fluid flows into the fatty tissue over the pectoral muscle and around the breast and extends upwards over the clavicle into the neck. Beneath this saline exudes into the pectoral muscles and is limited by the deep fascia on either side. Absorption is here rapid owing to the great vascularity of the part and to the pressure maintained by the fascial limitations. Lastly distension of the axillary space takes place and the normal concavity of the axilla is replaced by a rounded swelling.

Fluid is absorbed very rapidly when introduced in this way and two pints can be run into the tissues in twenty minutes, little trace of swelling being found. After an hour the cannula is left *in situ*, and the administration can be repeated as often as necessary.

This method has one disadvantage, and I think only one. The introduction is rather painful, but hardly more so than when the needle is merely inserted beneath the skin, while the pain resulting from distension is largely obviated. But in the majority of cases the patient is still under the influence of the anaesthetic when the administration is given or is so collapsed as to be insensitive to pain.

This objection is more than compensated for by the ease of introduction and rapidity of absorption of a large quantity of saline by means of a simple appliance which every practitioner has at his command.

ADRENALIN IN THE EMERGENCY TREATMENT OF NON-CORROSIVE POISONING BY THE MOUTH

(CYANIDE, STRYCHNINE, ACONITE, ETC.).

BY

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WHEN a chemical substance enters the stomach or bowel it must first be absorbed into the circulation before it can exert a general direct action on the body. One of the chief factors determining the rate of absorption of any substance introduced into any part of the gastro-intestinal tract is the vascularity of the part, and particularly of the lining membrane. Now if, after the introduction into the stomach of a poisonous chemical substance whose general toxic action depends partly upon the rate at which it enters the circulation, we are able to limit the rate of absorption of the drug—for example, by diminishing the blood supply to the mucosa of the stomach—time is provided for the preparation and adoption of methods to neutralize any possible action which would normally follow the introduction of the particular substance into the stomach, either by removing it altogether by means of a stomach tube and a stomach wash-out, or by inactivating it by means of a chemical antidote. Particularly valuable would such an agent be which would lower the rate of absorption into the circulation of a substance which, entering the blood in large quantity, would destroy the life of the individual, but which the body is able, by the exercise of special powers, to efficiently neutralize when it gains entry into the economy slowly. To such a category belong the cyanides. Theis⁸ and Buttrick¹ have demonstrated that when an animal has been killed by a lethal dose of KCN the amount of cyanide present in the organs diminishes on standing, while Lang⁴ and Grober⁵ have shown that when HCN is introduced into the diet of an animal the amount of cyanide in the stomach diminishes, while the amount of sulphocyanate in the saliva and urine is increased.

Intraperitoneal injection of adrenalin has been found by Exner² to diminish the rate of absorption of a poison, such as strychnine or potassium cyanide, when introduced into the stomach. This academical piece of work suggested the investigation of the effect of the introduction of adrenalin³ into the stomach on the absorption of rapidly-acting poisons, such as cyanides, strychnine, and aconite, also introduced into the stomach, and whether such administration of adrenalin had any value in the practical

treatment of cases of accidental poisoning by these rapidly-acting drugs.

CYANIDES.

The hitherto generally recognized antidote in cases of cyanide poisoning has been that advocated by Professor C. J. Martin and Mr. J. A. O'Brien.⁵ Its principle is the formation in the gastro-intestine of Prussian blue, which is a practically innocuous substance, by the administration subsequent to the cyanide poisoning of ferrous sulphate and alkali. They proposed that 30 c.cm. (1 oz.) of ferrous sulphate solution of 23 per cent. strength, 30 c.cm. (1 oz.) of KOH (5 per cent. solution), and 2 grams (30 grains) of magnesia, the former two kept in hermetically sealed phials, be mixed and immediately taken. In their experiments on rabbits, using a lethal dose of 0.01 gram, given as 10 c.cm. of a 0.1 per cent. solution of KCN per kilogram of body weight, they found that death invariably ensued unless the antidote were administered within five minutes. Considering that the antidote consists of three separate ingredients, which must be mixed before use, the preparation of the antidote must occupy time and would probably take about two minutes, even if everything were at hand; so that if about three minutes were lost before discovering that cyanide had been accidentally taken, the patient's chances of recovery would be very small, for we may legitimately assume that the respite or "latent period" would only be a little if any longer in the human being than in the rabbit. Also, the ordinary medical man might not have the antidote ready at hand, and the value of some means of delaying the absorption of the poison from the gastro-intestine is apparent, and this is especially so in the case of poisoning by cyanide, whose action is so rapid.

