that the cornea was not sensitive, but no observation was made before that time as to whether the cornea had been sensitive. Before the last injection no appreciable effect was produced on the blood pressure or on the respiration. Then after the last injection a rapid marked fall of blood pressure occurred. In other words, owing to the jugular being tied the injection did not really travel to the heart, but accumulated in the tied vein. In our experiments the chloroform was always injected into the vein directly by means of a hypodermic syringe, so that the circulation in the vein was bound to carry it on; in no case was it found possible by us to inject four doses of even 2 m each before producing a fall of blood pressure.

Then at 8 h. 13 mins. 20 m and at 8 h. 14 mins. 20 m were injected, followed by a still further fall of blood pressure, and then at 8 h. 33 mins. it was noticed that the cornea was slightly sensitive, the blood pressure at this time being on the

[14] *Report*, p. 21.

rise. In other words, after the injection of 120 ♏ of chloroform into the vascular system in addition to what had been given previously to a dog weighing 33¼ lbs., the cornea was sensitive half an hour after the first injection. Then at 8 h. 40 mins. 30 secs. another 20 ♏ injected; at 8 h. 42 mins. 30 secs. cornea still sensitive. At 8 h. 43 mins. 15 secs. another 20 ♏ injected; at 8 h. 45 mins. cornea insensitive with a falling blood pressure. At 8 h. 46 mins. another injection of 20 ♏; and at 8 h. 53 mins. 30 secs. respiration stopped with blood pressure very low; at 8 h. 54 mins. thorax opened, heart perfectly still, not irritable; and at 8 h. 55 mins. 30 secs. gasping from regular rhythmical movements of the diaphragm.

It appears to us that the conclusion to be drawn from this experiment is that a large amount of the chloroform injected stayed in the jugular vein, and was only gradually brought into the circulation. It is difficult to conceive that after so large an amount the cornea could have been still sensitive if it had been all in circulation.

The experiment seems to point directly to a weakening of the heart's action, especially when we find that only thirty seconds after the cessation of respiration the heart is described as perfectly still, not irritable.

From a similar examination of Experiment 91 we conclude that as in Experiment 92 no appreciable amount of chloroform reached the circulation until the fourth injection, and then the fall of blood pressure was not incompatible with the action of chloroform on the heart.

We conclude then that the experiments of the Hyderabad Commission, as well as our own, give no support to their conclusion that the fall of blood pressure in chloroform administration is not due to any weakening of the heart's action, but on the contrary their curves if rightly interpreted agree absolutely with our own, and both confirm the commonly accepted view that the fall of blood pressure due to the action of chloroform is mainly caused by the weakening of the heart's contractions.

Action of Chloroform on Blood Vessels Directly.

Finally the fall of blood pressure may be due not entirely to the action of the drug upon the heart, but also to its direct action upon the blood vessels. It is clear that a fall of pressure might be caused by the action of a drug upon the blood vessels, both if the drug causes constriction and also if it causes dilatation of blood vessels. In the first case the vessels to be constricted must evidently be the pulmonary vascular system, and any long continued fall must mean so excessive a constriction of the pulmonary vessels as greatly to hinder the passage of blood from the right to the left side of the heart. The physiological result of such a hindrance must manifest itself in two ways: (1) the right side of the heart must become greatly distended with blood while the left side remains empty, and (2) the pressure in the pulmonary artery must rise as the pressure in the systemic aorta falls. Such a condition of the pulmonary vessels has been asserted lately by Johnson[15] to be typical of the asphyxial condition, and he says that in all cases of death by asphyxia this condition is manifested by the enormous size of the right side of the heart and the remarkable whiteness of the lungs, due to the persistent contraction of the pulmonary vessels even after death.

Seeing the possibility that asphyxial conditions may play a decided part in death from anæsthetics such as ether and chloroform, we have made a few experiments for the purpose of testing the meaning of this extreme whiteness of the lungs when the animal is killed by occlusion of the trachea, and have found that the phenomenon depends upon the phase of respiration at the time when the tracheal tube is closed; if the lungs are distended in inspiration and the trachea closed at this moment, then upon death the symptoms described by Johnson are most manifest; if, on the other hand, the trachea is closed at the height of expiration, then upon death the lungs present the usual reddish colour and no sign of vascular constriction is to be seen. The phenomenon depends clearly enough on the emptying of the lung vessels by pressure and not by vascular constriction. There is, then, as far as we know, no evidence that the asphyxial condition brings about any special contraction of the pulmonary vessels, and so, too, there is no evidence that chloroform causes a contraction of those vessels, but rather evidence against it. The important point is the observation of Bradford that the pressure in the pulmonary artery, as measured from a branch, does not rise when chloroform is given, but falls *pari passu* with the pressure in the systemic aorta; such an experiment is the natural result if the fall of pressure in both is due to a weakening of the central organ—the heart, but is impossible if the fall of pressure in the aorta is due to the chloroform causing an obstruction to the flow of blood through the lungs.

