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On the Action of Anæsthetics. By Professor M'Kendrick.

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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.

The various agents used were administered to animals, and the effects on the heart and on respiration were observed. The committee used a method on frogs by which the effect on the heart could be observed; and, in the case of some of the agents, 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_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.

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

3. *Pyrrol* (C_4H_5N) 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_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, 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_5H_{10}) was administered to rabbits both by cloth and subcutaneously. No anæsthetic effect was produced.

6. *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.

7. *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.

8. *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.

9. *Ethyl Chloride* (C_2H_5Cl, 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* ($C_2H_5NO_2$) produced great excitement and convulsions, almost immediately followed by cessation of respiration.

It was apparent that the above substances all presented dis-

advantages 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_5H_9Cl). 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* ($C_2H_4Cl_2$, 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 anæsthetized 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.

Dr. M'Kendrick then described the methods of observation, and illustrated his remarks by showing diagrams, tracings, and apparatus. The complete report of the committee having appeared in the *British Medical Journal* of December 18th, 1880, No. 1043, it is necessary here to give only the general results arrived at by the committee. These were as follows:—

A.—Clinical.

I. The dose (administered 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 giving 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 ethidine—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 advantages are, to a great extent obviated by the use of ethidene; whilst the dangers of chloroform are also reduced to a minimum.