Intraperitoneal injections of adrenalin having been found to diminish the rate of absorption of strychnine introduced into the stomach,² it was therefore decided to try and see if adrenalin administered by the mouth would have any effect in giving us more time to treat a case of cyanide poisoning. As a preliminary investigation, KCN solution, of strength varying from 1 per cent. to 5 per cent., was painted on various mucous membranes (conjunctiva, buccal mucous membrane, gastric mucosa) for five minutes, and then adrenalin (1 in 10,000) painted on, when blanching occurred in every case.

These experiments showed that adrenalin will still exert its vaso-constrictor action even after the arteriolar wall has been subjected to cyanide.

Further experiments showed that when adrenalin solution was administered (about 4 to 5 c.cm. 1 in 10,000 solution per kilogram body weight, the rabbit receiving the lethal dose of 0.01 gram KCN per kilogram body weight) either with or subsequently to the administration of the poison the animal's life was prolonged, and if the adrenalin solution were administered within five minutes of the poison, and Martin and O'Brien's antidote given, or the stomach washed out within four or five minutes subsequent to the administration of the adrenalin, the animal's life would be saved. Thus, the administration of adrenalin "on sight" would give a respite of some minutes during which the antidote could easily be prepared and administered or the stomach contents evacuated.

The results of a few of the more crucial experiments are appended. A number of experiments have been discarded because the rabbits did not tolerate the washing out of the stomach to which many were subjected. It may also be stated at the outset, that Martin and O'Brien⁵ found that if a dose of cyanide were going to prove fatal the rabbit always died within thirty minutes, so that we may take it that if we are able to tide a patient over the fatal thirty minute limit by any means at our disposal, then the patient will have a very fair chance of recovery. Of course, if it be borne in mind that the adrenalin only delays the absorption of the poison (principally by its vaso-constrictor action on the vessels of the mucosa), it will be recognized (as Experiment No. 4 shows) that those cases are practically hopeless in which a large dose of the poison has been taken and in which the amount of poison being absorbed through the mucosa even under maximal adrenalin influence exceeds the lethal limit, unless the chemical antidote be immediately given or the stomach immediately evacuated. The time relation here indicated (namely, that the pathological effect depends to a certain degree upon the amount of poison coming into contact with the tissues per unit of time), and the fact that the administration of

* Throughout this investigation adrenalin (P. D. and Co.) and hemisine (B. W. and Co.) were both used with the same effect.

an amount of KCN below a certain limit is accompanied by very little, if any, evident effect on the animal, seem to suggest that we have in the case of the action of chemical substances on all tissues of the body a parallelism to the action of various strengths of stimuli acting on a motor nerve and affecting the muscular response in the presence of a limen or threshold, an optimum and maximal strengths of stimulation. Further research, however, is required to determine this.

Further experiments showed that the administration of doses of adrenalin far in excess of those recommended by the cited experiments left, as far as the eye could detect, no lasting effects on the animals. The general results obtained from rabbits were:

The animal (receiving a lethal dose of 0.01 gram KCN per kilogram body weight) will recover if—

1. Adrenalin (3 c.cm. 1 in 10,000 solution) be administered within five minutes of the poison.
2. Martin and O'Brien's antidote given or the stomach washed out within about four minutes of the administration of the adrenalin.
3. A further small dose of adrenalin be given.