Further, the observations of McWilliam point to a dilatation of both sides of the heart as the effect of chloroform and not of the right side only; and although in the absence of any tracings, and with a feeling of doubt as to the validity of the methods employed by McWilliam, we are not prepared to agree to all his statements, yet we can say with confidence that in a number of cases where the heart appeared dilated after death from chloroform, both sides were dilated.[16]

There is no evidence, then, that the fall of blood pressure is due in any way to obstruction of the flow of blood through the lungs. There remains the question whether it is due to any extent to a direct relaxing influence of chloroform upon the muscular tissue of the systemic vascular system. Such an action is *a priori* probable because of the close relationship between the muscular tissue of the heart and blood vessels; there is, however, no evidence that direct vascular dilatation, owing to the presence of chloroform in the blood, plays any great part in the fall of blood pressure.

The original experiments of Lister showed that not only a drop of chloroform when applied, but also the vapour of chloroform, was able to produce hyperæmia in the web of the frog's foot. The evidence, however, of any direct dilatation of vessels when chloroform is inhaled does not appear to exist, and, in fact, in such a book as Dastre's, on anæsthetics, the pallor of the face so often noticed is considered to indicate vascular constriction as the effect of the drug rather than vascular dilatation; but, as far as we can gather from his book, we see no reason to suppose that the pallor cannot be explained by weakening of the heart. Roy and Sherrington[17] assert that chloroform causes constriction rather than dilatation of the vessels of the brain, while, on the other hand, Hürthle[18] from his experiments finds at first dilatation of the brain vessels as the direct effect of chloroform. This is followed shortly before death by constriction. We ourselves have tried to produce a fall of blood pressure by allowing chloroform vapour to pass in and out of the abdominal cavity through two openings as far removed from one another as possible, expecting that a local dilatation of the vascular area governed by the splanchnic nerves might be produced in this way, and so lead to a considerable fall of blood pressure. The experiment was, however, negative, and gave no indication that the blood pressure fall of ordinary chloroform inhalation was to any degree whatever due to direct dilatation of the abdominal vascular area. The volume of such an organ as the spleen does not increase when chloroform is given to the animal, as it would if a dilatation of its vessels or a relaxation of its muscular tissue occurred, but, on the contrary, diminishes more than can be accounted for by the fall in general pressure, showing that there is some active constriction. From these imperfect observations we are inclined to think that whatever action chloroform has directly on the blood vessels, it is insignificant compared with its much greater effects, primary and secondary, indirectly through the vaso-motor centre.

The Dangers of Chloroform Administration.

The conclusions and report of the Hyderabad Commission deal with two distinct and separate questions (1) the physiological action of chloroform, and (2) the dangers of chloroform administration. We have already discussed the first question, and have shown why in our opinion the physiology of the Commission is wrong; it is therefore with all the greater pleasure that we can now turn to the second question, and state that in our opinion the principles which have guided Lieutenant-Colonel Lawrie

[15] *Proc. Roy. Soc.*, xlix, 144.

[16] The tracings have now been published in *Journ. o Physiol.*, xii, Dec 1892.

[17] *Journ. of Physiol.*, vol. xi, p. 97.

[18] *Pflüger's Archiv*, vol. xliv, p. 596.

in the administration of chloroform are entirely in the right; that the great value of the Hyderabad Commission, for which the thanks of the medical profession will always be given to H.H. the Nizam, is the confirmation of Lawrie's views as to the safe method of administering chloroform, and also the publicity which has been given to the fact that by this method chloroform has been administered to many thousands of persons, not by experienced anæsthetists but by the students of the hospital without the occurrence of a single death.

The principle upon which Lawrie administers chloroform may be summed up in a single sentence: "Never at any moment of the administration of chloroform administer it in so concentrated a form as to cause irregularity of respiration, and cease the administration as soon as complete anæsthesia has been induced." Nature herself provides the signs and symptoms which show when the drug is being given in too concentrated a form, for when the air breathed contains too great a percentage of chloroform vapour the animal endeavours in three different ways to safeguard itself against the poisonous vapour; it struggles for the purpose of getting away, it holds its breath for the purpose of not taking more in, and its heart stops beating for the purpose of not sending on the poison to the nerve centres. Great credit is due to the Hyderabad Commission for their strong insistence upon the safeguard action of these three occurrences. Snow had previously pointed out the absence of danger from holding the breath and from stoppage of the heart, as already mentioned, but the experimental evidence of the safeguard action of the vagus nerve is due to the Hyderabad Commission. The result of the struggling is to increase the rate and depth of the respirations and to raise the blood pressure, owing, according to Zuntz and Geppert,[19] to the action of the products of muscular activity in the blood.

