133

REPORT

ON THE

ACTION OF ANÆSTHETICS

TO THE

SCIENTIFIC GRANTS COMMITTEE OF THE BRITISH MEDICAL ASSOCIATION.

BY A COMMITTEE CONSISTING OF

JOHN G. McKENDRICK, M.D.,
Professor of Physiology in the University of Glasgow;

JOSEPH COATS, M.D.,
Pathologist to the Western Infirmary, Glasgow; and

DAVID NEWMAN, M.B.,
Pathological Chemist to the Western Infirmary, Glasgow.

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By a Committee consisting of JOHN G. McKENDRICK, M.D., Professor of Physiology in the University of Glasgow; JOSEPH COATS, M.D., Pathologist to the Western Infirmary, Glasgow; and DAVID NEWMAN, M.B., Pathological Chemist to the Western Infirmary, Glasgow.

AT the meeting of the British Medical Association in Manchester, in 1877, a committee was appointed to investigate the action of anæsthetics. The committee originally consisted of John G. M'Kendrick, M.D., Professor of Physiology in the University of Glasgow; Joseph Coats, M.D., Pathologist and Lecturer on Pathology, Western Infirmary, Glasgow; and William Ramsay, Ph.D., Assistant to the Professor of Chemistry in the University of Glasgow. Dr. Ramsay retired from the committee on his appointment to the Chair of Chemistry in University College, Bristol, when David Newman, M.B., Pathological Chemist, Western Infirmary, Glasgow, became a member of the committee.

Since the appointment of the committee, three preliminary reports to the Scientific Grants Committee of the Association have appeared in the pages of the JOURNAL.† The object of the present report is to

* Read at the Annual Meeting of the Association at Cambridge by David Newman, M.B., one of the Committee.

† BRITISH MEDICAL JOURNAL, vol. i for 1879, pages 1, 108, and 921.

give the Association a complete account of the investigation from the date of the appointment of the committee to the present time.

I.—Introductory Research.

In conducting our investigations, two lines of inquiry soon opened themselves to us: first, to discover wherein the special dangers of chloroform consist; and, second, to try if some anæsthetic agent could be found which would avoid these dangers. We also kept in view the investigation of the physiological action of anæsthetics in general, and the collection of evidence from the profession regarding the value and dangers of the anæsthetics at present in use.

In the first of these lines of inquiry, the much vexed question of the effects of chloroform on respiration and the heart presented itself. Without going into detail, we may say that it soon became apparent to us that chloroform, administered to dogs and rabbits, has a disastrous effect on the respiratory centres; it is easy to kill one of these animals by pushing the chloroform till respiration is paralysed. In observing the state of the heart during these experiments, it could often be determined by auscultation that its contractions were maintained after respiration had ceased. It was apparent, however, that, even when failure of respiration was more directly the cause of death, the heart was to some extent simultaneously affected; and there were even cases in which the heart appeared to fail at least as soon as, if not before, the breathing. Considering these facts, and bearing in mind that failure of the heart is often asserted in the reports of death from chloroform, we devised a method of experimentation by which respiration would be eliminated, and the effects of chloroform on the heart observed apart from that complication.

The frog is an animal in which the movements of respiration are not necessary to life, so far at least as the heart is concerned, as that organ continues beating long after these movements have ceased. After subjecting a frog to the vapour of chloroform under an inverted jar till it was anæsthetised, we exposed the heart by cutting the sternum in the middle line. The animal being replaced under the jar, it was found that the heart became rapidly weaker, till it ceased beating. A similar experiment with ether showed a very different result. The exposed heart continued vigorously beating for a considerable time—in fact, as long as the experiment was continued. These facts are quite familiar to physiologists.

With a similar view, a method was devised for warm-blooded animals. Rabbits were first used, and afterwards dogs. The animal was anæsthetised; then the trachea was opened, a tube introduced, and artificial respiration begun by means of a double-acting pump (one cylinder forcing air in, and another sucking it out). By an arrangement of India-rubber tubes, chloroform or any other anæsthetic could be introduced in the circuit between the pump and the trachea. It is to be understood that, in these experiments, the air passed into the animal's lungs was saturated with the vapour of the substance used. After artificial respiration had been set going, the heart was exposed by an incision in the middle line, which was carried by a pair of blunt scissors or bone-forceps through the ensiform cartilage and lower part of the sternum. This was effected generally with no serious bleeding. It soon became apparent that, when chloroform is given in this way, there is at once a most serious effect on the heart; the right ventricle almost immediately begins to distend, and the heart presently stops, with the right ventricle engorged with blood. The heart had often, in the case of rabbits, virtually come to a standstill within a minute of the introduction of chloroform by the method described. The contrast was most striking when ether was used instead of chloroform; the other steps in the experiment being the same. Ether may be given for an indefinite period without interfering with the heart. We kept up artificial respiration with ether in the circuit for an hour, not including twenty minutes occupied in producing anæsthesia; and, at the end of that time, the exposed heart was beating as vigorously as at first.

It was obvious, therefore, that, apart altogether from its action on the respiratory centres, chloroform has a disastrous effect on the heart, while ether has no baneful influence. While presenting in this respect an enormous advantage over chloroform, it was yet apparent, however, that ether has some great disadvantages. The chief of these is the tardiness of its action. In comparative experiments with rabbits, in which the anæsthetics were given on a towel, it appeared that, with chloroform, complete anæsthesia was produced in about three minutes; while, in the case of ether, it took fifteen to twenty minutes to produce this effect, although the cloth was kept saturated. It occurred to us, therefore, to endeavour to find an agent which should be as potent an anæsthetic as chloroform, and yet affect the heart and respiration as little as ether.

II.—Examination of Various Substances as to their General Anæsthetic Effect.

In testing the various agents used, we employed the methods described above. We administered them to animals, and watched the effects on the heart and on respiration. We used the method on frogs by which the effect on the heart could be observed; and, in the case of some of the agents, we performed the experiment on rabbits and dogs, using artificial respiration, and exposing the heart. It may here be remarked that, in these experiments, the anæsthetics were given intentionally in large doses, because, if any substitute for chloroform is to be found, it must be one which may safely be given in exceptionally full doses. The following substances were administered.

1. *Benzine* ($C_6 H_6$) was used with the frog. Its effects were nearly as slow as that of ether, and it produced struggling; weakening of the heart was apparent, but not so great as with chloroform.

2. *Acetone* ($C_3 H_6 O$) produced only slight anæsthesia in the frog, even after prolonged administration.

3. *Pyrrol* ($C_4 H_5 N$) produced anæsthesia in frogs with considerable less rapidity than chloroform, but great excitement and muscular spasm took place before complete anæsthesia. Administered to three young rabbits subcutaneously, it produced convulsive movements, chiefly of the jaws and fore-paws. Anæsthesia in these rabbits was doubtful.

4. *Bichloride of methylene* (so called, but, as it has not a definite and constant boiling point, it is obviously a mixture. Reputed formula, $CH_2 Cl_2$). With frogs, it was found that the heart became quickly affected, and soon stopped. With rabbits, respiration rapidly deteriorated and stopped, while the heart was still beating. In an experiment with artificial respiration and exposure of the heart (as described above), the heart was weakened and soon stopped, but not so rapidly as with

chloroform. As in the case of chloroform, the right ventricle became enormously distended—the first sign of paralysis being the commencement of this distension.

5. *Amylene* ($C_5 H_{10}$) was administered to rabbits both by cloth and subcutaneously. No anæsthetic effect was produced.

6. *Butyl chloride* ($C_4 H_9 Cl$) administered to rabbits affected respiration, but not very rapidly. In experiments with exposure of the heart, the cardiac pulsations became weaker, and ceased altogether after some time. In one experiment, it was noted that, almost immediately after complete anæsthesia, the respirations became shallow, and soon stopped.

7. *Ethene dichloride* (formerly named ethylene dichloride, or Dutch liquid, $C_2 H_4 Cl_2$) produced convulsive movements of both extremities, continuing up to death. There was no anæsthesia up to the commencement of the convulsions.

8. *Methyl chloride* ($CH_3 Cl$), which boils at the ordinary temperature, was obtained in alcoholic solution in a sealed tube, and allowed to boil off into a funnel, into which the muzzle of a rabbit was inserted. After somewhat prolonged use, there was not any abolition of reflex action, and the animal almost immediately recovered. The only effect was slight drowsiness.

9. *Ethyl chloride* ($C_2 H_5 Cl$, boiling at 12° Cent. = 53.6° Fahr.), administered to rabbits in the same way as the above, produced rapid anæsthesia; but in one case the respirations soon stopped, and in another, when air was admitted more freely, general convulsions occurred.

10. *Nitrous ethyl ether* ($C_2 H_5 NO_2$) produced great excitement and convulsions, almost immediately followed by cessation of respiration.

It was apparent that the above substances all presented disadvantages which rendered them unsuitable for general use as anæsthetics. There remained two agents, the actions of which were more promising. These were isobutyl chloride and ethidene dichloride.

11. *Isobutyl chloride* ($C_8 H_9 Cl$). *a. Experiments on frogs:* When it was administered under a glass jar, complete anæsthesia occurred in about five minutes. The heart was then exposed, and it was observed for thirty-five minutes, during which period its contractions were perfectly vigorous. *b. Experiments on rabbits:* When it was administered with a cloth, anæsthesia was produced in three to five minutes. It was continued after anæsthesia for nearly half an hour, without any interference with respiration. *c. Experiments on dogs:* It was administered on cloth; anæsthesia was produced in four minutes. It was continued for half an hour, and respiration was unaffected, except slight occasional stertor.

12. *Ethidene dichloride* ($C_2 H_4 Cl_2$, an isomeride of ethene dichloride produced from aldehyde). *a. Experiments on frogs:* Administered as before. The exposed heart continued beating slowly but regularly throughout the experiment, which lasted in one case twenty minutes, and in another twenty-six minutes. Anæsthesia was produced in four or five minutes. *b. Experiments on rabbits:* It was given on cloth, as usual. Anæsthesia was produced within four minutes. On one occasion, respiration stopped, but soon recommenced. In experiments with artificial respiration and exposure of heart, the cardiac contractions continued vigorous throughout, the observation being continued for forty minutes from the first administration. *c. Experiments on dogs:*

It was administered on cloth. Anæsthesia was produced in two or three minutes. In one case, anæsthesia was accompanied with some excitement, manifested by squealing; the animal was a young puppy. In another case, a large dog was kept fully anæsthetised for half an hour, without the slightest failure of respiration or heart. The anæsthesia in this case was very rapid, and the administration was intentionally pushed with successive doses at short intervals, as evaporation took place. The recovery was rapid, and the animal manifested remarkably good spirits. *d.* Two experiments were made on dogs, in which the heart was exposed, artificial respiration being kept up. No failure of the heart's action was observed, although the air passing into the lungs was saturated with the vapour of the substance. There was complete anæsthesia. On quickly removing the bottle containing ethidene dichloride, and substituting chloroform, the right side of the heart began almost immediately to become distended, and to be dark in colour, and the activity of the heart rapidly failed. The contrast between the effects of the two substances on the heart was most striking. Practically, a dog will live for a lengthened period in a state of complete anæsthesia under the influence of ethidene dichloride, while it will die in a short time when chloroform is used.

It is worthy of observation that two substances, butyl chloride and isobutyl chloride, which have the same chemical formula, exhibit such different actions. The same contrast is seen in the actions of ethene dichloride and ethidene dichloride, which are also isomeric. The first of these produced severe convulsions, while the second promises to be an excellent anæsthetic without any convulsive effects.

It was now necessary to test the effects of the two substances whose results seemed promising, and of any others of similar value, on the higher animals and on man.

III.—Special Investigation.

With reference to the physiological action of anæsthetics, our attention was, up to this time, mainly occupied with three inquiries, viz.: 1. The changes, if any, produced in the gases of the blood; 2. The changes effected in the gases of respiration; and, 3. The effect of anæsthetics on nervous conduction, and on mental phenomena as observed in man. All these experiments have been of a very laborious character, involving the use of complicated apparatus, and the methods employed can yield satisfactory results only after considerable practice.

1. *The Effect on the Gases of the Blood.*—The blood was collected by means of a graduated tube filled with mercury, and provided with a glass stopcock at each end. The upper end was placed in communication with the aorta or the inferior vena cava of a rabbit (immediately after it had been deeply anæsthetised) by means of a cannula; and, by opening the stopcocks, the blood flowed in at the upper end, replacing the mercury, which escaped at the lower extremity of the tube. It was thus possible to collect the blood without any admixture of air. The small portion of the tube above the stopcock was then washed and filled with a boiled solution of salt, and attached by an India-rubber tube to the tube entering the receiver of a Pflüger's air-pump. The lower end of the tube containing the blood was then inserted in mercury. On opening the stopcock of the receiver, and those of the tube containing the blood, the mercury in the vessel below displaced the blood, which flowed into the exhausted receiver, frothing and evolving gas.

The gas was collected in the usual manner, and carbonic acid and oxygen were successively estimated by known methods. Some boiled solution of tartaric acid was then allowed to enter the receiver, and displaced a further quantity of carbonic acid, which was in its turn collected and estimated. A sufficient number of reliable experiments have not as yet been made to permit our giving results.

2. *The Effect on the Air breathed.*—The gases of respiration were analysed as follows. The animal was placed in a tin box with glass sides, provided with a lid of thick brass plating above, fitting over a square hole, and secured tightly by means of a washer of India-rubber and eight strong screw-nuts. Very great difficulty was experienced in procuring an air-tight joint, but the above means proved the best. Air, deprived of carbonic acid by passing through potash solution, and then dried over sulphuric acid, entered the box by means of a tube at one side, and was drawn off at the other, through a tube filled with calcium chloride, and then passed through a set of bulbs filled with solution of caustic potash. The increase of weight of the bulbs in a given time gave the amount of carbonic acid expelled. An attempt was also made to estimate oxygen by passing the air, after absorption of carbonic acid, over a strong solution of ammonia; enough of that gas is carried over to ensure the combination of all the free oxygen with the hydrogen of the ammonia, when the mixture was passed over red-hot copper. Caustic baryta was used to absorb the water formed. The residue consists of a mixture of ammonia and nitrogen; and, after removal of ammonia by sulphuric acid, the remaining nitrogen is so pure that it does not tarnish melted sodium when a stream is directed against it.

The amount of carbonic acid accordingly is given by increase of weight in the potash-bulbs, and that of the oxygen by increase of weight in the tube filled with caustic baryta, after multiplication by eight, and division by nine, to reduce water to oxygen; for water contains eight-ninths of its weight of oxygen.

After ascertaining the normal amount of carbonic acid exhaled, and of oxygen absorbed, by an animal in a given time, it was removed from the box, anæsthetised, again placed in the box, and the gases of respiration estimated. Without giving detailed results, it may be stated that the *effect of chloroform pushed to anæsthesia is to increase the amount of carbonic acid exhaled within a given time.*

3. *Effects on Nervous Phenomena.*—Several curious facts have been elicited with regard to the effects of small doses of chloroform and ether on the rapidity of nervous and mental processes. By a refined method of experimenting with Regnault's chronograph, it was ascertained that a few respirations of air containing chloroform or ether produced remarkable retardation in the time of signalling back that a visual impression had been perceived, although the person operated on was quite unconscious of any such delay. These experiments are interesting chiefly from a psychological point of view.

At this period of the inquiry, ethidene dichloride yielded results so promising as to lead us to enter on a special investigation of its action as compared with chloroform and ether. When we first employed ethidene, we were led to give it a trial from a consideration of its chemical composition, and we were unaware that it had previously attracted notice; but, on looking into the literature of the subject, we ascertained that various observers had already noted some of its remarkable properties.

IV.—History of Ethidene Dichloride.

Ethidene was first employed as an anæsthetic by Dr. Snow, of London. He administered it in fifteen cases with good results (see Snow, *On Chloroform, etc.*, last paper, published in 1858). In 1870, it was used by Liebreich and Langenbeck in Berlin (*Berlin. Klin. Wochenschrift.*, Nos. 31 and 33, 1870, p. 401). In 1871, two papers appeared: one by Sauer, in the *Pharm. Centralblatt*, No. 14, p. 140; and the other by Steffen, in *Deutsche Klinik*, No. 44, p. 398. Sauer mentions one case of death in a patient suffering from heart-disease. In thirty-three cases, two vomited, and two suffered from nausea and headache. In 1872, Steffen published another paper in the same journal (p. 358), in which he gives details regarding twenty cases, and he states that the results were satisfactory (see also *Jahresb. der Medicin*, 1870, 1871, and 1872, where abstracts are given). It is worthy of note, however, that Snow, whose work in connection with anæsthetics is well known and much appreciated, was the first to use the substance. When he obtained it, it had been used in Paris as an application to joints in rheumatism. What led him to give it a trial as an anæsthetic, does not appear; but he states that the difficulty of obtaining it pure may prevent its general use. That difficulty chemists have now removed, and there is little doubt that, if required, ethidene may be made in a state of purity.