The area of a rabbit's stomach was found to be 95 sq.cm. That of a man is given as about 3,000 sq.cm.⁹ Therefore the dose of adrenalin which a man should take on this basis of, say, 3 c.cm. of 1 in 10,000 per 100 sq.cm. stomach area, would be about 90 c.cm., that is, 9 c.cm. (3 dr.) of the 1 in 1,000 solution, diluted (that is, 90 c.cm. or 3 oz. of 1 in 10,000 solution) followed afterwards by about 5 c.cm. (1½ dr.) of the 1 in 1,000 solution, diluted (that is, 50 c.cm., or nearly 2 oz. of 1 in 10,000 solution).

Method of Treatment.

The experiments seem to show that in a case of cyanide poisoning the following procedure is advisable:

1. Adrenalin be immediately given.
2. Then Martin's antidote if it be at hand.
3. Then wash the stomach out; and
4. After having washed the stomach out, administer some more adrenalin.

The object of the latter is to "follow up" any cyanide which has escaped the washing out process or Martin and O'Brien's antidote, and so retard its absorption, for Martin and O'Brien found that if death did not ensue within thirty minutes of administering the cyanide, the animal would live. It might also be advisable to give a brisk saline purge soon afterwards. Should Martin's antidote not be at hand, the order of procedure should be 1, 3, 4, as above.

There are two further considerations which must be taken into account before the recommendations made above are to receive acceptance. First, is the adrenalin affected by the HCl of gastric juice or by the pepsin? This question has been answered by Oliver and Schäfer⁷ who showed that gastric digestion (by pepsin—HCl) for twenty-four hours does not seem to lessen the physiological properties of extract of suprarenal gland. Secondly, how long will the adrenalin introduced into the alimentary canal continue to act on the lining membrane? The results obtained by Oliver⁶ furnish the desired information. To quote from his paper, "Suprarenal extract invariably produced the most decisive contraction, and one, moreover, which persisted for thirty to sixty minutes. The constriction was equally pronounced whether the spinal cord remained intact or was destroyed. The velocity of the circulation was likewise lessened, and at the acme of the constriction the onward flow might cease." Oliver's recommendation that these might be verified on the inflamed conjunctiva of a rabbit has been confirmed. It was also found that on administering adrenalin solution to a rabbit with a full stomach, there was a constricting action not only on the vessels of the gastric mucosa but also on the vessels of the mucosa some inches down the small intestine, which lasted for quite fifteen minutes.

STRYCHNINE AND ACONITE.

In the case of these poisons, too, a number of experiments were performed, and the efficiency of adrenalin in delaying absorption conclusively proved. With these poisons the administration of adrenalin until the stomach

can be thoroughly emptied is indicated, and in them the stomach *must* be emptied and the poison got rid of, otherwise the poison will be absorbed and exert its action on the body when the action of the adrenalin on the stomach has ceased. This is shown by Experiment No. 14.

Experiments were also tried with other rapidly acting poisons, such as potassium binoxalate (neutral), but the gastric mucosa was found (*post-mortem*) corroded, and free blood was found in the stomach, so that disturbing factors due to erosion and not remediable by adrenalin were present.

From these experiments on rabbits and dogs it is at once seen that in extract of the medulla of suprarenal gland—which is marketed under the names of adrenalin (P. D. and Co.), hemisine (B. W. and Co.), suprarenin, epinephrin, adrenine, renaglandin, etc.—we have an agent which will convert the stomach or other absorbing viscus on which it is acting into a practically non-absorbing bag in which the poison lies, ready to be absorbed when the action of the adrenalin passes off, but at the same time being absorbed in relatively small amount while the adrenalin is acting; and so a respite is gained during which the poison can be removed by mechanical means or neutralized *in situ* by some chemical antidote.