The result of holding the breath is an after-increase of respiration and the stoppage of the heart through the vagus is followed by a reaction in the opposite direction, so that as Snow points out and as the Commission emphasises, there is now a danger of an excessive amount of chloroform being taken in, with the evil results of over-concentration.

The logical conclusion is, as Lawrie points out, to remove the chloroform further from the face until the blood pressure and respiration have recovered, and seeing that the respiration is so easily and markedly affected, he fixes his attention on that and says—Wait till the breathing is regular before the chloroform is again placed nearer the face.

What is the danger of concentration?

Snow says the heart is only affected when the chloroform is given in too concentrated a form.

Lawrie says pushing chloroform overpowers the respiration and then the heart fails.

Cushny[20] says that too great concentration affects the heart.

Brunton considers the sequence of events to be as follows: first, the respiration is affected, with the result of causing an asphyxial condition of the blood, and then the combined action of chloroform and asphyxia affects the heart.

We see here another instance of an ever-recurring difficulty in physiological investigations, namely, to determine which is cause and which is effect; with an overdose, does death take place through weakening of the heart or through failure of the respiration?

What is true is this, as pointed out by the Hyderabad Commission—the respiration stops before the heart actually ceases to beat. This, however, does not necessarily imply that an overdose kills by its action on the respiration. Such a death may be brought about in two ways: 1. Weakening of respiration, causing insufficient aëration of the blood, which in its turn causes heart failure, through the combined action of asphyxia and chloroform. 2. Weakening of heart, causing an insufficient blood supply to the respiratory centre, which in its turn causes cessation of respiration through the combined action of chloroform and an insufficient blood supply.

In both cases the chloroform affects both heart and respiratory centre, in both the respiration stops before the heart ceases to beat; but (1) is a case of death from respiration failure mainly, and (2) from heart failure mainly. The rapid fall of blood pressure due to an overdose is clear evidence of a weakening of the heart, as already proved; so that if our statements are accepted, it follows that the first explanation is less likely than the second. In our experiments we have seen very distinct evidence that the respiratory centre is much more easily affected by chloroform when its blood supply is diminished to a considerable extent.

[19] *Pflüger's Arch.*, xxxviii, 337

[20] *Lancet*, March 14th, 1891.

Chloroform with Diminished Blood Supply to the Medulla.

We have been very much struck, both in the experiments on cross circulation and on the effect of ligature of the brain arteries, to find that, after the occlusion of two or more of the brain arteries, a very slight amount of chloroform inhaled is sufficient to stop respiration; the respiratory centre is apparently working at a great disadvantage with an insufficient supply of oxygenated blood, and is therefore easily placed *hors de combat* by any paralysing agent, such as chloroform.

In our cross-circulation experiments we attempted in a few cases to keep alive the brain of a rabbit by the blood from a dog, but found that the experiment was unsuccessful, as the rabbit always succumbed soon after the cross circulation was established. In these cases, then, we continued an experiment upon the dog, and noticed the effect of chloroform when two or three of the brain arteries were ligatured. Thus March 2nd and February 27th, 1891, were two instances, and in them we see another most striking result of chloroform under these circumstances, namely, the production of periodic respirations of the nature of Cheyne-Stokes respiration.

The amount of chloroform taken into the trachea of the dog was regulated by a slit in the cannula which could be left open or closed to a greater or less extent. When it was wide open only a small amount of chloroform was mixed with the air of inspiration, in fact under these circumstances a normal animal will continue breathing in a small amount of chloroform for a long time without any sign of danger. When the slit is completely closed the whole air of inspiration passes over the chloroform in the Wolff's bottle, with the result of causing a rapid fall of blood pressure and a speedy threatening of cessation of respiration.

In these cases, however, where two or more of the brain arteries were ligatured the connection of the tracheal cannula with the chloroform bottle, even when the slit was wide open, was sometimes sufficient to cause a marked alteration of the respirations of the nature of Cheyne-Stokes respiration. Thus on March 2nd, after both carotids were clamped, the chloroform bottle was connected with the trachea, the side slit being fully open, and the respirations, which were slow at the time, became quickly weaker and ceased in about one minute, the animal then remained for over one minute without breathing, then the respirations began again, quickly getting stronger and again dying away, till another pause of over a minute took place; the period of respiratory activity lasted about a minute, and during the whole time the trachea was in connection with the chloroform bottle, the slide slit being fully open. During the periods of respiratory activity the blood pressure rose; during the pauses it fell slightly. After the last pause the respirations again recommenced and then one carotis was unclamped, with the result that the respirations continued regularly with a regular blood pressure until by closing the side slit the chloroform was pressed and a rapid fall of blood pressure with cessation of respiration took place.