Since we directed attention to this substance in January, 1879, it has been used extensively throughout the country; and, not long ago, Mr. J. T. Clover published in the British Medical Journal an account of his experience derived from 1,877 cases (May 29th, 1880). In this interesting paper, he gives the particulars relating to a case of death from cardiac syncope after administration of ethidene and nitrous oxide gas, the nitrous oxide having been stopped before the ethidene was given. At the *post mortem* examination, the heart was found to be enlarged, and its fibres were shown to have undergone fatty degeneration. In some of his observations in connection with the cases in which ethidene has been used, Mr. Clover calls attention to its depressing action on the heart, a circumstance to which we will also particularly refer. The Committee believe that ethidene has frequently been used on the continent and in America; but they have found no published records except the above.

V.—Clinical Investigation of Ethidene and Chloroform.

In a report published in the British Medical Journal (January 25th, 1879), we related six cases in which we had used ethidene as an anæsthetic, and expressed our satisfaction with the results. Since then, we have instituted a series of observations, with the object of contrasting the effects of chloroform and ethidene; and, in order to facilitate the record of these, we drew up the following schedule.

Anæsthetic, . Quantity used, .
Posture of Patient, and Mode of Administration, .
Date, . Name, . Age, Ward, .
Occupation, . Disease, .
Operation, . Condition of Patient, .
General Habits,
Administration begun at . When completely under .
Administration stopped at . Time under

—	Pulse.	Respiration.	State of Pupil.	When Given.	Quantity.	Remarks.
Before Administration						
2 Minutes after ,,						
4 ,, ,,						
6 ,, ,,						
8 ,, ,,						
10 ,, ,,						
12 ,, ,,						
14 ,, ,,						
16 ,, ,,						
18 ,, ,,						
24 ,, ,,						
28 ,, ,,						
32 ,, ,,						
36 ,, ,,						
40 ,, ,,						
44 ,, ,,						
48 ,, ,,						
52 ,, ,,						
56 ,, ,,						
60 ,, ,,						

Remarks regarding Pulse and Respiration, .
Temperature of Apartment, .
Appearance of Surfaces, .
Loss of Blood during Operation, .
Vomiting or Sickness during Operation, .
Vomiting or Sickness within twenty-four hours, .
When food or drink last taken, .
State of Muscular System while under or on recovering from Anæsthetic, .
Patient's sensations while going under and after recovering from Anæsthetic, .
General Remarks. .

With the kind permission of the surgeons of the Western Infirmary, Glasgow—Professor Macleod, Professor Buchanan, and Dr. Patterson —we were enabled to make the following arrangements. To Dr. Buchanan's cases, ethidene was administered; to Dr. Macleod's, chloroform; and to Dr. Patterson's, ethidene and chloroform, in alternate months. The observations were, with a few exceptions, conducted in the operating-theatre, the temperature of which was on no occasion below 59 or above 64 deg. Fahr. The cases were not selected, except two cases of ovariotomy of Dr. Macleod's, in which ethidene was given; the others were taken as they presented themselves. The anæsthetics were given invariably on a towel, the usual way of administering chloroform in Scotland; and in all the cases the patients were lying upon the back. It is necessary here to explain what is meant by the phrases "When completely under" and "Time under", as they appear in the schedule. It is somewhat difficult to give an exact definition of what is understood when we say a patient is completely under an anæsthetic. In one sense, it might imply the death of the patient; for it is only when the anæsthetic has exercised all its powers, by subduing respiratory movements, and abolishing the functions of the cardiac ganglia, that we can say its action is complete. It is not, however, with this signification that we make use of the term. When sensation and voluntary motion are gone, and the reflex functions of the cerebro-spinal axis are in abeyance so far as concerns the voluntary muscles, so that they are perfectly relaxed and passive, it may be said—at least, from a clinical point of view—that the patient is "completely under". By the term "time under" is meant the time occupied from the beginning of the administration till the patient is so far recovered from the anæsthetic as to be sensible to pain, and able to understand what is said to him. In order to find out the time during which the patient has been *completely* under the anæsthetic, all that is necessary is to subtract the time required to put him under from the "time under", as recorded in the following tables. These tables are constructed from fifty cases of chloroform, and the same number of ethidene.

TABLE I.—*Showing the Time-relations, etc., in Fifty Cases of Administration of Ethidene Dichloride.*

No. of Case.	Time in Minutes required to put Patient under the Anæsthetic.	Time in Minutes under the Anæsthetic.	Time in Minutes between Stoppage of Administration and Recovery.	Dose in Cubic *Centimètres.*	Age of Patient.	Sex of Patient.	Sickness during Operation.	Sickness within 24 Hours after Operation.	Vomiting within 24 Hours after Operation.	Appearance of Surfaces.			
										Lips.	Face.	Skin.	Conjunctiva.
	I.	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.	X.	XI.	XII.	XIII.
1	4	35	3	63	11	F.	N.	Sl., 1 h.	N.	G.	G.	W. & D.	N.
2	5	36	4	46	16	F.	Sl.	Sl., 1 h.	Sl., 1 h.	G.	G.	W. & D.	N.
3	3	50	5	85	53	F.	N.	Sl., 6 h.	Sl., 6 h.	G.	G.	W. & D.	N.
4	3	32	2	66	22	M.	N.	Sev. (?)	Sev. (?)	G.	G.	W. & D.	N.
5	4	52	6	72	18	M.	N.	N.	N.	G.	G.	W. & D.	N.
6	4	36	3	66	43	F.	N.	N.	N.	G.	G.	W. & D.	N.
7	2	33	3	31	16m	M.	N.	N.	N.	G.	G.	W. & D.	N.
8	3	13	3	22	15	M.	N.	N.	N.	G.	G.	W. & D.	N.
9	6	35	11	63	—	M.	N.	Sl., 12 h.	Sl., 12 h.	P.	P.	P. & D.	N.
10	3	14	4	27	15	M.	N.	N.	N.	G.	G.	W. & D.	N.
11	4	25	7	40	18	M.	N.	Sl., 1 h.	N.	G.	G.	W. & D.	N.
12	9	16	2	57	14	F.	N.	Sl. 1½ h.	Sl., 1½ h	G.	G.	W. & D.	N.
13	3	16	4	35	45	F.	N.	N.	N.	G.	G.	W. & D.	N.
14	3	40	1	65	—	—	N.	N.	N.	G.	G.	W. & D.	N.
15	4	30	8	30	—	F.	N.	Sl., 2 h.	Sl., 2 h.	G.	G.	W. & D.	N.
16	3.5	33	4	56	18	F.	N.	Sl., 2 h.	N.	P.	P.	C. & M.	I.
17	5	30	5	55	—	M.	N.	N.	N.	G.	G.	W. & D.	N.
18	5	22	11	40	22	M.	N.	Sl. 1½h.	N.	G.	G.	W. & D.	N.
19	4	23	4	52	15	M.	N.	Sl., 3 h.	N.	G.	G.	W. & D.	N.
20	6	19	6	40	10	F.	N.	Sl. 1½h.	Sl., 1½ h	G.	G.	W. & D.	N.
21	9	34	9	48	25	M.	N.	N.	N.	G.	P.	C. & D.	N.
22	3	12	4	40	16	M.	N.	N.	N.	G.	G.	W. & D.	N.
23	7	18	3	40	68	M.	N.	Sl., 2 h.	N.	G.	G.	W. & D.	N.
24	4	17	2	30	13	M.	N.	Sl., 2 h.	N.	G.	G.	W. & M.	N.
25	3.5	16	3	25	45	M.	N.	N.	N.	G.	G.	W. & D.	N.
26	5	10	3	50	23	M.	N.	N.	N.	G.	G.	W. & D.	N.
27	6	12	4	36	56	M.	N.	N.	N.	G.	G.	W. & D.	N.
28	6	14	3	25	14	M.	N.	Sev. 12h.	Sev. 12h.	G.	G.	W. & D.	N.
29	2	23	4	25	3	M.	N.	N.	N.	G.	G.	W. & D.	N.
30	4	10	5	30.5	68	M.	N.	Sl., 2 h.	N.	G.	G.	W. & D.	N.
31	4	13	4	25	16	M.	N.	N.	Sl., 2 h.	G.	G.	W. & D.	N.
32	10	30	8	60	46	F.	N.	Con. 72 h	Con. 72 h	G.	P.	W. & D.	N.
33	3	25	7	34	14	M.	N.	N.	N.	G.	G.	W. & D.	N.
34	5	23	5	42	12	F.	N.	Sl., 12 h.	Sl., 12 h.	G.	G.	W. & D.	N.
35	5	30	7	45	45	M.	N.	2 h.	2 h.	G.	G.	W. & D.	N.
36	4	17.5	2.5	40	7	M.	N.	N.	N.	P.	P.	C. & M.	N.
37	3	15	2	31	27	M.	N.	N.	N.	G.	G.	W. & D.	N.
38	4	37	7	49	—	F.	N.	Sl., 1 h.	N.	P.	G.	C. & M.	N.
39	4	27	3	60	47	F.	N.	N.	N.	G.	G.	W. & D.	N.
40	3	17	7	33	14	M.	Sl.	N.	N.	G.	G.	W. & D.	N.
41	5	10	2	20	45	F.	N.	N.	N.	G.	G.	W. & D.	N.
42	4	17.5	4.5	31	45	M.	N.	Sl., 2 h.	Sl., 2 h.	G.	G.	W. & D.	N.
43	4	8	3	18	23	F.	N.	N.	Sl. 1½ h.	P.	P.	C. & M.	N.
44	3	30	4	66	35	F.	N.	Sl., 1 h.	Sl., 1 h.	P.	P.	W. & D.	N.
45	3	12	2	15	3	M.	N.	N.	N.	G.	G.	W. & D.	N.
46	4	10	2	20	10	M.	N.	N.	N.	G.	G.	W. & D.	N.
47	2	9	5	20	14	M.	N.	Sev., 2 h.	N.	G.	G.	W. & D.	N.
48	3	8	5	17	3	M.	N.	N.	N.	G.	G.	W. & D.	N.
49	2	10	6	12	9m.	M.	N.	Sl., 1 h.	N.	G.	G.	W. & D.	N.
50	2.5	10	7.5	19	14	F.	N.	N.	N.	G.	G.	W. & D	N.
	4.3	22.3	4.4	40.3—Averages.									

TABLE II.—*Showing the Time-relations, etc., in Fifty Cases of Administration of Chloroform.*

No. of Case.	Time in Minutes required to put Patient under the Anæsthetic.	Time in Minutes under the Anæsthetic.	Time in Minutes between Stoppage of Administration and Recovery.	Dose in Cubic *Centimètres.*	Age of Patient.	Sex of Patient.	Sickness during Operation.	Sickness within 24 hours after Operation.	Vomiting within 24 hours after Operation.	Appearances of Surfaces. Lips.	Face.	Skin.	Conjunctiva.
	I.	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.	X.	XI.	XII.	XIII.
1	7	25	13	38	32	M.	N.	N.	N.	G.	G.	C. & M.	N.
2	6	30	5	60	32	F.	N.	N.	N.	P.	P.	W. & D.	N.
3	2	35	15	36	18	F.	N.	N.	N.	P.	P.	C. & M.	N.
4	5	55	8	72	—	F.	N.	N.	N.	P.	P.	C. & M.	I.
5	5	34	11	42	47	—	N.	Sl., 12 h.	Sl., 12 h.	P.	P.	C. & M.	N.
6	12	18	14	35	50	F.	N.	Sl., 4 h.	N.	P.	P.	C. & D.	N.
7	7	39	4	72	67	M.	N.	Sl.	Sl.	P.	P.	C. & D.	N.
8	8	34	8	40	—	M.	N.	N.	N.	G.	G.	W. & M.	I.
9	5	14	8	—	—	F.	N.	N.	N.	P.	P.	C. & M.	I.
10	4	10	5	22	—	M.	N.	N.	N.	G.	G.	W. & D.	I.
11	6	14	4	22	—	M.	N.	N.	N.	G.	G.	W. & D.	I.
12	3	10	2	13	2.5	F.	N.	N.	N.	P.	P.	C. & M.	I.
13	5	12	4	23	50	M.	N.	N.	Sl.	P.	P.	C. & M.	I.
14	4	10	6	12	10	M.	N.	Sl., 24 h.	Sl., 24 h.	P.	P.	C. & M.	N.
15	3	22	7	35	36	F.	N.	N.	N.	P.	P.	C. & M.	N.
16	3	10	3	16	15	F.	N.	N.	N.	P.	P.	W. & D.	N.
17	5	22	3	49	47	M.	N.	Sl., 36 h.	N.	P.	P.	C. & M.	N.
18	8	13	2	25	—	F.	Sev.	N.	N.	G.	G.	C. & M.	N.
19	6	20	7	27	16	M.	N.	N.	N.	P.	P.	C. & M.	I.
20	10	13	3	32	30	F.	Sl.	Sl., 24 h.	N.	P.	P.	W. & D.	N.
21	5	20	5	45	44	F.	N.	Sev. 12h.	Sev. 12h.	P.	P.	C. & M.	N.
22	5	14	5	35	14	M.	N.	N.	N.	P.	P.	C. & M.	N.
23	4	15	4	37	30	F.	N.	Sl., 12 h.	N.	P.	P.	C. & M.	N.
24	7	12	2	18	15	M.	N.	N.	N.	P.	P.	C. & M.	I.
25	9	12	3	20	35	M.	N.	Sl., ½ h.	Sl., ½ h.	G.	G.	W. & D.	N.
26	3	16	3	36	3	F.	N.	Sl., 2 h.	N.	G.	G.	W. & D.	N.
27	4	30	8	37	12	M.	N.	Sl., 1 h.	Sl., 1 h.	P.	G.	W. & D.	N.
28	5	18	3	37	8	F.	N.	Sl., ½ h.	N.	G.	G.	W. & D.	N.
29	5	35	2	30	8	M.	N.	N.	N.	G.	G.	W. & D.	N.
30	3	18	8	38	16	M.	N.	Sl., 2 h.	Sl., 2 h.	P.	P.	C. & M.	N.
31	4	10	4	53	15	M.	Sl.	Sl., 3 h.	Sl., 3 h.	G.	G.	W. & D.	N.
32	7	16	4	34	22	M.	N.	Sl., 2 h.	Sl., 2 h.	P.	P.	C. & M.	N.
33	7	13	4	27	15	F.	N.	Sl., 2 h.	Sl.	G.	G.	C. & M.	I.
34	4	8	3	18	14	M.	N.	N.	N.	G.	G.	W. & D.	I.
35	4	10	2	20	12	M.	N.	N.	N.	G.	G.	W. & D.	I.
36	5	25	7	53	40	M.	Sl.	48 h.	N.	G.	G.	C. & D.	N.
37	4	16	8	10	3 m.	F.	N.	N.	N.	P.	P.	W. & D.	I.
38	5	12	2	25	24	M.	N.	N.	N.	P.	P.	C. & M.	I.
39	5	13	4	27	74	M.	N.	N.	N.	G.	G.	W. & D.	N.
40	5	16	4	19	19	F.	N.	Sev. 24h.	N.	P.	P.	C. & M.	I.
41	5	13	3	30	77	M.	N.	N.	N.	G.	G.	C. & M.	N.
42	5	10	3	19	27	F.	N.	Sl., 12 h.	N.	G.	G.	W. & D.	N.
43	3	10	3	25	49	M.	N.	Sl., 2 h.	N.	P.	P.	C. & M.	I.
44	4	10	5	20	33	M.	N.	N.	N.	P.	P.	W. & D.	N.
45	5	18	3	23	16	F.	N.	Sl., 2 h.	Sl., 2 h.	P.	P.	W. & D.	N.
46	6	16	2	35	38	M.	N.	N.	N.	G.	G.	W. & D.	N.
47	6	11	4	21	20	M.	N.	Sl., 4 h.	Sl., 4 h.	G.	G.	W. & D.	N.
48	7	20	5	40	24	M.	N.	N.	N.	G.	G.	W. & D.	N.
49	8	15	2	33	16	F.	N.	Sl., 2 h.	Sl., 2 h.	G.	G.	& D.	N.
50	5	10	1	24	13	M.	N.	Sl., 4 h.	N.	G.	G.	C. & M.	N.
	5.4	18	4.8	31.8—Averages.									

TABLES I AND II.—*Explanation of letters used in columns* VII, VIII, IX, X, XI XII, *and* XIII.—N., in column VII, is intended to indicate that in the cases where it is used, *no* sickness occurred during the operation ; in column XIII that there was *no* change in the condition of the conjunctiva. Sl. signifies *slight;* and N., with a figure before it, shows the length of time the vomiting or sickness lasted, h. being a contraction for hour. N., in columns VIII and IX, mean *no* vomiting or sickness occurred. In the columns showing the appearance of surfaces, G. signifies that the colour was *good;* P., that it was *pale;* W., that the skin was *warm;* C., *cold;* M., *moist;* and D., *dry;* I., that the conjunctiva was *injected*.

