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PRELIMINARY REPORT

ON

THE ACTION OF ANÆSTHETICS

TO THE SCIENTIFIC GRANTS COMMITTEE OF
THE BRITISH MEDICAL ASSOCIATION,

By a Committee consisting of JOSEPH COATS, M.D., Pathologist to the Western Infirmary, Glasgow; WILLIAM RAMSAY, Ph.D., Assistant to the Professor of Chemistry; and JOHN G. MCKEN-DRICK, M.D., Professor of Physiology in the University of Glasgow.

THE present is intended merely as a provisional report, and no attempt will be made to give details of observations.

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 have 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 the 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 set about devising a method of experimentation by which respiration would be eliminated, and the effects of chloroform on the heart observed apart from that complication.

In the frog, we have an animal in which the movements of respiration are not necessary to life, so far as the heart is concerned, as that organ continues beating long after these movements have ceased. After exposing this animal to the vapour of chloroform under an inverted jar till it was anæsthetised, we exposed the heart by cutting into the thorax in the middle line. The animal being again 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.

With a similar view, a method was devised for warm-blooded animals. Rabbits were first used, and afterwards dogs. The animal was first 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 the air passes into the animal's lungs 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 en-

gorged 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 the respiratory centres, chloroform has a disastrous effect on the heart, while ether has no such effect. While presenting in this respect an enormous advantage over chloroform, it was yet apparent 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, 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, yet affect the heart and respiration as little as ether.

In testing the various agents used, we employed the methods described above. We administered them to animals, and watched the effects 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 them, 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.

Benzine (C_6H_6) was used with the frog. Its effects were nearly as slow as those of ether, and it produced struggling; weakening of the heart was apparent, but not so great as with chloroform.

Acetone (C_3H_6O) produced only slight anæsthesia in the frog, even after prolonged administration.

Pyrrrol (C_4H_5N) produced anæsthesia in the frog with considerably less rapidity than chloroform, but great excitement and muscular spasms 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.

Bichloride of methylene (so-called, but, as it has not a definite and constant boiling point, it is obviously a mixture: reputed formula CH_2Cl_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 as 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.

Amylene (C_6H_{10}) was administered to rabbits both by cloth and subcutaneously. No anæsthetic effect was produced.

Butyl chloride (C_4H_9Cl) 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.

Ethene dichloride (formerly named ethylene dichloride, or Dutch liquid, $C_2H_4Cl_2$) produced convulsive movements of both extremities, continuing up to death. There was no anæsthesia up to the commencement of the convulsions.

Methyl chloride (CH_3Cl), 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.

Ethyl chloride (C_2H_5Cl , boiling at 12 deg. C. = 53.6 deg. Fahr.) administered to rabbits in the same way as the above, produced rapid anaesthesia; but in one case the respirations soon stopped, and in another, when air was admitted more freely, general convulsions occurred.

Nitrous ethyl ether ($C_2H_5NO_2$) produced great excitement and convulsions, almost immediately followed by cessation of respiration.

It is apparent that the above substances all present disadvantages which render them unsuitable for general use as anaesthetics. There remain two agents, the actions of which are more promising. These are isobutyl chloride and ethidene dichloride.

Isobutyl chloride (C_4H_9Cl).—1. *Experiments on the frog.* When it was administered under a glass jar, complete anaesthesia 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.—2. *Experiments on rabbits.* When it was administered with a cloth, anaesthesia was produced in three to five minutes. It was continued after anaesthesia for nearly half-an-hour without any interference with respiration.—3. *Experiments on dogs.* It was administered on cloth; anaesthesia was produced in four minutes. It was continued for half-an-hour, and respiration was unaffected, except slight occasional stertor.

Ethidene dichloride ($C_2H_4Cl_2$, an isomeric of ethene dichloride, produced from aldehyde).—1. *Experiment 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. Anaesthesia was produced in four or five minutes.—2. *Experiments on rabbits.* It was given on cloth as usual. Anaesthesia 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.—3. *Experiments on dogs.* It was administered on cloth. Anaesthesia was produced in two to three minutes. In one case, anaesthesia was accompanied with some excitement manifested by squeaking; the animal was a young puppy. In another case, a large dog was kept fully anaesthetised for half-an-hour without the slightest failure of respiration or heart. The anaesthesia 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.

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 anaesthesia. 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 anaesthesia under the influence of ethidene dichloride, whilst 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 fact is illustrated by 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 anaesthetic without any convulsive effects.

We purpose continuing similar researches on substances which, from their chemical relations, hold out the hope of being serviceable. It will now be necessary to test the effects of the two substances whose results seem promising, and of any others of similar value, on the higher animals and on man.

With reference to the physiological action of anaesthetics, our attention has been 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 anaesthetics on nervous conduction and on mental phenomena as observed on man. All of 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 anaesthetised) 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 insure 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 the 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, anaesthetised, again placed in the box, and the gases of respiration estimated. Without giving detailed results, it may be stated that the effect of anaesthesia with chloroform 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.

The Committee will be happy to have the co-operation of any interested in the inquiry, which must still be regarded as being merely in its first stages. Any accounts of cases of death during the administration of anaesthetics, or references to journals where those may be found will be gladly received. The Committee has under consideration a scheme for collecting the evidence of the profession upon some questions connected with anaesthetics, which they hope soon to submit to the consideration of the Scientific Grants Committee.

SOUTH LONDON SCHOOL OF PHARMACY.—The sixth annual dinner took place at the Horns Assembly Rooms on Friday, the 20th ult. There were about one hundred and thirty old and new students present, together with a large number of gentlemen interested in the progress of the school. Dr. Julius Pollock presented the prizes to the following successful students: Senior Chemistry—Medal, Mr. Pocock; Certificate, Miss Stammwitz. Junior Chemistry—Medal, Mr. Harrison; Certificate, Mr. Newbigin. Botany—Medal, Mr. Lord; Certificate, Mr. Scammell. Materia Medica—Medal, Mr. Newbigin; Certificates, Mr. Lemmon and Mr. Harrison, equal. Practical Pharmacy and Dispensing—Medal, Mr. Lemmon; Certificate, Mr. Lord. Silver medal of the School for session 1877-78—Mr. John E. Phillips.