We conclude, then, that the respiratory centre is better able to resist the paralysing action of chloroform when it is freely supplied with oxygenated blood than when it is becoming exhausted by an insufficient supply of blood insufficiently aërated, and that Lawrie's supposition that the fall of blood pressure is in itself of the nature of a safeguard, because of the diminished amount of chloroform conveyed to the medulla oblongata, is not at all likely, as the smaller amount of chloroform so conveyed is more effective on the centre already suffering from want of a sufficient blood supply. The only safeguard action throughout is at the commencement of the chloroform administration, as already mentioned, when we see struggling, stoppage of heart, and holding of breath. Afterwards, when anæsthesia is induced, the fall of blood pressure, which is due to weakening of the heart, is no safeguard, but, on the contrary, is a danger to be avoided as far as possible.

Chloroform with Plenty of Air.

The rapidity and depth of this fall is directly dependent upon the concentration of the chloroform, so that if care is taken to give the chloroform with plenty of air it is possible to obtain anæsthesia with very little fall of pressure, for the heart is very little affected by blood containing only a small amount of chloroform. On the other hand, administration of chloroform with plenty of air, continued after complete anæsthesia has been produced, does ultimately overpower the respiration, although the heart is beating sufficiently well to maintain the blood pressure at a fairly good level.

These statements are well illustrated by an experiment on December 11th, 1890 (Fig. 11),[21] where chloroform was administered to a rabbit continuously for a long period of time by dropping it on to a cloth placed round the head of the animal in a conical shape, so as to leave a free opening for air about two inches in diameter. Every now and then the part of the cloth upon which the chloroform was poured was brought closer to the nose and mouth of the animal, and the moment of bringing the chloroform nearer and of removing it again was noted on the kymograph paper. In the tracings *a*, *b*, *c*, *d*, *e*, *f*, Fig. 11, samples of the respiration and blood-pressure curves are given at various times throughout the experiment; as stated already, chloroform was steadily administered during the whole time.

In Tracing *a*, taken before the administration of chloroform at 3.34 we see: mean blood pressure, 64; pulse rate per minute, 222; respiration rate per minute, 30. The chloroform was then placed on the cloth, and the effect of bringing the chloroform nearer and removing it further tried for a number of times. An example of the effect produced is given in Tracing *b*, showing the inhibition of the respiratory movements, the slowing of the pulse, and the rise of blood pressure owing to the stimulation of the trigeminal and pharyngo-laryngeal nerves, when the chloroform is more concentrated; immediately the cloth is removed further from the nose the blood pressure returns to its normal condition, and the slowened respiration gradually quickens up to its previous rate. This experiment was repeated again and again with similar results.

The effect of the continuous administration of chloroform in this way for 14 minutes is given in Tracing *c*, taken at 4.48, where we see: mean blood pressure, 67; pulse rate per minute, 218; respiration rate per minute, 31. Further continuation of the same experiment shows that the inhibition of the respirations and the slowing of the pulse when the chloroform is brought nearer to the nose become less marked; and, finally, after 3.56—that is, 22 minutes after the beginning of the experiment—the blood pressure and the respirations remained absolutely unaffected when the chloroform was brought close to the nose. At the same time, it was noticed that the corneal reflex was entirely abolished.

Tracing *d*, at 3.57, shows the absence of any effect upon temporary concentration of the chloroform, and we see: mean blood pressure, 69 mm.; pulse rate per minute, 204; respiration rate per minute, 42. It is noticeable that at this period, when all reflexes were abolished and the animal was in a condition of complete anæsthesia, the blood pressure was not lower than before the commencement of the experiment, and the only sign of the action of the anæsthetic is to be found in the quicker respiration.

At 3.58 the respiration rate per minute had increased to 46, the pulse tracing and respiration both remaining absolutely regular. At 3.59 the respiration was 45 per minute, at which it remained till 4.1, the mean blood pressure being then 62 mm. Both respiration rate and blood pressure continued steadily to diminish, and at 4.3, when Tracing *e* was taken, we see: mean blood pressure, 50 mm.; pulse rate per minute, 218; respiration rate per minute, 37. At 4.5 the respiration rate was 35; at 4.7, 31; at 4.8, 29; and at 4.9 the respiration had ceased. The termination of the experiment is shown in Tracing *f*, in which is seen the diminishing force of the diaphragm contractions, with the final rate, and we see: mean blood pressure, 48 mm.; pulse rate per minute, 126; respiration rate per minute, 24.