In Table I, the observations, as recorded in the ethidene schedules, are inserted so as to show at a glance the history of each case, and, at the same time, in such a form as to facilitate the comparison, not only of individual cases, but also the general results of our investigations. It will be observed that, at the foot of the first four columns, figures are given showing the average time in minutes required to put the patient under the anæsthetic; time under the anæsthetic; time occupied in recovery; and the average dose in cubic *centimètres*. The same plan is adopted in Table II. Let us first contrast these results. It may be here stated that, before making up these tables, our general impressions as to the comparative results were somewhat different from what is shown in the figures before us. The average dose of ethidene may be stated as 40.3 c. c.; or, in other words, 1.8 c.c. for each minute during which the patient is under the anæsthetic; whereas, in the case of chloroform, the average dose is 31.8 c. c., or 1.7 c. c. for each minute.* It will be further seen, that the time required to put the patient under chloroform is greater by 1.1 minute (5.4—4.3) than what is necessary to anæsthetise with ethidene. In connection with these observations, there are several points which must be taken into consideration. First, owing to the average time during which the chloroform patients were under the anæsthetic being less (18 m.) as compared with those who had ethidene (22.3), the dose per minute (1.7 c. c.) is proportionately increased in the case of chloroform; for it is during the first few minutes that the greater quantity of the entire dose is administered. When the patient is once under the anæsthetic, a comparatively small quantity is required to keep him under. The same cause may also account for the difference in the time necessary for recovery from the effects of the agents. In chloroform, the average time required is 4.8, with ethidene 4.4, minutes. The chloroform average is considerably augmented by the figures given in Cases 1, 3, 5, and 6; in all of which the time occupied was more than twice, and in one case (No. 15) more than three times, the average. Deducting these five cases, the average will be found to be 4.1 in the place of 4.4 minutes. There are only three cases in which the time necessary for recovery from ethidene was more than double the average (Nos. 9, 18, and 21).

In two cases in which ethidene was employed, sickness during the operation is recorded. In Case No. 2, it is accounted for by the fact that the patient, shortly before the operation, had taken a glass of milk. (The usual practice in the Western Infirmary is to allow the patients to have a cup of beef-tea five or six hours before the operation, but nothing after that time.) The sickness in the other case (No. 40) occurred as the patient was recovering from the anæsthetic. In twenty-four cases, sickness is recorded as occurring within twenty-four hours after the operation, in fifteen of which it was associated with more or less vomiting. In most of the cases, the vomiting was slight; in three cases

* The method we adopted for administering the anæsthetic (on a towel) prevents us from arriving at a conclusion as to the actual amount of anæsthetic vapour which entered the patient's lungs: the results in respect to the doses given are, therefore, only comparative.

(Nos. 4, 28, 32), however, it was severe. The average length of time during which the sickness and vomiting lasted is shown in Columns VIII and IX. Taking the average (omitting Case No. 32), in which it is questionable whether or not the vomiting was due to the anæsthetic, it will be found that the mean is 3 hours 17 minutes in the twenty-two cases of sickness, and in the thirteen cases of vomiting the average is 4 hours 21 minutes. These averages are considerably increased by Cases Nos. 9 and 28, in each of which the sickness and vomiting lasted for twenty-four hours. If we take the mean of the time occupied in putting the patients who have suffered from sickness and vomiting under ethidene, it will be noticed that it is equal to 4.6 minutes, while the average dose of the anæsthetic is 43.5 c. c. or 1.4 c. c. per minute. Both of these it will be observed are a little above the general average. In two cases, there was vomiting without sickness.

Let us now examine the condition of things in the cases where chloroform was administered. In four cases, we had vomiting during the operation; in three it was slight, in one severe. One of these cases was an out-patient (No. 31), so there was some doubt as to the time he last partook of food. It is a remarkable coincidence that, as with ethidene, there are twenty-four cases of sickness after the operation ; and of these, fourteen suffered from vomiting, whilst one complained of vomiting without sickness. In two cases, the sickness was severe; in the others, it was comparatively slight. The mean duration of the sickness is ten hours, and of the vomiting five hours fifty minutes. In one case of sickness, and three of vomiting, the duration is not noted ; it was, however, only for a short time. With some of the cases, as Nos. 14, 17, 20, 36, and 40, the sickness was prolonged ; in the last four of these, it will be noticed that there was no vomiting. The mean time occupied in placing these cases under the anæsthetic is 5.7 minutes; whilst the average dose is 33.5 c. c., or 2 c. c. per minute. As with ethidene, both of these figures are slightly above the general average, but in neither of them is the increase sufficiently regular, or of such an amount as to lead us to believe that the actual increase in the dose is in any way responsible for these symptoms, nor has the time during which the patient is anæsthetised any relation to them. Thus, in the case of ethidene, the mean is 24 minutes, as compared with 22 minutes in the cases all over; and with chloroform, 17 minutes as contrasted with 18. The condition of surfaces is best seen by referring to the tables.

VI.—Influence of Ethidene and Chloroform on Pulse-Respiration Ratio.

The next point to which we desire to direct attention is one of considerable importance, and the only one in which there is much distinction between the action of the two anæsthetics: namely, their influence on the pulse-respiration ratio. Of the fifty cases in which ethidene was given, in only one instance did the pulse fall to 64 per minute, and the lowest number of respirations in the same time may be stated as 16. Both the pulse and respiration are particularly regular in a number of cases ; as, for instance, in No. 4, Table I, where the mean of the respirations per minute is 18.2, the maximum 19, and the minimum 17 ; the pulse mean 83.2, the maximum 92, and the minimum 80. With chloroform, the results are somewhat different. In five cases, the pulse fell to 64, in seven to 60, in five to 56, and in one to 48 per minute; and the respirations rose in five cases to between 30 and

35, in six to between 35 and 40, and in five to 40 or slightly over it; in one case (No. 37) to 72 respirations per minute. With chloroform, as with ethidene, in some cases there is particular regularity in both the pulse and respirations, as in case No. 33 (the one in which the pulse-respiration changes are least marked), the mean number of respirations per minute is 24.2, the maximum 26, and the minimum 23; whilst the pulse mean may be stated as 96.8, the maximum 108, and the minimum 92 per minute. The cases are, however, few in which chloroform does not produce a greater effect upon the pulse and respiration. In a certain class of cases, the pulse-respiration ratio is greatly altered, the pulse falling as the respirations rise. With ethidene, such cases are comparatively rare, and the changes observed are not so marked. Out of fifty cases in which chloroform was given, nine show the changes to which we refer; whilst in only two of the ethidene cases are they seen, and even in these they are not very striking.

The following charts show the comparative effect of ethidene and

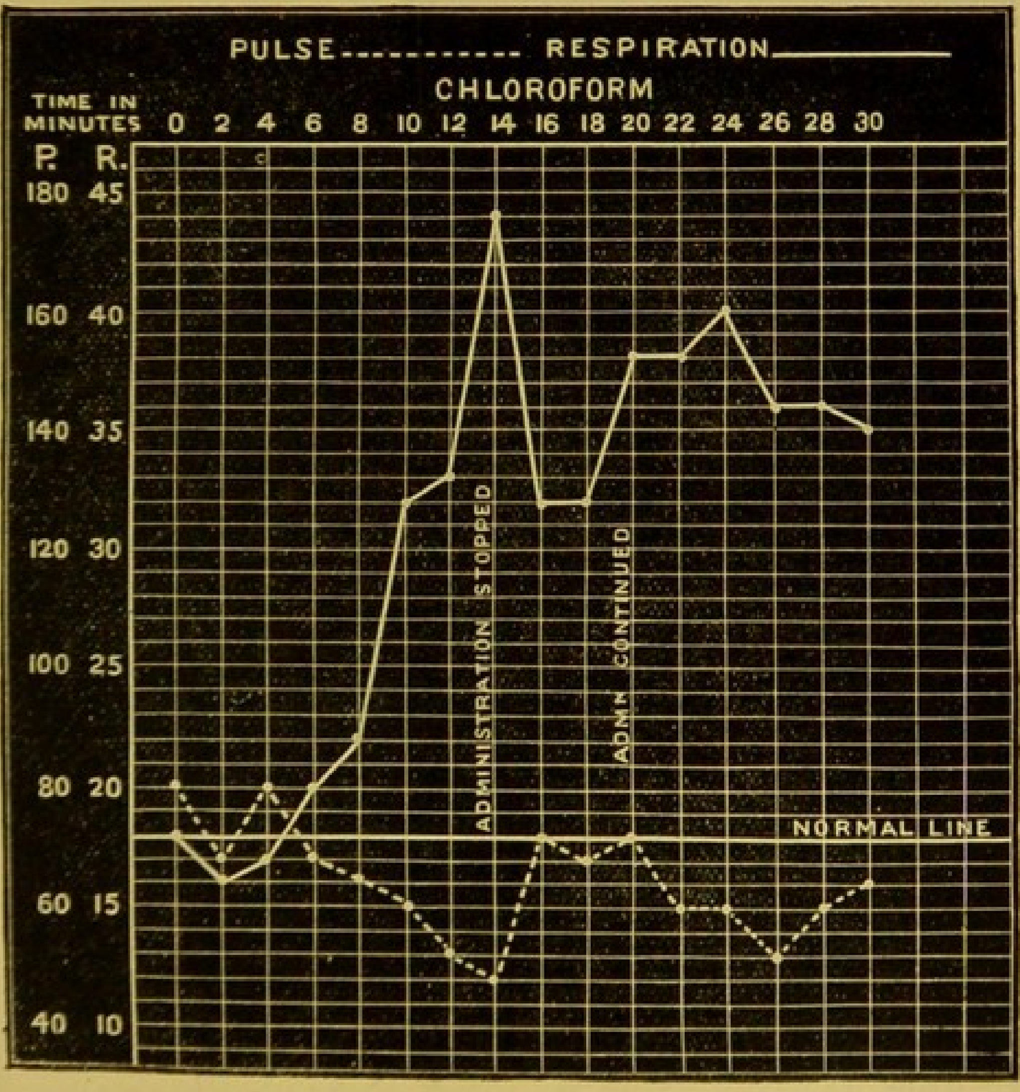


Fig. 1.

chloroform in this respect; the ethidene case is selected as the most marked of the two; the chloroform one shows about the average of the nine cases above referred to.

Take first the chloroform chart (Fig. 1). The normal line is fixed a little below that of the ethidene (Fig. 2), on account of the difference in

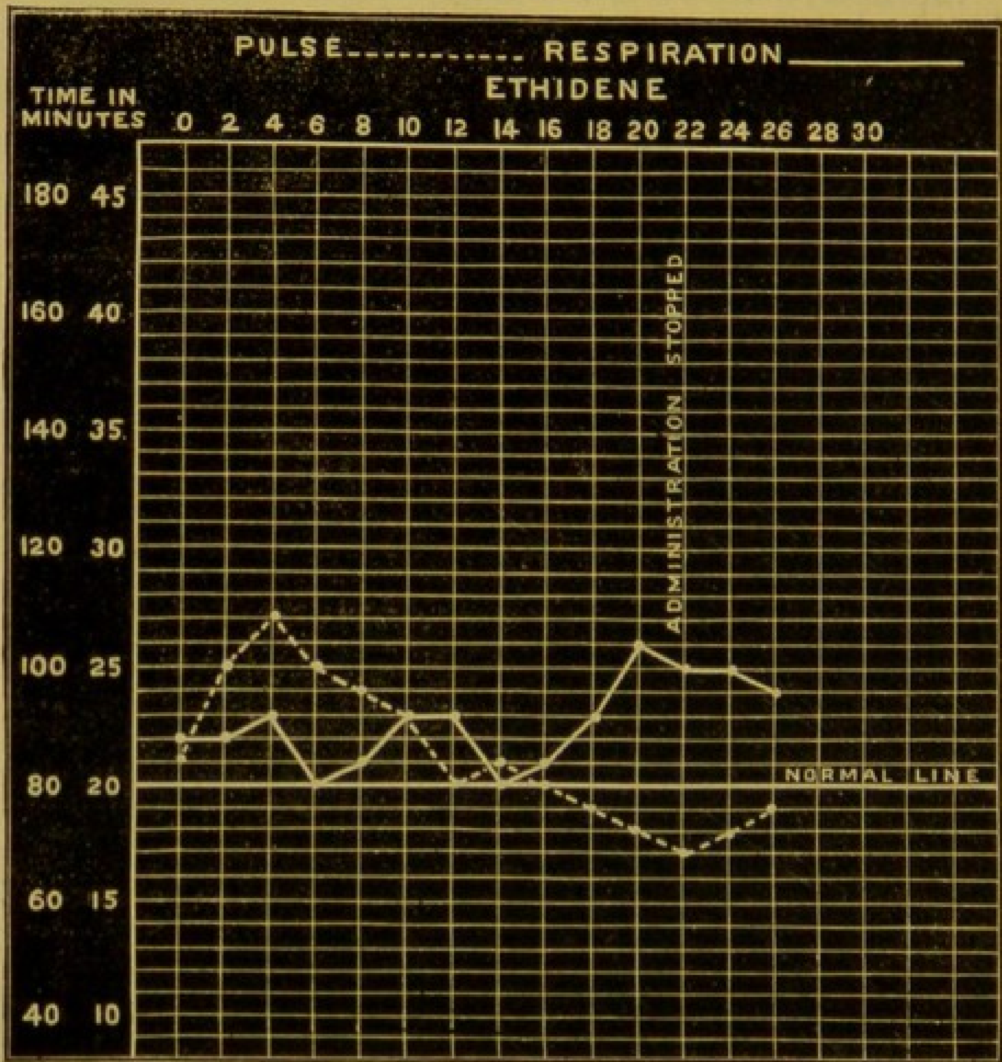


Fig. 2.

the ages of the patients: the one (chloroform) aged 40, the other 11 years. The continuous line shows the respiratory, the dotted line the pulse curve. The most striking feature in the chart is the great rise in the respirations, and fall in the pulse below the normal line. Shortly after the commencement of the administration of chloroform, there is a slight fall in the pulse (from 80 to 68) and the respiration (from 18 to 16), followed by an increase from 68 to 80 in the former, and 16 to 17 in the latter. For the next ten minutes, there is a continuous fall of the pulse (to 48 per minute) and rise in the respiration (to 44 per minute). Within the next two minutes, the pulse rises to the normal line, and the respiration falls to 32. This change corresponds with an interruption in the administration of the anæsthetic for four minutes. The subsequent administration of the chloroform is followed by a similar, though not so extensive, alteration in the pulse-respiration ratio. It will be observed that the fall in the pulse is concomitant with the rise in the respiration. It is also to be observed that, in those cases where the pulse-respiration ratio was considerably altered, the pulse showed a tendency to become dicrotic, so that a double impulse was communicated to the finger. Thus, a pulse where the beats equalled sixty per minute might easily be mistaken for one where the impulses were a hundred and twenty. Associated with these changes, we have also indications of low arterial tension. Although the ethidene case is selected as being the one in which pulse-respiration changes are most marked, yet there is a manifest difference as contrasted with the chloroform one. There is a slight rise in the pulse for the first four minutes, followed by a gradual but almost continuous fall from 108 (at four minutes) to 68 (at twenty-two minutes), succeeded by a slight rise, corresponding with the stoppage of the administration. The first rise in the pulse is in advance of a fall in the respiration, and the subsequent rise in the respiration is preceded by a diminution in the frequency of the pulse; after the fourteenth minute, the respiration slowly rises to 26, and again falls to 25 before the administration of the ethidene is stopped. In only one case in which ethidene was given, did the pulse become dicrotic.

So much for our researches from a clinical point of view; we will now call attention to a series of experiments performed with the object of investigating the conditions of blood-pressure in animals under chloroform, ethidene, and ether.

VII. Influence of Chloroform, Ethidene, and Ether on Blood-Pressure.

In the report of a Committee* of the Royal Medical and Chirurgical Society, to inquire into the uses and effects of chloroform, published in the *Transactions* for 1874, vol. xlvii, there is a very excellent but brief record of the blood-pressure under chloroform and ether. The instrument used in these experiments was the hæmadynamometer of Poiseuille, which consists of an U-shaped tube, with mercury in the bend. One limb of the tube was connected with the femoral artery, and the rise of the mercury in the opposite limb indicated the blood-pressure. By means of this instrument, the committee were enabled to report that, on administering chloroform, there was at first a transient rise of the blood-pressure; after which, there was a gradual, but not a regular, fall. They also noticed that, when the force of the heart was reduced by chloroform to the full extent, the respiration of fresh air was at once followed by a rise of the mercury. In regard to ether, it was found that the primary rise in pressure was greater and more constant than with chloroform; and that the depressing effect was very slight or altogether absent.

In our experiments, we have been able to amplify these results; and, by means of more delicate instruments, to obtain more exact records. We have used a very complete kymograph, in the Physiological Labora-

* The members of this committee were T. B. Curling, Thomas Bryant, Samue Cartwright, Arthur Farre, Geo. G. Gascoyen, Geo. Harley, Prescott Hewett, F. W Mackenzie, William Marcet, Charles H. Moore, James Paget, William O. Priestley, Richard Quain, Francis Sibson, R. Dundas Thomson, Charles West, Septimus W Sibley, George W. Callender, John Birkett, and J. T. Clover, assisting.

tory of the University of Glasgow, made by Rudolph Rothe of Prague,* by means of which the variations in the column of mercury, produced by the pulsations in an artery, are written (by means of a stem which floats on the mercury) on a sheet of blackened paper, which is carried round by a clockwork arrangement. A sheet of paper, eight feet long, is adapted to the machine; and, as three or four lines of tracing can be taken at different levels on the same sheet, a continuous tracing may be obtained of twenty-four, thirty-two, or even more feet. But, further, the sheets can be changed in a few seconds and so it is possible to take tracings of almost any length.† The instrument has also appliances by which time could be recorded in seconds, half seconds, or otherwise, immediately beneath the tracing of the blood-pressure. (See Tracing C.) Lastly, there are two arrangements by which the exact time of administering and discontinuing an anæsthetic can be marked. (See Tracing C.) In this way, we have obtained records of experiments in rabbits and dogs; those on dogs, being of much the greater value.