SUMMARY OF PRINCIPAL EXPERIMENTS.*

Experiments with Cyanide.

Experiment 1.—Rabbit. *Conjunctiva*: KCN (0.1 per cent.) painted on for five minutes. Adrenalin (1 in 10,000) applied. *Blanching. Mucosa of Lips*: Same as conjunctiva.

Experiment 2.—Rabbit. Chloralized. Stomach opened. One spot on mucosa painted with 5 per cent. KCN for five minutes (and another control spot with normal saline). Adrenalin (1 in 10,000) then painted on both spots, and blanching produced in both.

Experiment 3.—Two rabbits in full digestion. Chloralized. Stomach tube passed per oesophagus.

Rabbit A, 1,100 grams. 11 c.cm. KCN solution (0.1 per cent.) administered. Three minutes after giving KCN respirations ceased.

Rabbit B, 1,100 grams. 11.5 c.cm. KCN solution (0.1 per cent.) administered. Eight minutes after giving KCN respirations reduced to mere flicker, then respirations improved and became normal, then gradually shallower. Thirty minutes after giving KCN respirations ceased. On opening the stomach the mucosa was seen to be red.

Experiment 4.—Two rabbits in full digestion. Chloralized.

Rabbit A, 1,000 grams. 4 c.cm., 0.5 per cent. KCN solution. Two and a half minutes after giving KCN respirations ceased.

Rabbit B, 1,200 grams. 4 c.cm., 0.5 per cent. KCN solution:

2 minutes after giving KCN, 4 c.cm. 1 in 10,000 adrenalin given.

2½ minutes after giving KCN, respirations ceased.

Experiment 5.—Rabbit, 1,600 grams in full digestion. 16 c.cm. KCN (0.1 per cent.) solution given:

2 minutes after giving KCN, 6 c.cm. adrenalin (1 in 10,000) were given.

6 minutes after giving KCN, rabbit had a few convulsions which passed off.

10 minutes after giving KCN, commenced washing stomach out, but washing out process was unsuccessful.

24 minutes after giving KCN, further convulsions.

29 minutes after giving KCN, respirations ceased.

The stomach-tube was found blocked with a piece of stomach content (mucus).

Experiment 6.—Rabbit, 1,600 grams in full digestion. Etherized, 16 c.cm. KCN solution (0.1 per cent.) given:

2 minutes after giving KCN, convulsions.

4½ minutes after giving KCN, 4 c.cm. adrenalin (1 in 10,000) given.

7 minutes after giving KCN, stomach washed out.

65 minutes after giving KCN, respirations ceased.

There were signs of hypostatic congestion and oedema of the lungs on *post-mortem* examination.

Experiment 7.—Rabbit, 1,300 grams. Chloralized (lightly), 13 c.cm. KCN solution (0.1 per cent.):

2 minutes after giving KCN, convulsions.

2½ minutes after giving KCN, 6 c.cm. adrenalin solution (1 in 10,000).

6 minutes after giving KCN, stomach washed out.

7 minutes after giving KCN, 3 c.cm. adrenalin solution (1 in 1,000).

Recovery.

*Some of these results originally appeared in the *Intercolonial Medical Journal of Australasia*, July 20th, 1909.

Experiment 8.—Rabbit, 700 grams, in full digestion. Chloral-ized lightly.

7 c.cm. KCN solution (0.1 per cent.) given.

4 minutes after giving KCN, 6 c.cm. adrenalin (1 in 10,000 given).

9 minutes after giving KCN, stomach washed out.

19 minutes after giving KCN, 3 c.cm. adrenalin (1 in 10,000 given).

Recovery.

Experiment 9.—Rabbit, 950 grams, 9.5 c.cm. KCN solution (0.1 per cent.) given:

5 minutes after giving KCN, 6 c.cm. adrenalin (1 in 10,000 given).