It is noticeable in this case, as in others (Figs. 1, 2, and 3),[22] how markedly the muscle strip of the diaphragm elongates when the respiration is failing. This points strongly to the conclusion that the respiratory centre possesses a distinct tonic influence on the diaphragm muscle, so that the failure of its action causes a loss of tone in the muscle as well as a diminution in the strength of each contraction. The pressure of 48 mm. at the time when the respiration ceased is not very low for a rabbit, and, indeed, the heart continued beating well for a considerable time, and then, by means of artificial respiration, the animal was easily recovered, and both blood pressure and respiration became normal, as is seen in Fig. 1, Tracings *a* and *b*, which represent the final ending of the experiment.

The danger, then, of chloroform administration consists (1) of causing a serious fall of pressure owing to weakening of heart from too great a percentage of chloroform in the air, which, combined with the action of the chloroform on the respiratory centre, in its turn causes failure of respiration; and (2) cessation of respiration after long administration owing to keeping on the chloroform, although given with plenty of air, too long a time after complete anæsthesia has been established.

[21] British Medical Journal, January 28th, 1893, p. 169.

[22] British Medical Journal, January 21st, 1893, p. 108.

Hans Meyer*

Zur Theorie de Alkoholnarcose

(Arch. f. exper. Pathol. Pharmakol 42:109-118, 1899)

Contribution to the theory of alcohol narchosis

First Communication

Which property of anesthetics causes their narcotic action?

Translated by

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*Hans Meyer's Harvey Lecture "The Theory of Narcosis," dating from 1905, is reprinted in Part Seven of the History of Anesthesiology Reprint Series.

The term "alcohol narcosis" here describes the typical action that is characteristic of innumerable substances of widely different composition and character, mainly neutral aliphatic compounds such as simple and substituted carbohydrates, alcohols, ethers, aldehydes, ketones etc.

Schmiedeberg, in his "Fundamentals of Pharmacology," discusses this "chloroform and alcohol group" and states that among the countless bonds formed by the fatty series the anesthetic action derives from those formed by the carbohydrate groups. Since these groups are not electrically dissociated, this cannot imply a direct chemical action, in the narrow sense of the term, on the substance of the ganglion cells. On the contrary, it implies only an indirect action involving either the entire ligand or the residue secondary to removal of a radical. This last is a priori excluded in connection with stable compounds, such as the saturated carbohydrates. Numerous other compounds, such as nitrous oxide and carbon dioxide, also possess a typical "alcohol-like" action. The carbohydrate group therefore cannot be the determining one. For similar reasons one cannot accept the recently proposed hypotheses that ascribe narcotic action specifically to the ethyl group,[1] or to activation of oxygen by the chloride, bromide or iodide.[2] The cleavage or ionization of these groups in the organism has neither been shown to occur nor shown to be likely. Nor would this explain the narcotic action of the many anesthetics that are halogen- and ethyl-free.

Von Bibra and Harless in 1847 published an experimental investigation into the effect of sulfuric ether which they felt supported a specific chemical-physical theory of its mode of action. They weighed the fat content of the ether extract of brain and liver from a large number of animals of uniform weight, half of which had been deeply anesthetized with ether immediately before sacrifice. They found that in the anesthetized animals the liver was richer and the brain poorer in ether extract than in the controls. They deduced that ether circulating in the blood during anesthesia defatted the brain and ascribed to this the diminished excitability of the organ.

That remarkable research was certainly not free from objections and was never repeated and confirmed. However, in 1866 Hermann drew renewed attention to it on the basis of quite different observations and considerations. Hermann, had demonstrated the presence of lecithin in red blood corpuscles and had discovered that all aliphatic anesthetics solubilize the corpuscles.[3] He concluded that, since lecithins, cholesterol and lipids are also found in nervous tissue, these substances might be the point of attack for the anesthetic action of fat-soluble agents. Some support for this viewpoint was seen in the older data of Lallemand, Perrin and Duroy (1859), according to which alcohol anesthesia was regularly accom-

panied by a considerably higher level of alcohol in the brain and liver than in tissues of lesser lecithin and lipid content such as the blood; however, this was contested by Schulinus[4] on the basis of more accurate measurements. On the other hand Pohl[5] has recently shown that in circulating blood chloroform is carried mainly by the red blood corpuscles, where it is bound to lipid lecithin and cholesterol, and that the brain, which is rich in lecithin and cholesterol, sometimes has a higher chloroform content than the blood. From this data, however, Pohl refrained from drawing any definite conclusion as to the applicability of Hermann's theory. Since then, except for the unfounded and unilluminating hypothesis of Nageli-Loew[6] purporting to explain anesthetic action as a catalysis-engendered oscillatory change, the only attempt to formulate a general explanation of anesthesia has been that of Raphael Dubois. Dubois[7] observed the effect of the vapors of chloroform, benzene, ether, acetic acid, and alcohol in causing droplets of water to form on the surface of the abascular, unvacuolated tissues of plants such as Echeveria glabra. He interpreted this to be an expulsion of water from the protoplasm, brought about by the anesthetic vapor.[8] Such water-depleted tissue does not function normally, and this was said to explain the anesthetic action of these vapors on animals and plants.