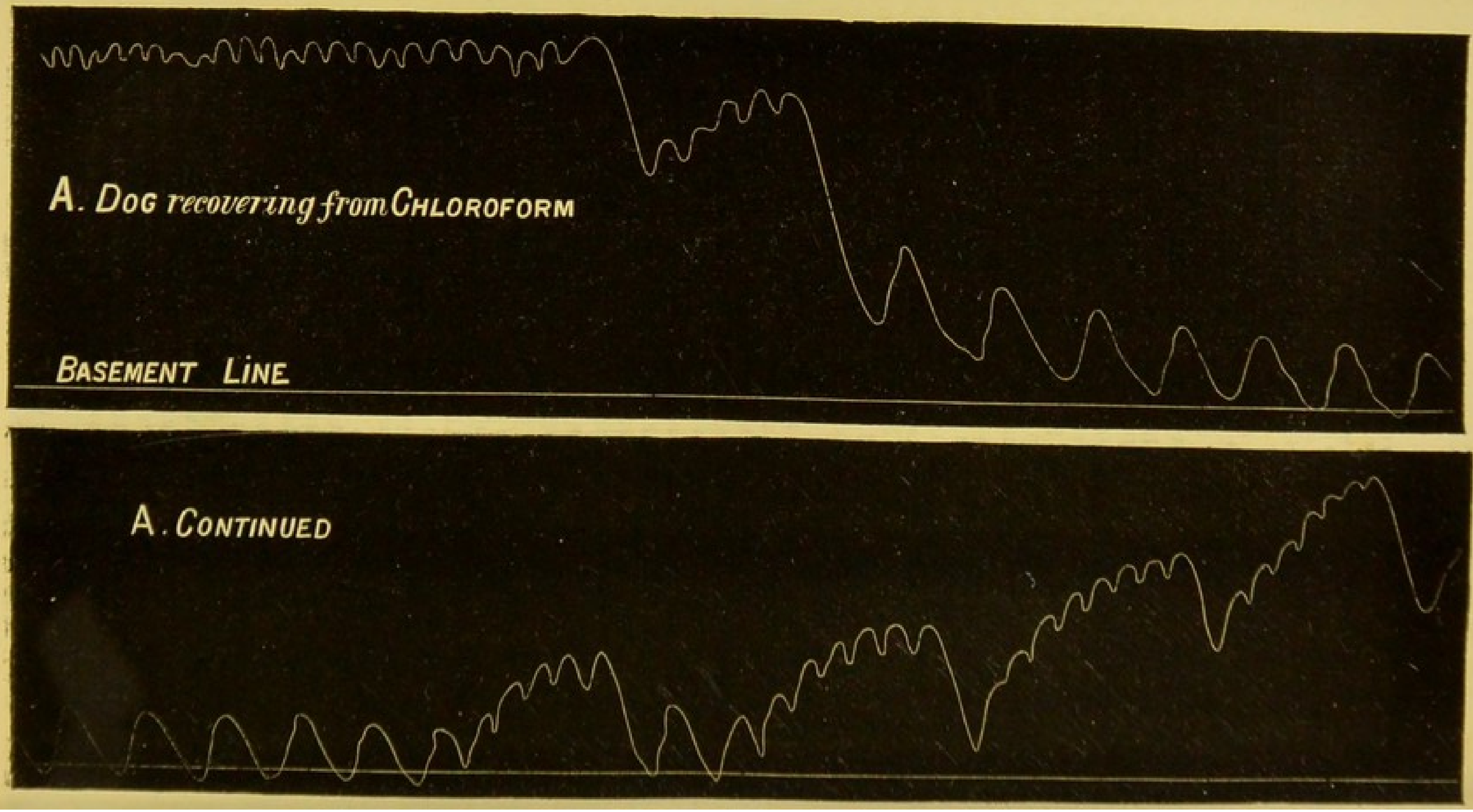
In the case of the rabbit, there is one fact of considerable interest which seems to be deducible from these records. When the animal is not fully under chloroform, any fresh administration causes most remarkable variations in blood-pressure, with retardation of the heart's contractions. (See Tracings G and H.) There is frequently a sudden dip in the pressure, to the extent of forty *millimètres* out of a total of one hundred and ten *millimètres;* and in the next few contractions, there is a very rapid rise up to the former level, to be succeeded by another sudden dip. This occurrence followed so uniformly in certain stages of chloroform-narcosis, on every approximation of a sponge containing the agent, even for a few seconds, to the animal's muzzle, that it was regarded as probably reflex. This is rendered all the more probable by the known fact that ammonia-vapour, applied to the nostrils of a rabbit, causes stoppage of the heart's action.‡ When the chloroform is given continuously, these variations gradually cease, and there succeeds a regular and gradual fall of pressure down to zero, if the agent be pushed. It was noticed that, in one or two instances, ethidene produced sudden variations in pressure similar to those of chloroform, but that ether did not. Our experiments were not fully prosecuted on rabbits in regard to the more permanent effects of these two agents; but it may be said in general that ether seemed to have no effect on blood-pressure, while ethidene reduced it to a considerable extent, but not to total extinction, like chloroform.

Turning to our experiments on dogs, the very first observation made was an exceedingly striking one. (See Tracing A.) The animal used was a black retriever, six or seven months old. Chloroform was given, and during deep anæsthesia a cannula was introduced into the carotid artery, and connected with the kymograph. By the time connection with the kymograph was established, no chloroform had been given for about two minutes. On first making the connection, the pressure registered 104 *millimètres*, which may be regarded as nearly normal; but now, without any fresh dose, the pressure rapidly fell to zero, with a remarkable retardation of the heart. Each pulsation had a height of 9 *milli-*

* See Dr. McKendrick's *Outlines of Physiology*, page 358.

† In one case, a tracing one hundred and fifty feet long was obtained.

‡ See Professor Rutherford's paper in *Journal of Anatomy and Physiology*, vol. vii, p. 283, "Cause of the Retardation of the Pulse which follows Artificial or Voluntary Closure of the Nostrils of the Rabbit".


A. Dog recovering from Chloroform
Basement Line
A. Continued

*mètres,** and a duration of a second and a half. After this the pressure rose with remarkable variations, equal to from 13 to 16 *millimètres*, referable to the respiratory movements. (See right-hand part of Tracing A.) It is to be remembered that the animal had at this time, to a great extent, recovered from chloroform, as evidenced by the high initial pressure; and this sudden fall of pressure is apparently reflex in character; the heart being, perhaps, more liable to such influences under the conditions present. A fresh administration of chloroform at this time led to a fresh variation of pressure, somewhat resembling those already referred to in the case of rabbits. On continuing the administration, all irregular variations were abolished, and the presure gradually fell; but the agent was not in this instance pushed very far. During recovery from this administration, seventy seconds after the chloroform had been removed, and when the pressure had risen to 66 *millimètres*, there was, without any apparent cause, an occurrence somewhat like that at the outset, but less in degree. (See Tracing B.) The pressure fell to 20 *millimètres*; and the heart's pulsations became unfrequent, each pulsation taking a second and half. This continued for six beats, when the pressure rose slowly to 100 *millimètres*, with recovery of the frequency of the pulsations.

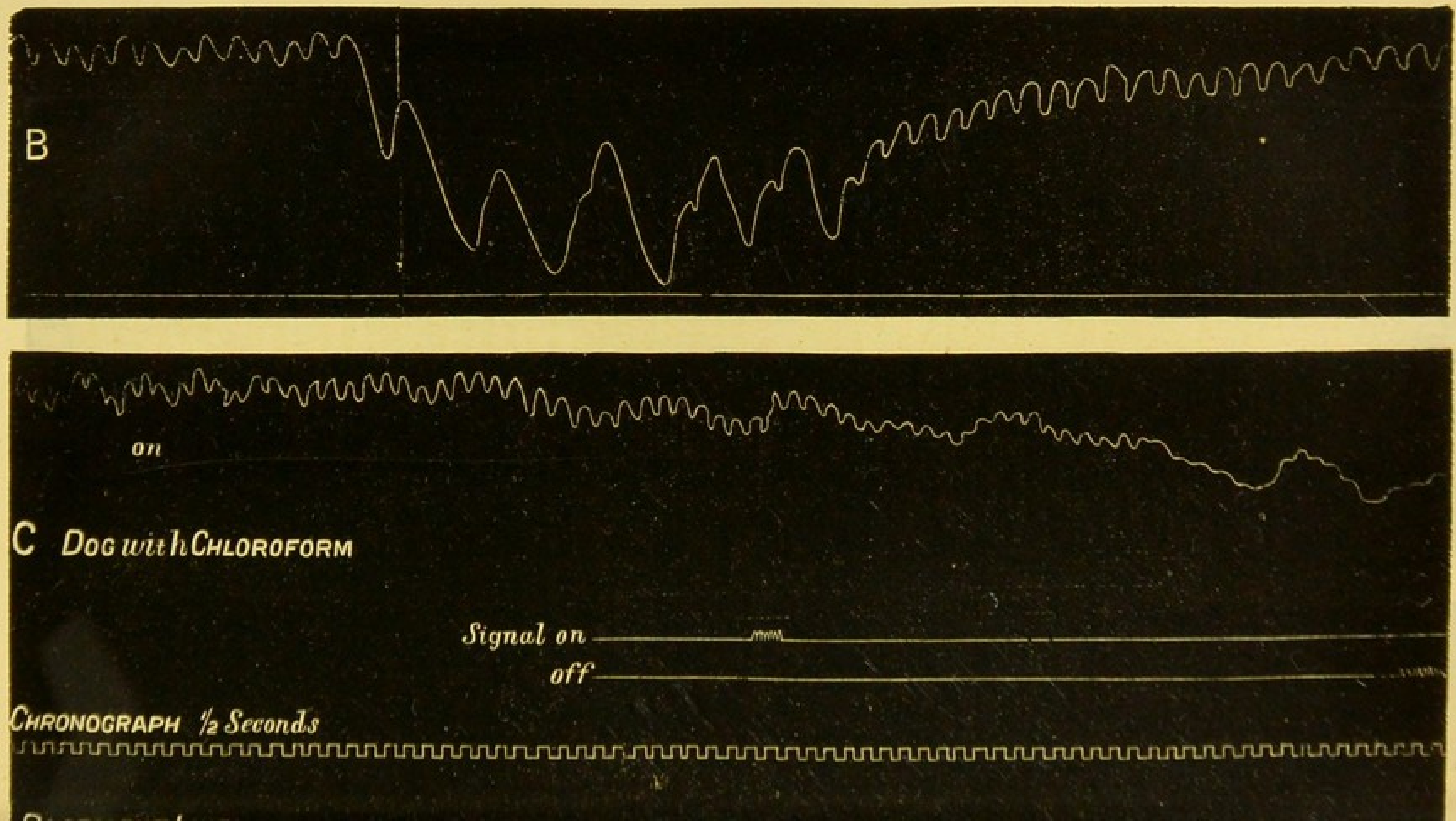
Ether administered to this dog produced little effect on the pressure; if anything, it improved it. There was slight diminution of pressure when the animal was struggling and howling.

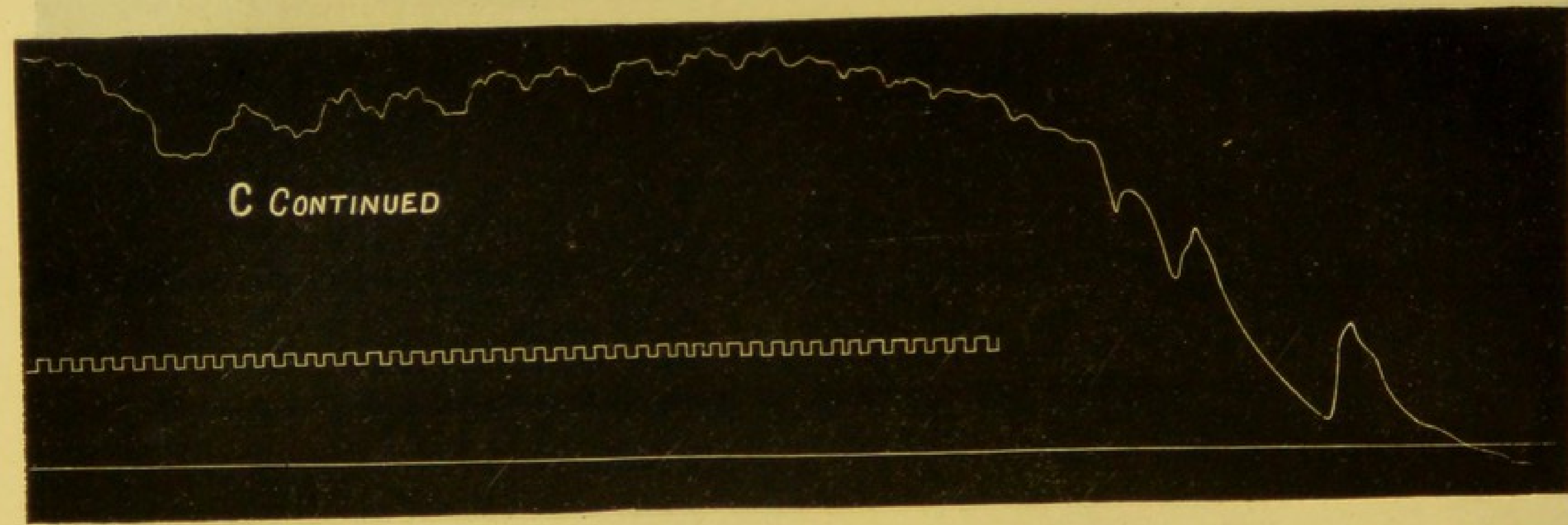
Ethidene was given while the animal was still to some extent under the influence of ether. The pressure gradually but very slowly fell, and, under repeated doses, reached a minimum of 20 *millimètres*. The agent being still continued, the pressure began to rise, and had reached 28 *millimètres* when it was removed. Subsequently, ethidene was again given; and, after prolonged and constant use, the pressure was gradually brought down to 7 *millimètres*, when the administration was stopped. It should be noted that all this time the respiratory movements were uninterrupted.

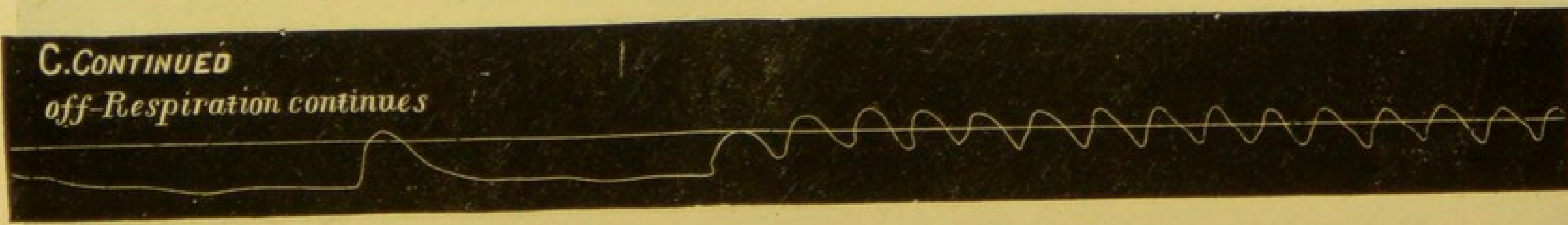
The same dog was used for a further set of experiments, which were prosecuted after a short interval, during which the animal partially recovered.† The pressure at the beginning of this series registered 110 *millimètres*, and the variations of pressure with respiration were well-marked. (See Tracing C. The respiratory curve is seen at the left of the tracing.) Chloroform being given, there was an almost immediate fall of pressure, with considerable variations, and reduction in the frequency of the heart's pulsations. The pressure remained about 70 or 80 *millimètres* for about half a minute; and then there was a very rapid fall, with great retardation of the pulsations, till the heart almost ceased. There was an interval of three seconds between two of the pulsations, of nine seconds between the next two, and of six seconds between the next; the pressure in these intervals being *nil*. (See Tracing C.) The chloroform was removed when this rapid fall occurred. During this period, the respiration continued. The pulsations were now resumed; but between each pulsation the pressure was *minus*, and the pulsation, only raised the mercury 10 *millimètres*, generally just to the basement-line; while the beats occupied about one second and three-quarters.

* It will be understood that the figures given represent the column of mercury, raised, or the difference in level of the mercury in the two limbs of the U-shaped tube. This will always be double the distance from the point at which the mercury in the two limbs is level, or from the basement-line in the tracing.

† During the whole of these experiments anæsthesia was complete, and the partial recovery referred to, was indicated by a return of blood-pressure to the normal.