8½ minutes after giving KCN, Martin's antidote administered.

Convulsions. Recovery.

Experiment 10.—Rabbit, 1,250 grams. 12.5 c.cm. KCN solution (0.1 per cent.):

4 minutes after giving KCN, 3 c.cm. hemisine (1 in 10,000).

8 minutes after giving KCN, convulsions.

12 minutes after giving KCN, Martin and O'Brien's antidote given.

25 minutes after giving KCN, respirations ceased.

Experiment 11.—Rabbit, 1,300 grams. 13 c.cm. KCN solution (0.1 per cent.) administered:

3½ minutes after giving KCN, 3 c.cm. adrenalin (1 in 10,000) given; convulsions.

11 minutes after giving KCN, Martin's antidote + 2 c.cm. adrenalin (1 in 10,000) given; respirations were slowed.

15 minutes after giving KCN, respirations were of expiratory type for about one minute.

Conjunctival reflex absent and pupils dilated till about twenty-two minutes after poisoning. Pupils then began to contract somewhat. At this time the breathing was alternately mouth and nasal, and respirations were sixteen per minute. About thirty-seven minutes after poisoning respirations were twenty per minute, and breathing still mouth and nasal alternately. Conjunctival reflex returning fifty-two minutes after poisoning; respirations twenty-four per minute, and nasal in character. Animal apparently asleep, and breathing quietly, when it was left tied up in the laboratory two hours after administering the cyanide. Found dead next morning. There was a strong smell of gas in the laboratory and it is quite possible that the animal died of CO poisoning.

This experiment shows the beneficial effect to be derived from giving the animal a further small dose of adrenalin.

Experiment 12.—Rabbit, 1,300 grams. 23 c.cm. adrenalin (1 in 10,000) given. Twenty-four hours afterwards stomach examined. No pathological condition of mucosa apparent.

Experiment 13.—Rabbit. 35 c.cm. adrenalin solution (1 in 10,000) administered. Twenty-four hours afterwards no abnormal appearances in stomach, intestines, kidneys, liver, heart.

Experiments with Strychnine, Aconite, and Other Poisons.

Experiment 14.—Two rabbits, in full digestion, were taken.

Rabbit A, weight 950 grams. Received 11.5 c.cm. strychn. sulph. solution (that is, 12 c.cm. per kilogram body weight) into its stomach. Death occurred forty-two minutes after.

Rabbit B, weight 1,150 grams. Received 13.8 c.cm. strychn. sulph. solution + 4 c.cm. adrenalin (1 in 10,000) into its stomach. It was still alive four hours twenty minutes after, but was found dead next morning in position of opisthotonos.

Exner² showed that rabbits which received a dose of 0.0052 gram strychnine sulphate on the average exhibited convulsions in ten minutes and death in twenty minutes.

Experiment 15.—Dog, weight about 8½ kg.; starving; was morphined, and received ½ grain (0.025 gram) strychn. sulph., dissolved in 30 c.cm. saline.

10 minutes after giving the strychnine, 12 c.cm. adrenalin (1 in 10,000) were given.

16 minutes after giving the strychnine, stomach washed out.

21 minutes after giving the strychnine, 8 c.cm. adrenalin (1 in 10,000), immediately followed by 1 oz. mag. sulph.

Recovery.

A dog of about the same weight, size, age, and breed received ½ grain strychn. sulph., and died in six hours.

Experiment 16.—Eighteen days after Experiment 15. The same dog used; in full digestion; morphined. Received ½ grain (0.026 gram) strychn. sulph., dissolved in 30 c.cm. water.

12 minutes after giving the strychnine, 12 c.cm. adrenalin (1 in 10,000) given.

18 minutes after giving the strychnine, commenced washing stomach out.

27 minutes after giving the strychnine, 8 c.cm. adrenalin (1 in 10,000), immediately followed by 1 oz. mag. sulph.

Recovery.