However distinct this explanation might at first sight seem from all the others, it is really not far removed. According to Dubois' observation anesthesia is the result of a competition between water and chloroform and similar substances with respect to the ability to penetrate certain cell components for which both possess an affinity. This attribute of the cell components arises from their content of lecithin and its combinations with protein. Whether the water visible on the surface comes from vacuoles and tissue spaces, or from neighboring hydrated tissue, is unimportant. The important point is that the normal relationship between complexes containing lecithin and similar compounds essential for the normal functioning of protoplasm on the one hand, and other cell constituents (water, salts, proteins) on the other is disturbed, and that this disturbance is brought about by the difference in their solubilities for chloroform, alcohol etc.[9]

It seems remarkable to me that such a relatively simple interpretation of anesthesia has received so little attention in modern pharmacology, notwithstanding that no valid objections to it have been expressed. One is justified in proposing in quite general terms that the anesthetic action of chloroform etc., is a function of solubility in lipid (affinity for lipid substances). Developing this idea, I now propose the following thesis;

1. All lipid-soluble virtually inert chemical substances must, to the ex-

tent that they are taken up by it, have a narcotic action on living protoplasm.

2. The action will be earliest and most intense in those cells in which lipids predominate and mediate a characteristic function, notably in the nerve cells.

3. The relative potency of such anesthetics must depend on their mechanical affinity for lipids on the one hand and for other tissue constituents, especially water, on the other. Consequently, it will depend on the partition coefficient determined by their distribution in a mixture of water and lipid.

As regards statement No. 1, it should be noted that all volatile substances without exception, as well as all non-volatile ones that are soluble in water or salt solutions, even if only very sparingly, are capable of being absorbed and dissolved by protoplasm. In contrast, non-volatile paraffins and neutral fatty oils are not taken up by the cells even after subcutaneous injection, but spread in connective tissue planes and via lymphatic vessels into the three major body cavities without provoking any toxic reaction.[10] It is hardly worth mentioning that few if any of the substances in question act by dissolving fat. Most of them, like alcohol, have a specific affinity for certain other cell components that may occasion various side effects. Moreover, lipids (lecithin, cholesterol, etc.), themselves have widely differing affinities for individual anesthetics. One should not expect, and indeed does not find, more than a qualitative similarity in the side-effects of the successive compounds of a series. Only the principal action is the same for all of them. Finally, it must also be pointed out that such substances, though chemically relatively inert, nevertheless often undergo metabolic transformation. These principles are not contradicted by the fact that labile or active substances or ones possessing specific affinities (nitriles, aldehydes, nitrogenous compounds) produce various functional disturbances in addition to anesthesia. The circumstances are quite similar to the temporary consequences of so-called salt-action — stimulation, disturbance of metabolism, diuresis, diarrhea, etc. — which may be caused by any water-soluble crystalloid whatsoever. These result from measurable physico-chemical properties, although often complicated or overshadowed by chemical (ionic) action in a narrower sense, as in the case of cyanides, alkaloid salts, etc.

As concerns statement No. 3, one should explain that it implies only a broad equivalence between potency and partition coefficient, and not a strict proportionality. First, because the intensity of action of pharmacological agents is not proportional to their size, but increases much more

rapidly.[11] Second, because the lipid of protoplasm is not a single entity but is known to be a mixture of components having similar but unequal affinities for individual anesthetics. "Lipid-solubility" is here a necessarily imprecise entity, a rough value impossible to determine exactly but nevertheless valuable as a guide in research.

The second of the above three statements accords with known facts. The other two are open to experimental verification. The results of a few studies that support the first statement will be briefly reported here. The third statement is tested by Dr. Baum in the next article.

The following chemically neutral substances have been investigated for their narcotic action on frogs, pigeons, rabbits, dogs, etc.

1. Monochlorhydrin and dichlorhydrin. Their effect is predictable by analogy with that of trichlorhydrin[12] and innumerable other halogenated aliphatic compounds. In practice, the chlorhydrin anesthetics can be extremely dangerous because of early depression of the respiratory center and fatal cardiac paralysis if administration is prolonged.[13] This delayed effect can probably be attributed to chemical reactivity and involvement of the chlorine moiety, as in the case of chloroform.