B
on
C Dog with Chloroform
Signal on
off
Chronograph ½ Seconds


C CONTINUED


C. CONTINUED
off-Respiration continues

After twenty-nine of these pulsations, the breathing stopped, while the pulsations went on regularly as before. After a few seconds, artificial respiration was used, by alternately compressing the chest and leaving it to expand. This being prosecuted for thirty seconds, spontaneous respiration was resumed, and the pulsations became more marked, having a rather higher excursion than before, but still returning to a pressure of zero between each two pulsations. This continued for about forty-two seconds, when the pressure began to rise; and this went on continuously till, in a hundred and sixty seconds, a height of 100 *millimètres* was reached.

We have dwelt in some detail on this last experiment, because we regard it as one of unusual interest and importance. It is to be remembered that this animal got chloroform in the usual way, by a cloth saturated with the agent being held over his mouth and nose. He received no overdose, and the administration only lasted seventy seconds. As bearing on at least one mode of death under chloroform, the relation of the heart's action to respiration is of particular significance. The blood-pressure is enormously reduced, and the pulsations have become so unfrequent as to be virtually ineffectual, yet respiration continues. But respiration stops forty seconds after the heart has resumed, the pulsations being still, however, so ineffectual, that the pressure is even minus.* We believe that the legitimate inference to be drawn is that the stoppage of respiration was not due directly to the chloroform, the inhalation of which had ceased for about forty-eight seconds. It seems likely that the failure of the heart in the first instance, and the insufficiency of its subsequent pulsations, were the cause of the failure of respiration. In such a state of the circulation, the respiratory centres would probably be insufficiently supplied with blood, and be consequently liable to cease acting. In this case, if death had occurred, it would only apparently have been due to the failure of the respiration, the primary failure being that of the heart. To what extent this may apply to human cases, we do not venture to speculate.

We now resume consideration of this set of experiments. The animal was allowed to recover considerably, and the pressure had reached 106 *millimètres*, when ethidene was administered. There was a slow but steady fall of pressure, the lowest point being reached in about 120 seconds, when the height was 36 *millimètres*. Continuing the administration, there was a slight rise, up to 50 *millimètres*, when the administration was discontinued. During the administration, the cardiac pulsations were regular in frequency, with slight variations in the height of the waves, probably depending on respiration.

It will not be necessary to give our further experiments in such detail. In one set, we kept up artificial respiration by means of the pump,† administering the anæsthetics by passing the air through a Wolff's bottle containing the respective agents. In these experiments, chloroform promptly reduced the pressure, which began to recover almost immediately on its removal. On continuous administration, the pressure fell much more gradually than by the ordinary method, and the lowest point reached still represented a considerable pressure, about 65 *millimètres*. The initial pressure was 132 *millimètres*. Ethidene

* That there was no fallacy here, was determined by testing the instrument afterwards, when the zero line was found to indicate no pressure.

† The apparatus for artificial respiration used in the Physiological Laboratory, University of Glasgow, is the double-piston pump, made by Rudolph Rothe of Prague, and figured in his price-list.

was begun at a pressure of 80 *millimètres*, the recovery from the chloroform depression being incomplete. After prolonged use, there was a fall to 54 *millimètres*. On removal, a gradual recovery ensued, which attained to 80 *millimètres*. Ether was then given, when again a slight fall in pressure ensued.

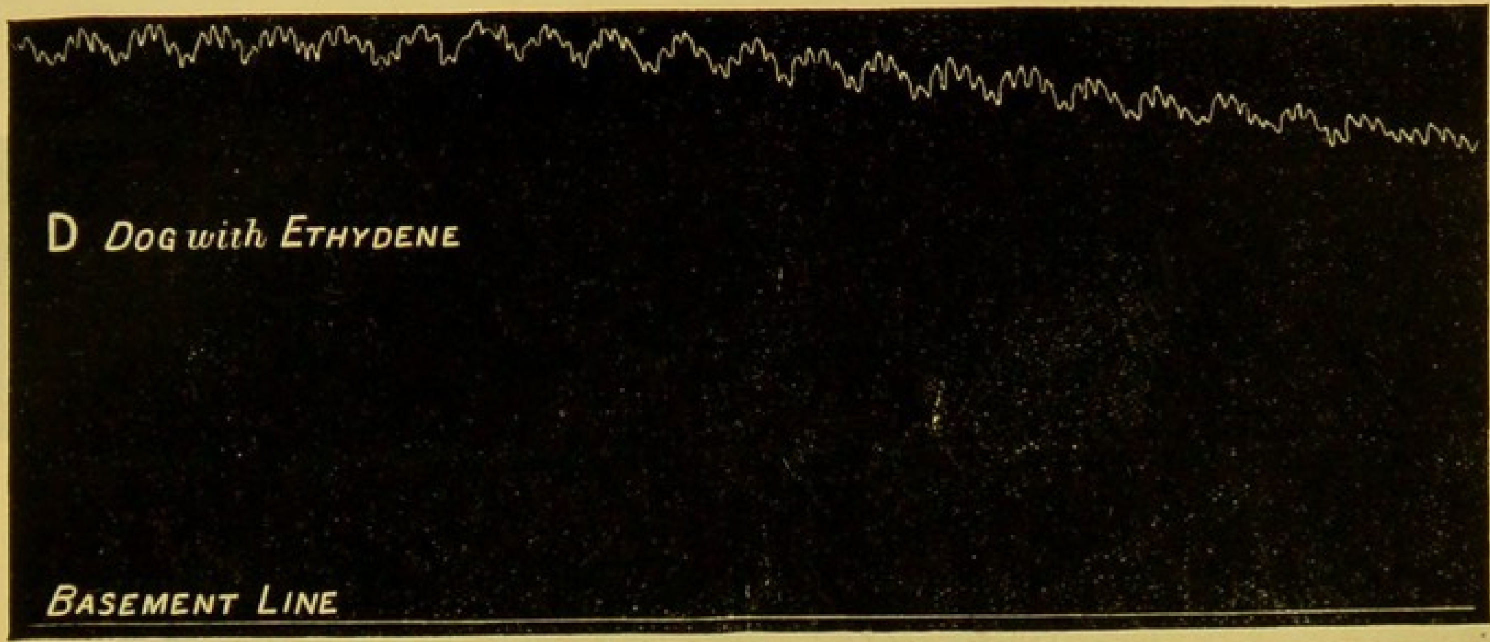
It may here be incidentally remarked that with artificial respiration there were very exaggerated variations of pressure, as shown in Tracings H and K; these respiratory variations, however, only occurred when the animal made respiratory movements coincidently with the pumping. When as a result of deep anæsthesia, respiration ceased on the part of the animal, the respiratory variations also ceased, although the artificial respiration was kept up.

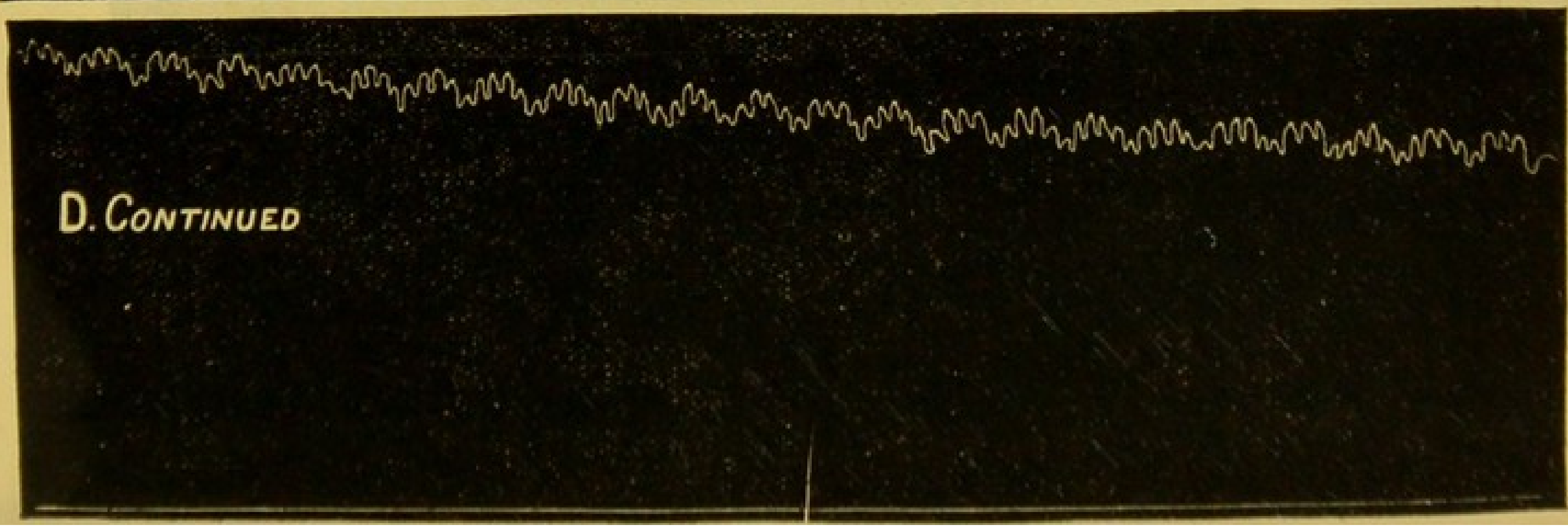
The next experiment is a somewhat interesting one, offering in a certain sense the converse of one already narrated. The same animal was used as in the last experiment; the tracheal tube was left in, and the animal breathed through it. The anæsthetics were administered by holding a cloth soaked with the agent over the mouth of the tube. Chloroform was given, and there was an almost immediate fall of pressure, but the fall was gradual, and in 234 seconds had reached 28 *millimètres*, when the chloroform was stopped. The respiration ceased just after the chloroform had been removed. Artificial respiration was at once resorted to; but in spite of this, the heart ceased beating twenty-one seconds afterwards. It is remarked, however, that although there were no indications of the heart's pulsations on the tracing, the pressure was maintained at 28 *millimètres*, and it is just possible that there may have been slight pulsations too feeble to be recorded. The pause of the heart continued for twenty-one seconds, and the pulsations were then resumed very feebly and irregularly. The pressure rose gradually to 46 *millimètres*, when a spontaneous respiration was given; then, with long intervals, spontaneous respiration was resumed, and the artificial respiration was stopped, as it was not required.

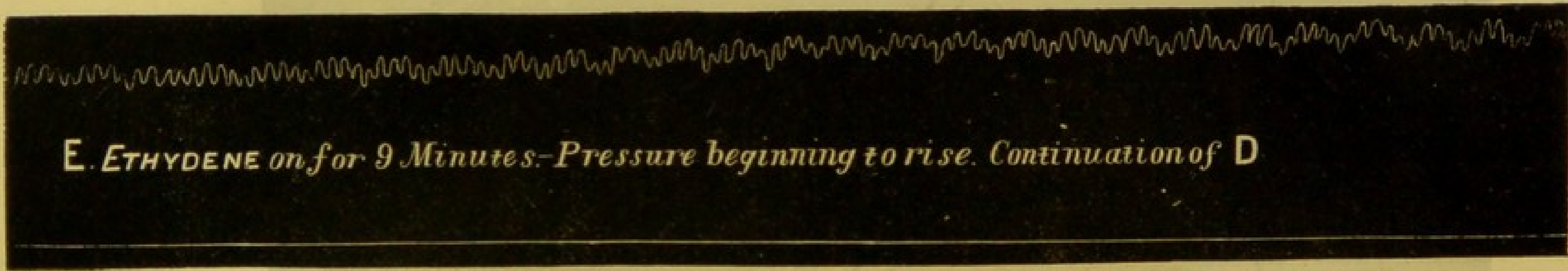
In this observation, it seems undoubted that the respiration failed first. The rapid failure of the heart is a remarkable circumstance, especially when the comparatively high pressure is considered. It is possible that the introduction of artificial respiration may have had to do with it. The respirations before they ceased were shallow; and though the air in the lungs was saturated with chloroform, little of it would find its way into the blood in the very limited respiratory movements. The introduction of artificial respiration would at first force the saturated air rapidly through the lungs, which would be vigorously inflated, and a large amount of chloroform would be introduced into the blood.

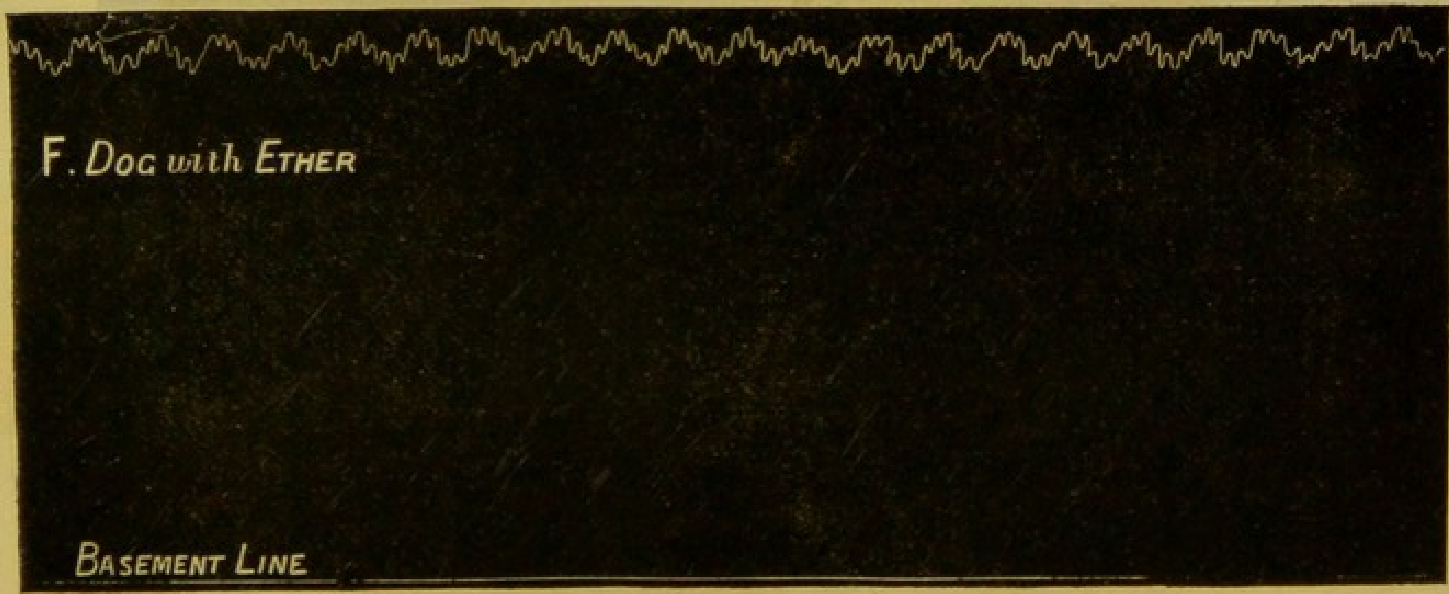
After the animal had recovered from this experiment, ethidene was given. There was a fall of pressure; but, though administration was continued in frequently repeated doses for nine minutes, the blood-pressure only fell to 38 *millimètres*, and there was no failure of respiration. Before the ethidene was removed, the pressure had risen to 60 *millimètres*. (See Tracings D and E; E is continuous with D after a considerable interval.) The respiratory curve was preserved even at the point of lowest pressure, and the regularity of the heart's pulsations was not interfered with.

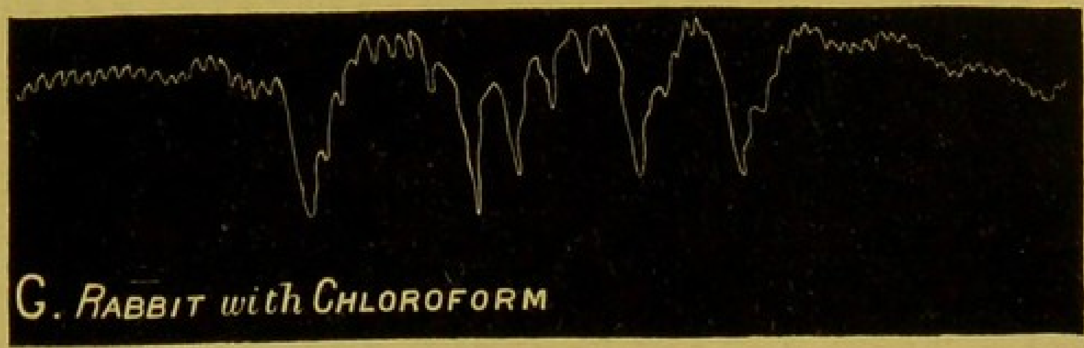
In this animal the pneumogastrics were now cut, and the observations were repeated both with and without artificial respiration. It cannot be said that any essential difference was apparent in the results. The


D Dog with Ethydene
Basement Line


D. Continued


E. Ethydene on for 9 Minutes:-Pressure beginning to rise. Continuation of D


F. Dog with Ether
Basement Line



G. Rabbit with Chloroform

H.

pressure fell both with chloroform and with ethidene, but the fall was perhaps not so rapid nor so great as under other circumstances. While artificial respiration was used, ethidene and chloroform were successively pushed to a very great extent, the Wolff's bottle being heated to facilitate the evaporation of the agents. Yet the blood-pressure was not reduced to the lowest, even with this treatment; and in the case of ethidene it even began to rise under it. The effect on the respiratory variations in pressure was remarked during these experiments. In the case of ethidene, even when the agent was given to the fullest extent, the respiratory curve, though very much diminished, did not entirely disappear. In the case of chloroform, the respiratory curve disappeared completely, and that shortly after the commencement of administration. The cardiac pulsations in the case of chloroform became scarcely perceptible, the pressure, however, not falling below 40 *millimètres*. With ethidene, in the same circumstances, the cardiac pulsations remained of nearly normal amplitude.

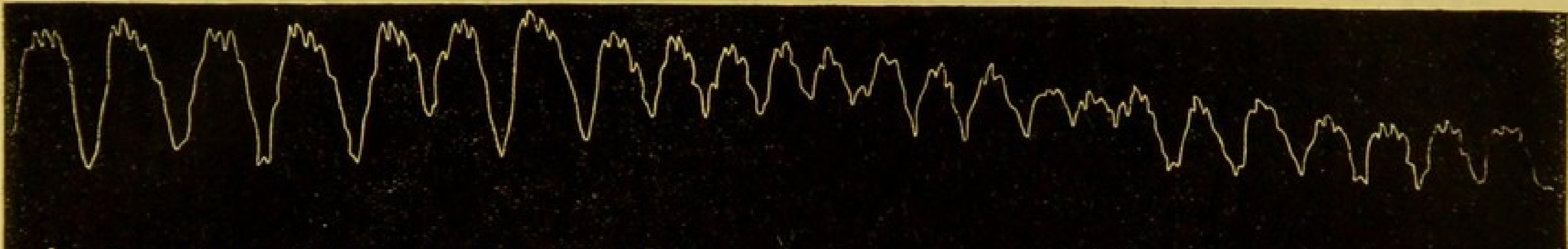
As a result of the whole set of experiments with this dog, it may be said that the heart showed throughout a remarkable state of vigour. It only exhibited signs of giving way on one occasion, and in that case the blood-pressure was maintained at a comparatively high position. On the other hand, respiration failed during the administration of chloroform very readily. In these respects, this animal contrasts with the former one. It is quite obvious, also, that on those occasions when the breathing ceased, the animal would almost certainly have died, but for the use of artificial respiration.

In some further experiments which we made with another dog, using Fick's kymograph,* a more remarkable result was obtained. Both respiration and heart had stopped under the use of chloroform, but by means of artificial respiration (by the pump) there was ultimate recovery, although the pulsations of the heart had ceased for a considerable time. In this case there could not be any feeble pulsations keeping up the circulation at a slow rate, as was supposed to be possible in a former case, because Fick's arrangement registers very accurately the slightest variations in the pressure produced by the heart's action. In the case of this dog also it was observed that several times, after a period of shallow respirations, the breathing stopped for a brief interval, the heart beating with considerable vigour. As respiration had ceased, no more chloroform was admitted to the blood, and after a time, the respiratory movements returned. So much was this the case that difficulty was experienced in killing the dog with chloroform, and this was only effected by administering it by artificial respiration, after the spontaneous movements of respiration had ceased. By artificial respiration an additional quantity was introduced, and the heart soon succumbed.

These facts are of considerable importance, as they show the varying effects of chloroform in the same animal at different times. At one period, respiration and the heart failed nearly at the same time. At another, respiration failed, and the heart, being still vigorous, was able to carry on the circulation till the chloroform had been sufficiently eliminated to allow the recovery of the respiration.

Some of the tracings referred to in the text are here reproduced. The basement line represents the point at which the

* Shown in Dr. McKendrick's *Outlines of Physiology*, page 357.



J Dog. Artificial Respiration CHLOROFORM.

K. ETHYDENE

needle was when the mercury in the two limbs of the manometer was level. According to the pressure, the mercury is pressed down in the one limb and raised in the other, the tracing giving the latter. As the actual pressure equals the weight of the column of mercury raised, this will be represented by the difference in the levels in the two limbs, and will be double the distance from the basement line to the tracing. The tracings are to be read from left to right.

A. Represents the occurrence mentioned in the text, in which, while a dog was recovering from chloroform, a sudden fall of pressure occurred, with great reduction in the frequency of the heart's contractions. There is a gradual recovery, with striking inequalities of pressure, corresponding with respiratory movements.

B. Another sudden fall of pressure and retardation of the heart's contractions, occurring seventy seconds after the removal of the chloroform, and when the pressure had returned nearly to the normal.

C. The arterial pressure in a dog under the influence of chloroform. There is a progressive but somewhat irregular reduction of pressure, ending in a stoppage of the heart, while respiration continues. There is an imperfect recovery of the heart, the contractions barely causing the pressure to reach the basement-line. Beneath this tracing are copies of the markings made with the chronograph, half-seconds being registered. The markings used to indicate the administration or leaving off of an agent are also reproduced.

D. The arterial pressure in a dog under the influence of ethidene. There is a perfectly regular and gradual reduction in the pressure, the respiratory variations being preserved.

E. This is a continuation of D, after an interval. Ethidene has been given all the time, and the illustration begins at the point where the pressure is lowest. The pressure is now beginning to rise, the ethidene being still continued.

F. The arterial pressure in a dog under the influence of ether. No effect on the pressure is produced, and the respiratory variations are perfectly preserved.

G and H show the variations in pressure produced in rabbits by the administration of chloroform, the animals being at this time imperfectly under its influence. These variations are presumed to be reflex.

J and K show the exaggerated respiratory variations produced while artificial respiration was being carried out. It is to be understood that the animals made synchronous respiratory efforts. The arrangement for artificial respiration not only blew air into the lungs, but also sucked it out.

VIII.—Effect of Anæsthetics on Pulmonary Circulation.

We now pass on to the consideration of the effects of anæsthetics upon the pulmonary circulation and the lung-tissue itself.

One of the most striking effects of anæsthetic agents is the engorgement of the right side of the heart and the large veins near it. This has been directly observed by the Committee, and is well known. It is evidently a matter of importance to ascertain the causes of this phenomenon, which might be due to debility of the heart, to some change occurring in the lung resulting in obstruction, or to some influence on the circulation acting through the nervous centres governing it. The research now reported has reference to the effect on the pulmonary circulation.

At the very outset, it was found necessary to devise a special apparatus for carrying on artificial respiration in the frog; so, before considering the results of the experiments, it will be requisite to describe it, and narrate the mode of procedure.

The apparatus, a drawing of which is shown in Fig. 3, consists of two graduated cylinders, B and C, capable of holding 100 c. c. each; the former being a reservoir for air, the latter containing a supply of anæsthetic vapour. Associated with each of these is a series of tubes, the connections and uses of which may be seen by referring to the drawing. From the pressure-bottle (A) passes a tube (*a*), which divides into three portions, two of which (*b* and *c*) pass under the keys

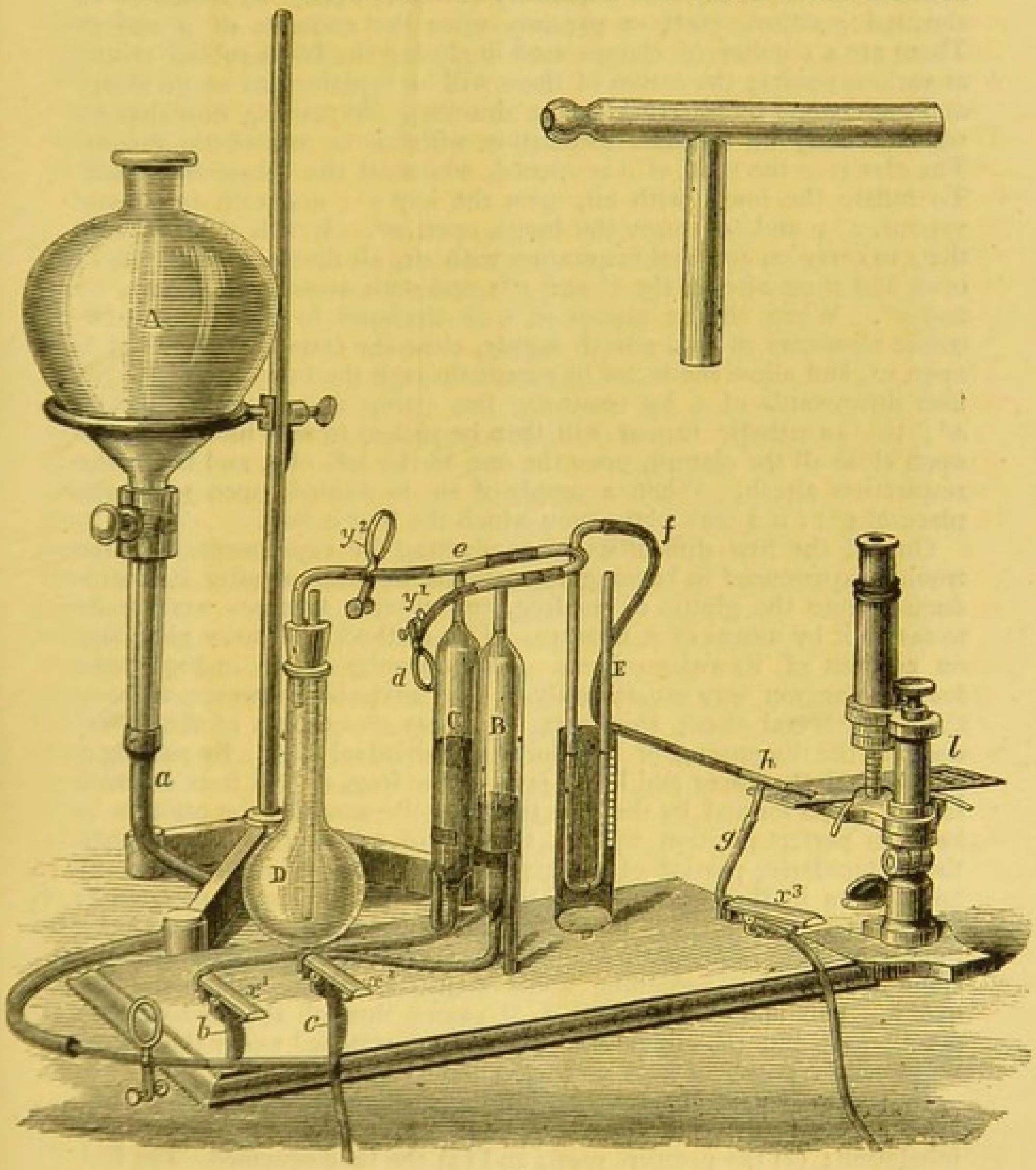


Fig. 3.

(x^1 and x^2) to C and B; while the third branch passes downwards, and is fastened with a clamp the same as y^2. The glass cylinder C terminates in a T-tube (*e*), one limb of which conducts to a flask (D) containing the anæsthetic, while the other passes to the manometer E. The upper part of the vessel B likewise terminates in a T-tube, the one limb leading to the manometer, the other (*d*) communicating with the air. From the manometer (E) passes a tube (*f*) going to the cannula (*h*). The cannula is different from what is commonly used, and is represented on the upper right-hand corner of Fig. 1. It consists of a glass T-tube, one limb (that introduced into the glottis of the frog) of which is about 15 mm. in length; this, after being slightly constricted, terminates in a small ball.

Let us now explain the method of working the apparatus. The pressure-bottle (A) contains a quantity of water, which, by reason of its elevated position, exerts a pressure upon the contents of B and C. There are a number of clamps used in closing the India-rubber tubing at various points; the action of these will be explained as we go along, and understood by referring to the drawing. Supposing now that we wish to carry on artificial respiration with air or anæsthetic vapour. The clamp to the right of *b* is opened, whilst all the others are closed. To inflate the lungs with air, open the key x^2; and with anæsthetic vapour, x^1; and to empty the lungs, open x^3. It will thus be seen that, to carry on artificial respiration with air, all that is necessary is to open and close alternately x^2 and x^3; and with anæsthetic vapour, x^1 and x^3. When all the vapour in C is displaced by water, and it becomes necessary to have a fresh supply, close the clamp to the left of *b*, open y^2, and allow the water to escape through the tube, the prolongation downwards of *c*, by removing the clamp and opening the key x^1; the anæsthetic vapour will then be sucked from D into C; thereupon close all the clamps, open the one to the left of *b*, and begin the respiration afresh. When a supply of air is wanted, open y^1 in the place of y^2; *l* is a cork plate upon which the frog is laid.

One of the first difficulties in conducting the experiments was the trouble experienced in keeping the cannula in position after its introduction into the glottis of the frog, and several attempts were made to fasten it by means of a ligature. This method was soon given up, on account of its awkwardness. The cannulæ shown in Fig. 3 are found to answer very satisfactorily. It is advisable, however, to have them of several sizes; this being necessary on account of the differences in the dimensions of the glottis in individual frogs. By passing a pin through the upper and lower jaws of the frog, so that it is external to the angle formed by the two limbs of the cannula, the cannula is kept in perfect position without the use of a ligature. To complete the manipulative portion of the experiment, it is now requisite to make an incision in the thoracic wall, through which the lung is protruded; this is best accomplished by placing the frog upon its back, making a longitudinal cut of about three-quarters of an inch halfway between the spine and sternum, beginning about a quarter of an inch below the axilla. The lung being inflated, it passes through the incision just mentioned; and the circulation may be now watched under the microscope with a power of from 50 to 300 diameters.

In conducting the experiments, certain points require to be observed: (1) the quantity of air or anæsthetic vapour passed into the lungs during inhalation; (2) the pressure used; and (3) the time occupied. The first of these was regulated by measurement; the second indicated by the manometer. To save the trouble, however, of measuring the quantity for each inspiration, the following method was adopted. The lung having been distended by a suitable quantity of air (from 3 to 4 c. c., according to circumstances), and a certain point brought into focus, the condition of the circulation was observed. By opening the key x^3, the lung collapsed. Now, instead of inflating, and again focussing, the microscope was kept fixed, and air or anæsthetic vapour, as the case might be, passed into the lung till, by distension, the same point as before came into view. The focus may be as accurately fixed by gently pressing upon the keys x^1 or x^2, as by the adjustment of the microscope. This method had not only the advantage of submitting the same portion of lung for examination, but also guaranteed its equable distension throughout the experiment, and so obviated fallacies which might arise from variation in the quantity, or in the pressure of the atmosphere in the lung. The average quantity of air or vapour used to inflate the lung of a good-sized male frog equals 4 c. c., and the pressure 55 mm. (water manometer). During the experiment, the exposed surface of the lung was kept moist with a few drops of saliva applied occasionally. We will now give a few examples from a series of experiments.

Experiment 1.—A frog was placed in a bell-jar containing a piece of blotting-paper saturated with chloroform; the web of the right foot (the one to be subsequently examined) being, however, kept outside the jar. In two and a quarter minutes, when reflex action was destroyed, the cannula was introduced into the glottis, the frog laid upon the cork plate, and its right lung exposed, as described above. On inflating the lung with air, the circulation both through the capillary and large vessels was found to be active; pulse 18 per minute. Artificial respiration was now carried on by means of the apparatus, 50 c. c. of an atmosphere containing chloroform being inspired in fifty seconds. Fifteen seconds after the first inspiration, a distinct change could be observed in the rapidity of the flow of blood through the capillaries, even though the circulation in the larger vessels was unimpaired, and the number of the heart's impulses remained unchanged. By fifty seconds, however, not only had the pulse become diminished in number to a fourth, but the capillary circulation of the lung and web ceased; and by seventy-five seconds the flow of blood through the large vessels both of the lung and foot entirely stopped; while the heart-beats, as observed through the thoracic walls, were four per minute. Air was now substituted, and 400 c. c. passed through the lungs in eight minutes. By this time the heart-beats had increased to nine per minute, and the blood began to flow slowly through the larger vessels of the lung. No movement could be detected in the web. When, however, 600 c. c. of air had been expended in artificial respiration (the time occupied being twelve minutes), the pulse rose to 15; the flow of blood through the lung became as vigorous as before; while the circulation in the foot gradually increased, and in a few minutes became as active as before chloroform was administered by artificial respiration.

Experiment 2.—This experiment was performed in exactly the same manner as the last, with the exception that ethidene dichloride was used in place of chloroform. Instead of taking two and a half minutes, as with chloroform, to lose reflex action, it required nearly five minutes.

On exposing the lung, its substance was found to be brighter in colour, and the circulation more active, than when chloroform was administered. The pulse was 23 per minute ; 250 c.c. of ethidene vapour were now passed into the lung (time 180 seconds). Forty-five seconds passed before any change could be observed. In 105 seconds, however, the capillary circulation in the lung and web ceased, and in 180 seconds the flow through the vessels stopped, at which time the heart's impulses were seven per minute. The stoppage of the circulation was almost simultaneous in the web and lung. Artificial respiration was now carried on with air. After 100 c.c. had been given (time 50 seconds), a slight movement of the corpuscles was observed in the vessels of the lung, and in 75 seconds in the foot. When 250 c.c. (time 120 seconds) of air had been passed through the lung, the capillary circulation gradually became established ; and, by the time (240 seconds) 250 c.c. had been respired, it was as active as at the beginning of the experiment, and the pulsations of the heart rose to 18 in the minute.