2. The acetic esters of glycerol,[14] mono- di- and triacetin. By permission of Mr. Bucholz, I briefly quote from his work while omitting the protocols.

MONOACETIN. In medium-sized frogs doses of less than 0.1 g produced no effect. 0.1 g minimally obtunded sensibility; 0.2 g produced light anesthesia. The animals remained quiet, or showed infrequent, awkward movements; pain sensibility was obtunded. Larger doses, 0.25 - 0.5 g, given either undiluted or diluted with water, caused considerable depression of sensibility, motility, equilibrium, and reflexes, and 0.5 g invariably killed the animals. In these cases the heart beat slowed gradually and ceased in diastole, although mechanically excitability persisted much longer.

In a pigeon, 0.6 g produced considerable depression of cerebral function. The injection was made into the pectoral muscles, and one-half hour later the animal was deeply asleep, unreactive to handclap, and could be dragged by the beak or the feet without awakening. It recovered gradually and seemed normal by the next day. Vomiting did not occur. The animal survived.

The anesthetic action of this substance was also observed in a small rabbit.

DIACETIN. Tests on frogs and pigeons demonstrated only small quantitative differences from monoacetin.

Doses of 0.05 g administered to medium-sized frogs produced little effect: the animals moved infrequently and could easily be hypnotized. 0.1 g induced distinct depression of all nervous system functions in 15 minutes. Strong, prolonged pressure caused one frog to jump and slide right out of the dish with clumsy, atactic movements. 0.2 g impaired equilibrium within 2 minutes and abolished it in 12 minutes. The frog remained motionless after being turned over on its back. The corneal reflex was very sluggish and pain sensibility was greatly diminished. One half-hour after the injection the animal became unreactive and died; the cardiac contractions slowed and ceased in diastole, although the heart remained excitable for several hours.

Experiments on a pigeon also showed an action similar to that of monoacetin.

The effect on blood pressure was investigated in a rabbit. Slow injection of 1 g per kg in 10 percent solution to the point of abolition of reflexes and deep sleep produced marked dyspnea, together with a rise of blood pressure followed by a sudden fall. There was little change in the action of the heart until the terminal slowing. Death ensued in respiratory arrest with profound cyanosis while the heart continued beating.

TRIACETIN. In frogs, the earliest signs of light anesthesia usually developed after doses of 0.02 - 0.05 g. Movements were infrequent and clumsy, and the animals did not attempt to escape. 0.1 g mostly produced deep narcosis. This dose was given to several animals but only one of them died. 0.15 g was always lethal, and a large dose such as 0.5 g was fatal within a few minutes.

Additional experiments were performed on pigeons. Doses of 0.3 to 0.5 g injected into the pectoral musculature produced medium deep anesthesia without side effects and followed quickly by recovery. A larger dose, 1.0 g given in two portions within 25 minutes, produced deep anesthesia and death in dyspnea. Respiratory and cardiac standstill occurred within 20 minutes of the second portion. An attempt to administer triacetin by mouth in a dose of 0.5 g produced not the slightest effect.

Subcutaneous administration of 1.2 g in 4 divided doses of 0.3 g to a 1490 g rabbit did not elicit anesthesia but did accelerate respiration initially.

Introduction of 4.0 g by stomach tube into a 1250 g rabbit produced slight depression after about 2 h but not true narcosis. The animal remained quiet but was easily frightened and made occasional munching movements from time to time.

Since neither of the above modes of administration had any effect on rabbits, I tried direct slow introduction into the blood stream via the jugular vein, using an aqueous 10 percent solution of triacetin.

1. 2.4 g (24 c.c. of solution) in 3 divided doses administered to a 1620 g rabbit.
2. 4.5 g (45 c.c.) in 2 doses to a 1920 g rabbit.
3. 2.0 g (20 c.c.) in 12 minutes to a 1365 kg rabbit.

In each case the animal was deeply asleep within a few minutes and pain sensibility and reflexes were markedly depressed. Interruption of the injection was soon followed by recovery of reactivity. Renewed administration quickly reinstituted anesthesia, and this sequence was repeated several times. Respiration was eventually affected and became slow, laborious, and dyspneic. Death ensued with the usual appearances of respiratory arrest. At autopsy, a small pulmonary infarct was seen in one animal, pulmonary edema in another, but nothing else worthy of note.

3. GLYCEROLETHER.[15] Distillation of glycerol with calcium chloride yields an anhydride of diglycerol with the probable formula:

$$\begin{array}{ccccc} CH_2 & - & CH_2 & - & CH_2 \\ O & & O & & O \\ CH_2 & - & CH_2 & - & CH_2 \end{array}$$

It is a clear, easily flowing liquid almost as transparent as water and has a neutral reaction and a pleasant taste and smell. In water heated to 100°C the ether converts back to glycerol.