Experiment 3.—In this experiment, ether was used as the anæsthetic. The frog, placed in an atmosphere of ether, took eight and a half minutes to lose reflex action (pulse 24 per minute). The naked eye and microscopic appearances of the lung were much the same as when ethidene was administered. 500 c.c. of ether vapour were given before the circulation in the large vessels of the lung could be stopped (time twelve minutes), whilst the capillary circulation required 175 c.c. (time 110 seconds) before any change could be noticed, and 300 c.c. to make it stop completely—the pulse being 6½ in the minute. The frog was now made to inhale air. When 150 c.c. had been given, the circulation began to be re-established in the larger vessels, the pulse being nine per minute, and, when the air passed into the lungs amounted to 200 c.c., the capillary circulation also returned to what it was before the ether was given artificially. Chloroform vapour was now given for 180 seconds to the same frog with the following results. In fifteen seconds, a marked change was observed in the capillary circulation ; in thirty, it stopped ; and in forty-five, the flow through the large vessels ceased.

Before passing to the consideration of the minute changes in the lung, let us contrast the following points as regards the comparative effects of chloroform, ethidene, and ether.

1. The time required to produce complete stoppage in the pulmonary circulation.

2. The amount of anæsthetic vapour employed.

3. The quantity of air necessary to re-establish the circulation in the lung.

4. The time occupied in restoring the circulation.

By glancing at the above experiments, it is, in the first place, to be observed that the changes produced by the three anæsthetics employed differ only in the rapidity of their occurrence, not in kind. Thus chloroform may be placed at one extreme, ether at the other, whilst ethidene occupies an intermediate position. The relative effects of these anæsthetics are shown in the following table, constructed from the above experiments, which were chosen as showing strictly average results.

	Chloroform.	Ethidene.	Ether.
1. Time required to produce complete stoppage of pulmonary circulation ..	75 seconds	180 seconds	.270 seconds
2. Amount of anæsthetic vapour employed..	50 c.c.	250 c.c.	500 c.c.
3. The quantity of air necessary to re-establish circulation in lung	600 c.c.	250 c.c.	200 c.c.
4. Time occupied in restoring the circulation.	720 seconds	240 seconds	180 seconds
5. Heart's impulses before artificial respiration	18	23	24
6. Heart's impulses when circulation has stopped.	4	7	6½

The difference in the action of these anæsthetics will be seen, from the above table, not only to depend upon a variation in the amount of anæsthetic vapour required to produce complete stoppage of the circulation in the lung, but also on the want of uniformity in the quantity of air necessary to restore it to its former condition. For instance: the chloroform vapour necessary to stop the circulation is 50 c.c., administered in 75 seconds; ethidene, 250 c.c., administered in 180 seconds; and ether, 500 c.c., in 270 seconds. Now, it might be expected that the amount of air required to eliminate the ethidene taken up by the lung, during its exposure to the action of 250 c.c. of vapour, should be greater than that needed to free the circulation from the effects of 50 c.c. of chloroform; and more particularly when it is observed that the time during which the ethidene vapour was in contact with the lung amounted to almost two and a half times as long as the chloroform. But this is not the case. In fact, the contrary may be affirmed. The longer it takes to place the circulation in abeyance, and the greater the amount of anæsthetic vapour used, the shorter is the time requisite to re-establish the pulmonary circulation, and the smaller the amount of air necessary to do so; in other words, the length of time and the amount of air employed in artificial respiration, with the object of restoring, is in an inverse ratio to time and amount of anæsthetic vapour required to stop, the circulation. The impulses of the heart, both in relation to their frequency and other characters, will be more carefully studied further on.

The next question which presents itself for our consideration is one of considerable importance and interest, namely: what are the changes which take place in the lung when anæsthesia is pushed to its utmost point; and how are these alterations to be explained? We will first attempt to describe the changes, and then proceed to the consideration of the causes which bring them about.

When anæsthetics are administered in excessive quantities, the first change noticed in the circulation in the lung is a diminution in the rapidity of the flow of blood in the capillaries; and this, notwithstanding that the number of the heart's impulses remains unchanged, and the circulation through the larger vessels is unimpaired. Very shortly after this, instead of the flow of blood being constant, it gradually becomes intermittent—first in the capillaries, afterwards in the arterioles, and subsequently in the larger vessels. This intermission in the flow of blood is followed by a swinging to-and-fro movement of the corpuscles, just previously to the stoppage of the circulation through the capillaries.

It must now be observed that the stoppage of the circulation in the lung takes place first in the capillaries, then in the arterioles, and, last of all, in the larger vessels; further, that the sequence in recovery is exactly the reverse. Again: it is to be noticed that the circulation in the foot stops—not previously to, but shortly after, that of the lung; and its re-establishment never occurs before, but always subsequently to, the restoration of the pulmonary circulation. The more minute changes to be observed in the lung are represented in the woodcuts, figures 4 and 5.

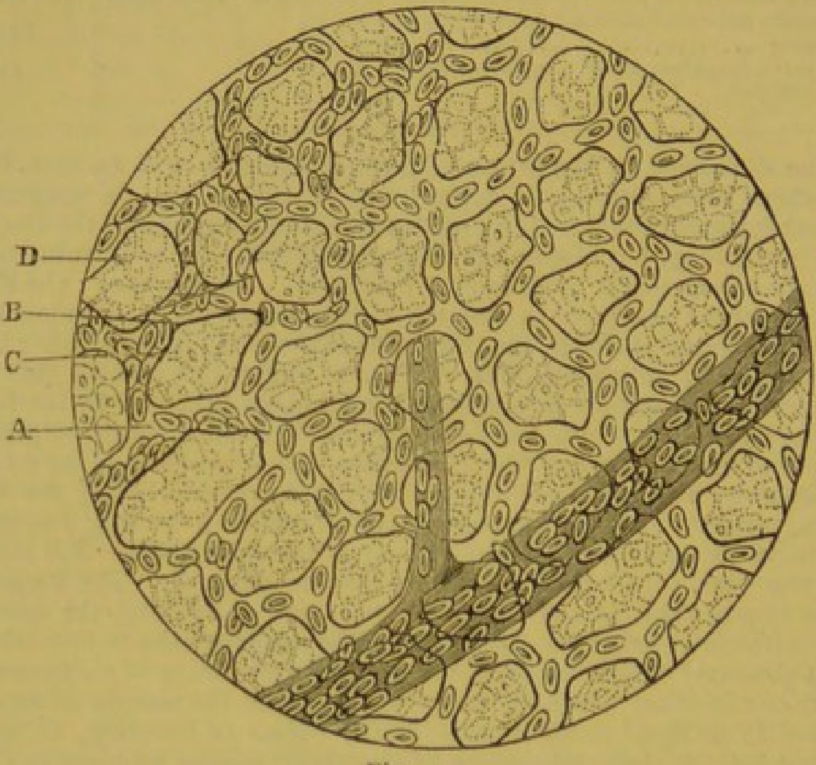


Fig. 4

When the lung is *not* over-distended, and the amount of anæsthetic vapour administered is moderate, a plexus of irregularly shaped meshes may be observed, formed in the alveoli by the capillary vessels. The diameter of the capillaries varies from .0225 to .0275 mm.; while the size of the corpuscles may be laid down as from .020 to .025 mm.; and the enclosed spaces from .040 to .060 mm., or even more. The meshes (Fig. 4, B) not only vary in size amongst themselves, but also at different times, according to the pressure exerted upon the air in the pulmonary sac. So much is this the case, that, should the lung be over-distended, the meshes become so stretched that they diminish the calibre of the capillaries, and so retard, or even prevent, the flow of blood; hence the necessity of having the lung equally inflated throughout the experiment. While the circulation is active, the contour lines of the flat, irregular-shaped alveolar epithelium (Fig. 4, D) of the meshes, as well as their nuclei (Fig. 4, C), may be distinctly seen, and the outline of the capillaries (Fig. 4, B) is well marked. When, however, the anæsthetic has been pushed so as to stop the pulmonary circulation, the individual epithelium-cells become at first indistinct; the nuclei also become less evident, and subsequently disappear; so that, instead of presenting the aspect of cellular structures, the meshes enclosed by the capillaries show themselves as if they were spaces filled with granular protoplasm. Further, the limitation of the meshes themselves (Fig. 5, B) becomes so indistinct, that it is with considerable difficulty that the course of the capillaries can be traced. This difficulty is increased by the tendency of the corpuscles to aggregate themselves at certain points (Fig. 5, A), and so leave empty spaces where the capillaries, partly on account of this deficiency, become invisible (Fig. 5, B). The want of

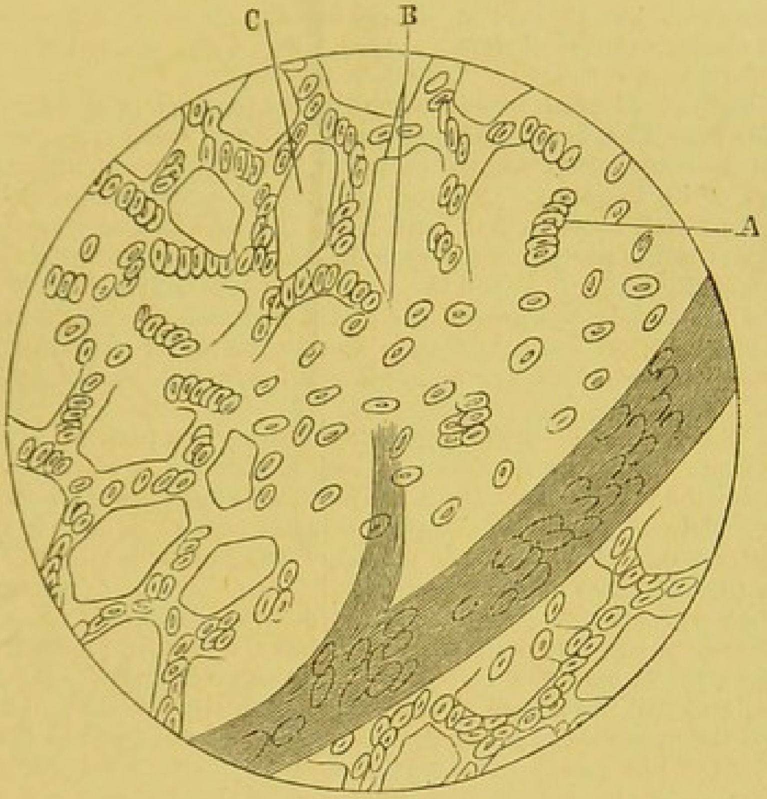


Fig. 5.

clearness in the definition of the capillaries is not, however, entirely due to the absence of corpuscles; for even where the corpuscles are abundant (Fig. 5, A), the capillary walls are less distinct than when the circulation is active. As regards the calibre of the arterioles and capillaries, it may be roughly stated that the former contract a sixth, the latter a ninth, from what they were previous to the administration of the anæsthetic vapour by artificial respiration. The causes of this contraction will be considered hereafter. Should repeated supplies of air be now passed into the lung, the condition of that organ will be restored to what it was before the anæsthetic was given.

The corpuscles themselves appear also to be altered by the action of the anæsthetic vapour, in so far that, at some points, they appear as if they had become completely disintegrated, and their place filled by a mass of a reddish-coloured material, which disappears on the re-establishment of the circulation.

The granular appearance presented by the contents of the meshes, and the disintegrated condition of the corpuscles, are not represented in Fig. 5, in which figure the outline of the corpuscles is too distinctly shown.

In order to determine the effect of anæsthetics upon the cardiac impulses, another series of experiments became necessary. These experiments were performed by means of the same apparatus referred to at page 18. A sheet of paper, eight feet long, and broad enough to accommodate ten tracings at different levels, was adapted to the cylinders, so that a continuous tracing of eighty feet, if necessary, might be obtained; at the same time, a record of time was taken, corresponding to each individual tracing; and, besides, by means of electro-magnetic arrangements, the periods at which anæsthetics were administered or certain changes observed were recorded. Fig. 6 shows selected portions of these tracings.

The method adopted in recording the movements of the heart was very simple. The heart was supported upon a small stage, so as to prevent the movements occasioned by artificial respiration affecting the tracings of its impulses. A lever, 20 c.m. long, was placed obliquely across the heart, so as to rest both upon the auricle and ventricle—in order that the first portion of the upstroke might correspond with the contraction of the auricle. When the ventricular contractions closely follow those of the auricle, the ascent line is straight, and no indication of the latter as separated from the former can be detected; whereas, if the ventricular contractions are delayed, the lower portions of upstrokes become curved (Tracing VIII, Fig. 6).

With the purpose of instituting a standard of comparison, a tracing of the heart's impulses is shown in Fig. 6, Tracing I, where the frog was under the influence of curare. The heart's impulses were 40½ per minute, while the period of activity may be said to occupy 2.5 hundredths of a minute, so that the period of rest, as far as indicated by the tracing, may be regarded as *nil*.

Chloroform was now given for fifteen minutes, by means of artificial respiration, to the curarised frog, and another tracing taken (Fig. 6, Tracing II). It may now be observed that the heart's beats are 23 per minute, and still the period of rest is not distinctly marked. In these tracings the up-strokes are rapid, and the periods occupied in the contractions are not great. Tracings III and IV show the pulsations of the heart under the influence of ether, the former immediately on the heart being exposed, the latter after ether had been administered for seven minutes by artificial respiration. The pulsations in III and IV are 21 and 19 respectively, so that, as contrasted with Tracing I, they may be said to be diminished in number by about a half. The period of rest is not well marked in either of these tracings. Tracings V and VI were taken from a frog under the influence of ethidene, the one on exposing the heart, the other after ethidene had been given by artificial respiration for five minutes.

Let us now examine these tracings more carefully. In Tracing V, the pulsations are 16 per minute. The period of activity occupies about 2.8, and that of rest 3.5 hundredths of a minute. The ascent-line is not quite straight, there being a slight curve both at the apex and base; the apex is rounded, and the descent line slightly sloped. In tracing VI, the impulses are diminished in number to 7 per minute. This diminution will be seen to be due to two causes: first and principally, to prolongation of the period of rest; and, second, to lengthening of the period of action, so that not only are the spaces between the waves greater, but the intervals between the origin of the ascent-lines and the termination of the down-strokes are also increased. To represent this in figures, it may be said that the period of activity equals a little more than four-hundredths, and the period of rest ten-hundredths

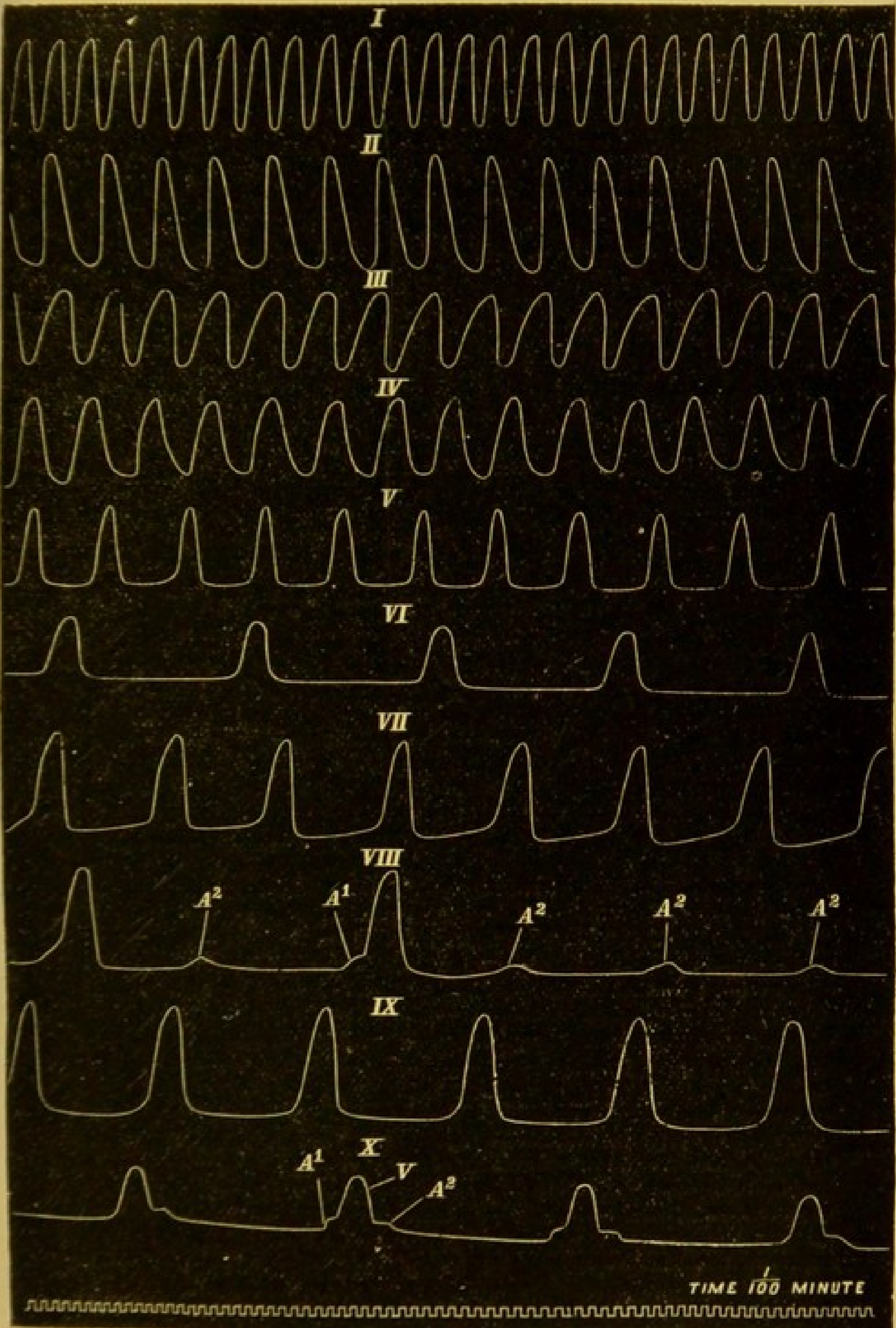

I
II
III
IV
V
VI
VII
VIII
A2
A1
A2
A2
A2
IX
X
A1
V
A2
TIME 1/100 MINUTE

Fig. 6.

of a minute. Tracings VII, VIII, IX, and X are those of a frog under the influence of chloroform. Tracing VII, immediately on exposure of the heart; VIII, after artificial respiration with chloroform for two minutes, 150 c. c. of vapour having been employed; IX, recovery after artificial respiration with air for three minutes; and X, after giving 200 c. c. more of chloroform-vapour, the time occupied being two minutes. The impulses in Tracing VII are 11 per minute. It will be observed that, from the termination of the down-stroke to the beginning of the following ascent-line, there is a gradual rise in the tracing. This is due to the slow filling of the cavities of the heart. The up-strokes are slightly curved, the apices rounded, while the descent-lines are almost straight. By pushing the chloroform by means of artificial respiration, we always get tracings similar to what is represented in VIII. Take, for instance, the large wave in the centre of the tracing: instead of the up-stroke arising directly from the basement-line, it is preceded by a small wave (A^1), corresponding with the contraction of the auricle. From the apex of this wave it rises slowly so as to form the ascent-line, which terminates in a rounded apex. The descent-line frequently terminates in a smaller wave (Tracing X, A^2), which also corresponds with a contraction of the auricle. It is further to be noted that the auricular contractions (Tracing VIII, A^2) are not always followed by corresponding ventricular movements, the auricle continuing to contract at regular intervals, although the ventricle ceases to respond.

Let us now consider the facts demonstrated by the tracings, placed alongside the changes observed in the lung by means of the microscope.

It is evident that the interference with the proper action of the heart accounts to a considerable extent for the changes in the pulmonary circulation and tissue. Thus the slowing of the circulation through the lung, and the diminution of the calibre of the arterioles and capillaries, correspond exactly with the impairment of the heart's impulses; but then, again, it may be questioned, how far the stoppage of the heart depends upon increased resistance to the flow of blood through the pulmonary vessels. We have shown above that, when the lung is exposed, the current of blood is continuous, there being no intermittent movement, as a result of the ventricular contractions; when, however, anæsthetics are administered in larger quantities, the flow becomes interrupted, the arterioles and capillaries diminish in calibre, and certain changes are observed in the pulmonary tissue. The changes in the diameter of the vessels may be regarded as a result of a retardation, and less forcible contracting of the ventricle; or it may be due to local effects of the anæsthetic upon the lung, producing greater resistance to the flow of blood, and so preventing the heart emptying itself. The latter idea is supported by the fact that, when the animal is deeply under the influence of the anæsthetic, particularly chloroform, the heart is greatly distended. Another fact which must not be forgotten is the change in the condition of the corpuscles and of the capillaries. The mutual relationship of these may be so altered, by the direct action of the anæsthetic, that the force of the heart required to propel the blood through the pulmonary vessels is increased; while, by reason of the action of the anæsthetic upon the heart, the power at its disposal is considerably diminished. The disintegration of the blood-corpuscles, as pointed out above, shows distinctly that the anæsthetic vapour has a direct effect upon the blood,

IX.—SUMMARY.

From the observations recorded, we feel warranted in drawing the following conclusions.

A.—Clinical.

I. The dose (admininistered on a towel) is greater with ethidene than chloroform; but the time necessary to anæsthetise the patient is longer with the latter than the former agent.

II. The number of cases of sickness and vomiting is about the same with the two agents, but the duration is considerably protracted in the case of chloroform; the occurrence of these symptoms have no relation to the length of time the patient has been under, or reference to the quantity of anæsthetic administered in a given time.

III. With both agents, the pulse-respiration ratio is considerably altered in a certain number of cases, the pulse falling as the respirations increase in frequency. With chloroform, this change is not only, much more marked, but its occurrence is also more frequent than with ethidene; the proportion, in our experience, being nine of the former to two of the latter. There is also a greater tendency in cases of chloroform to retardation of the heart's movements, and to dicrotism.

B.—Physiological.

I. The effect of anæsthesia with chloroform is to increase the amount of carbonic acid exhaled in a given time. The results of our investigations, in connection with the effects of anæsthetics on the gases of the blood, are not sufficiently reliable to permit us to give results.

II. Both chloroform and ethidene, administered to animals, have a decided effect in reducing the blood-pressure; while ether has no appreciable effect of this kind.

III. Chloroform reduces the pressure much more rapidly, and to a greater extent, than ethidene.

IV. Chloroform has sometimes an unexpected and apparently capricious effect on the heart's action, the pressure being reduced with great rapidity almost to *nil*, while the pulsations are greatly retarded, or even stopped. The occurrence of these sudden and unlooked-for effects on the heart's action seems to be a source of serious danger to life—all the more that, in two instances, they occurred more than a minute after chloroform had ceased to be administered, and after the recovery of the blood-pressure.

V. Ethidene reduces the blood-pressure by regular gradations, and not, so far as observed, by these sudden and unexpected depressions.

VI. Chloroform may cause death in dogs either by primarily paralysing the heart or the respiration. The variations in this respect seem to depend to some extent on individual peculiarities of the animals; in some the cardiac centres are more readily affected, in others the respiratory. But peculiarities in the condition of the same animal very probably have some effect in determining the vulnerability of these two centres respectively; and they may both fail simultaneously.

VII. In most cases, respiration stops before the heart's action; but there was one instance in which respiration continued while the heart had stopped, and only failed a considerable number of seconds after the heart had resumed.

VIII. The use of artificial respiration was very effective in restoring animals in danger of dying from the influence of chloroform. In one instance, its prolonged use produced recovery even when the heart had ceased beating for a considerable time.

IX. Under the use of ethidene, there was on no single occasion an absolute cessation either of the heart's action or of respiration, although they were sometimes very much reduced. It can, therefore, be said that, though not free from danger on the side of the heart and respiration, this agent is in a very high degree safer than chloroform.

X. In regard to the effect of anæsthetics upon the pulmonary circulation, as in the experiments on the effects of the anæsthetics upon the blood-pressure, it may be stated that chloroform produces the most immediate effect, ether the least, whilst ethidene occupies an intermediate position.

XI. The quantity of air, and the length of time required to restore the circulation in the lung, are in an inverse ratio to the amount of anæsthetic vapour, and time necessary to stop it.

XII. The changes produced in the lung are the same in all ; the only difference being in the rapidity of their occurrence.

XIII. The anæsthetics produce the following changes in the lungs—(1) retardation and ultimate stoppage of the circulation in the lung: first in the capillaries, then in the arterioles, and subsequently in the larger vessels; (2) the epithelium-cells of the meshes and their nuclei are no longer apparent ; (3) the capillaries contract slightly, and their walls become less distinct, or even disappear from view, and the enclosed corpuscles may become more or less disintegrated.

XIV. The effect of ether and ethidene upon the heart, after artificial respiration for seven and five minutes respectively, is simply to produce a retardation of the impulses—ethidene having the most marked effect. Chloroform not only produces a retardation of the pulse, but the ventricular contractions are delayed and slightly separated from the auricular, and an auricular contraction may immediately follow the ventricular. The auricular contractions frequently occur without any corresponding ventricular movements.

C.—Practical.

The conclusions to be drawn from the above observations are these.

I. It is not only necessary to watch the effect of the anæsthetic upon the pulse, but it is also requisite to have regard to the respiration. We must not only take into account the danger of sudden stoppage of the respiration, but must also remember that, in the event of abnormal increase of respiratory movements, it may become essential, for the safety of the patient, to temporarily discontinue the administration.

II. Owing to the tendency of chloroform and ethidene—particularly chloroform—to reduce the blood-pressure suddenly, not only during the administration of these agents, *but also after they have been stopped for some little time* (a source of serious danger), it is necessary for the person who has charge of the administration of the drug to be on the look-out for symptoms of this occurrence, both during the time the agent is being given, and for some time after the patient has recovered from its more evident effects.

III. The danger of death, from stoppage of the respiratory functions, must be borne in mind in every case in which anæsthetics are given ;

but, of perhaps greater importance is the danger from interference with the proper action of the heart—particularly when it is remembered that, by artificial means, we can combat the former contingency. It might even be advisable, in certain cases, to introduce a tracheal-tube by the mouth—so as to enable us to force air into the lungs by means similar to those adopted in experiments with animals; or, in circumstances where such a procedure was impracticable, tracheotomy might be performed, with the same object in view. Artificial respiration should be continued, even though all evidence of cardiac action has ceased.

IV. As regards comparative danger, the three anæsthetics may be arranged in the following order: chloroform, ethidene, ether; and the ease with which the vital functions can be restored may be conversely stated, thus: the circulation is more easily re-established when its cessation is due to ether than to ethidene; and when the result of ethidene, than when chloroform has been used. The advantages which chloroform possesses over ether—in being more agreeable to the patient and more rapid in its action, in the complete insensibility produced by it, and the absence of excitement or movements during the operation—are more than counterbalanced by its additional dangers.

V. The chief dangers are: (1) sudden stoppage of the heart; (2) reduction of the blood-pressure; (3) alteration of the pulse-respiration ratio; and (4) sudden cessation of the respiration. The danger with ether approaches from the pulmonary rather than from the cardiac side—so that, by establishing artificial respiration, we have a means of warding off death. Its disadvantages are, to a great extent, obviated by the use of ethidene; whilst the dangers of chloroform are also reduced to a minimum.

FUTURE STUDIES.

In the event of the Scientific Grants Committee considering it advisable for us to continue our observations, we propose the following lines of research. 1. Specific action of anæsthetics upon the heart; to determine whether they act, *a*, on ganglia; *b*, muscular protoplasm; or *c*, on both. 2. The action of anæsthetic agents on the medullary centres; *a*, cardiac; *b*, respiratory; *c*, vaso-motor. 3. Specific action of anæsthetics on pulmonary tissue.

The Committee now feel that it is unnecessary for them to undertake clinical observations, except in the way of taking simultaneous tracings of the pulse and respiration; and for this purpose they have devised a special apparatus. They would respectfully suggest that schedules, similar to the one in this report, be now circulated, at home and abroad—so as, if possible, to collect information of the kind required regarding chloroform, ethidene, and ether, or other anæsthetic. They especially think it desirable to get specific information from America, as they have found it impossible to get cases of ether administration, in this country, sufficiently numerous for the purposes of comparison.*

The apparatus used by the Committee for taking simultaneous tracings of the heart's impulses and the respiratory movements is represented in Fig. 7. For the sake of description, it may be divided into two

* They were not aware, at the time of writing this report, that the use of ether is rapidly making way in this country, and that it is now solely used in several large provincial hospitals.

portions : (1) the transmitting and (2) the recording. We shall first describe the former of these. Owing to the difficulty of tracing the movements of the heart and thoracic will by any direct method, we were compelled to employ Marey's tambours, although we are aware that there are certain objections to this mode of transmitting and recording impressions. The tambours (J) are fixed to a brass plate (M) by means of two horizontal bars (X). These bars may be moved from right to left along a slot in the brass plate, and fastened in position by a pinching screw (K); by altering the length of the levers (L), tracings of various dimensions may be obtained ; while, by the same arrangement, the pens may be adjusted so that simultaneous movements are recorded on the paper in the same line. The tube T communicates with the cardiograph, while V passes to the pneumograph. The recording portion of the apparatus is very simple. Coiled on the drum (A) is a ribbon of paper (G) about two inches broad. The paper, on leaving the drum, slides over a flat stage (B), and then passes between two rollers (C and D). The stage (B) may be elevated or depressed so as to suit the height of the paper on the drum, and fastened in position by the screw (I). The plane-roller (C) is made to revolve from right to left by means of clockwork placed on the other side of the brass plate (M). The purpose of the double-flanged roller (D) is simply to keep the paper in contact with the plane-roller (C). By altering the size of the plane-roller, the paper may be made to move at various rates, as desired. The movement of the paper may be stopped without interfering with the clockwork, by turning the eccentric (H) from right to left, when, by pressing back the roller (D), the paper will be relieved from its contact with C ; and so, although C still revolves, the paper will remain stationary. The spring (F) presses upon the axle of A, in order to retard its movement sufficiently to keep the paper stretched as it passes over the stage (B), where it is written upon by the pens. The pens consist of small pieces of glass tubing (sufficiently large to hold a drop of ink), with a capillary prolongation, through which a cotton-thread is passed. The pens having been charged, the ink passes down the thread, and is transferred from it to the paper, without the point of the tube touching the paper ; the friction is, therefore, extremely slight. By using inks of various colours, movements which closely resemble one another in appearance may be distinguished at a glance. Time, if required, may be recorded alongside the tracings.

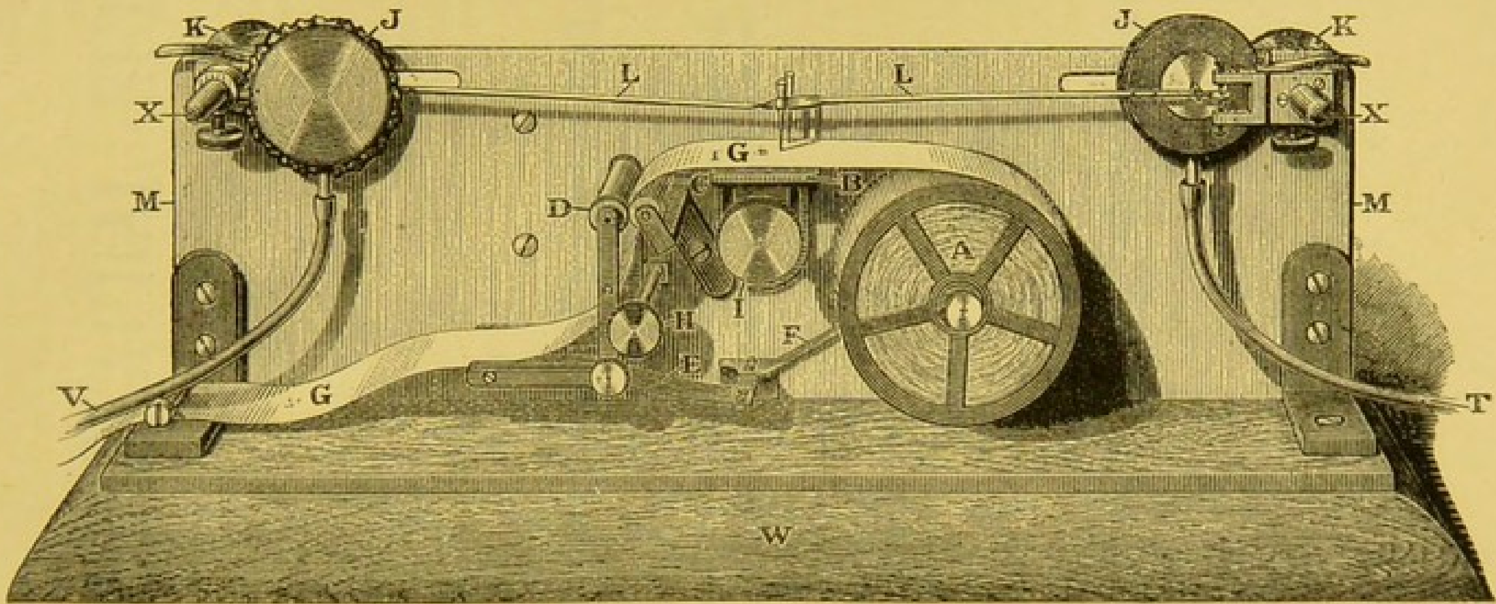


Fig. 7.

Description of Plate.—I. Tambours. X. Horizontal Bars, sliding in slot and fastened by Screw K. T. Tube to Cardiograph. V. Tube to Pneumograph. Z. Levers. A. Drum. B. Stage. C. Plane Roller, moved by clockwork. D. Flanged Roller. E. Spring for pressing D against C. F. Spring controlling A. G. Ribbon of Paper. H. Eccentric for pressing back D. I. Finching-Screw for fixing stage. M. Brass Plate, supported on wooden stand, W. Scale, ¼.