The commercial product, which was purified by dissolving it alternately in water and ether, had a density of 1.146 at 17,5°C (pure, 1.16 at 0.0°C) and boils at 171-174°C at a pressure of 753 mmHg (pure, 172°C).

In doses of 0.025 - 0.05 g administered intramuscularly to frogs this substance produced clear-cut anesthesia, as did doses of 0.1 - 0.2 g in pigeons. The anesthesia lasted 1 - 2 hours and cleared up without aftereffects. Subcutaneous application of 0.6 g to a rabbit was ineffective but 0.7 g in 10 percent aqueous solution intravenously produced complete

areflexia and profound but short-lasting sleep. The animal recovered suddenly after ½ hour and thereafter behaved normally.

4. ACID AMIDES.[16] The amides of lower fatty acids are neutral substances. Formamide is a liquid slightly soluble in water and alcohol but insoluble in ether and lipids, whereas acetamide, propionamide and butyramide are crystalline and water-soluble as well as soluble in ether and lipids. The acid amides are readily saponified, hence accompanying ammonia-like reactions were expectable. And indeed, formamide and acetamide provoked convulsive phenomena resembling those of picrotoxin, as did propionamide and to a lesser degree butyramide.[17] Conversely, butyramide, proprionamide, and acetamide were decreasingly effective as anesthetics, and formamide was ineffective. Lactic acid amide and oxybutyric acid amide were as active as proprionamide.[18]

Nebelthau[18] has previously reported the action of aromatic acid amides; we recall here his two concluding remarks:

a) The primary pharmacological effect of the aromatic acid amides[19] resembles alcohol anestheisa; the specific nature of the acid radical is unimportant.

b) Substitution of the ammonium residue by alcoholic radicals of aromatic acid amides results in stimulatory effects and convulsions in mammals, similar to those of poisoning by ammonia. These may mask or completely suppress the anesthetic action.

Without exception, all these investigations confirmed statement No. 1. The anesthetic actions that were observed cannot be attributed to decomposition products or to saponification. The neutral, intact compounds themselves must therefore be considered to be the bearers of the anesthetic action, and this again strongly supports the general validity of the first statement.

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4. Schulinus, Dissertation, Dorpat 1865.
5. Pohl. Archiv. f. experiment Pathol. u. Pharmakol, Vol 28, 1891.
6. Loew, Ein naturl. System der Giftwirkungen, Munich, 1893.
7. Dubois, Compt. rend. Soc, Biol. 1884, p. 583.
8. An analogous example is the displacement of water from fresh brain by ether vapor, known from Baumstark's investigations (Zeitschr. f. physiol. Chemie, Vol 9, 1885).

9. Dubois himself, however, does not seem to be thinking of actual affinity of specific cell components for ether, chloroform, etc., but rather of the diffusion of the vapors and water. He refers to the expulsion in silicic acid of water by alcohol, of alcohol by ether, etc., observed by Graham (1864). To me the analogy does not seem correct.
10. Compare Juckuff, Archiv f. exper Pathol. u. Pharmakol, Vol 32, 1893.
11. Compare Juckuff, Versuche zur Auffindung eines Dosirungsgesetzes, 1895.
12. Romensky, Pflueger's Archiv, Vol 5, 1875.
13. Bucholz, Beitr. zur Theorie der Alkoholwirkung. Dissert. Marburg, 1895. Also compare Marshall and Heath, The Pharmacology of the Chlorhydrins etc. Journ of Physiol, Vol 22, 1897.
14. Bucholz, loc. cit., gives further details of the purification and testing of the commercial preparation and the properties of the pure compound.
15. Bucholz, loc. cit.
16. Bucholz, loc. cit. Gibbs and Reichert confirm his findings concerning formamide, acetamide, and propionamide.
17. It remains uncertain whether this a purely NH3 effect or also involves a specific amide. In favor of the latter is the observation of Schultzen and Nencki that acetamide is partly excreted unchanged.
18. Compare Nebelthau, Ueber die Wirkungsweise einiger aromatischen Amide etc. Archiv f. experiment. Pathol. u. Pharmakol, Vol 36, 1895, p. 455.
19. The investigation included benzamide, salicylamide, acetylsalicylamide, dibenzamide, and hippuric-, paratoluyl-, tetramethylbenzoic-, salicylmethyl-, ethylether-, metoxynaphthoic-, alpha-toluyl-, and cinnamylic acid amides. All of these, to varying degrees, are soluble in water and ether and fatty oils.