Experiment 17.—Two rabbits in full digestion taken.

Rabbit A, weight 1,150 grams. Received 11.5 c.cm. lin. A.B.C. Died fifty-nine minutes after.

Rabbit B, weight 1,250 grams. Received 12.5 c.cm. lin. A.B.C. + 5 c.cm. adrenalin (1 in 10,000). Died two hours four minutes after.

Experiment 18.—Two rabbits in full digestion taken.

Rabbit A, weight 1,350 grams. Received 13.5 c.cm. lin. aconit. (lin. aconit. B.P., diluted ½). Died fifty-seven minutes later.

Rabbit B, weight 1,350 grams. Received 13.5 c.cm. lin. aconit. (lin. aconit. B.P., diluted ½) + 5 c.cm. adrenalin (1 in 10,000). Died six hours twenty-five minutes later.

Experiment 19.—Two rabbits in full digestion.

Rabbit A, weight 1,300 grams. Received 2 grams pot. oxalate in 20 c.cm. water. Died fifty minutes after poison.

Rabbit B, weight 1,400 grams. Received 2 grams pot. oxalate in 20 c.cm. water + 5 c.cm. adrenalin solution (1 in 10,000). Died fifty-eight minutes after poison.

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REFERENCES.

- ¹ Buttron, H., Inaug. Diss. (Gießen), 1909, p. 24.
- ² Exner, A., *Archiv f. Exper. Path. u. Pharm.*, Bd. 50, S. 313.
- ³ Grober, J. A., *Arch. klin. Med.*, 69 (1901), p. 243.
- ⁴ Lang, quoted by F. N. Schulz, *Hand. d. Bioch.* (edited by C. Oppenheimer), Bd. III, 1te Hälfte, p. 34.
- ⁵ Martin, C. J., and O'Brien, R. A., *Intercol. Med. Journ. of Aust.*, 1901, p. 245.
- ⁶ Oliver, G., The Action of Animal Extracts on Peripheral Vessels, *Proc. Physiol. Soc.*, March 20th, 1897; *Journ. Physiol.*, vol. xxi (1897), p. 22.
- ⁷ Oliver, G., and Schäfer, E. A., *Proc. Physiol. Soc.*, March, 1895; *Journ. Physiol.*, vol. xvii, p. 13.
- ⁸ Theiss, A., Inaug. Diss. (Gießen), 1909, p. 27.
- ⁹ Vierordt, H., *Daten u. Tabellen für Mediziner* (3te Aufl.), S. 115.

THE LATE VASOMOTOR PARESIS DUE TO ADRENALIN.

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A GENTLEMAN consulted me on account of multiple exostoses of the external auditory meatus, which so far occluded the lumen that beyond them only the finest Eustachian bougie was passable, and nothing was visible. Presumably the marked tinnitus, which was his chief complaint, was due to an accumulation of sebum and epithelial debris deep to the growths; for this tinnitus remained absent so long as he regularly used drops of hydrogen peroxide.

His unwillingness to persist with this treatment; a moderate degree of obstructive deafness to speech, acoumeter, and tuning-fork; and the danger that an infection of debris between the growths and the membrane might lead to perforation and otitis media, were the indications for surgical interference.

The external meatus was unusually tortuous; the growths, only one of which was pedunculated, were very deep, and at subsequent operation proved to be actually continuous with the annulus tympanicus. The difficulty of access emphasized the necessity for a clear bloodless field in operating. Therefore, before making the post-aural incision, adrenalin chloride was injected along the growths—5 drops of a 1 in 2,000 solution in each situation. The whole area became and remained remarkably bloodless, and a branch of the posterior auricular was the only vessel tied during the operation, at the conclusion of which a rubber tube, of such a length that its outer end hitched just under the tragus, was pushed down to the intact drum.

At the first dressing, on the third day, the tube had become slightly unhitched from the tragus, and had slipped out about 1 in. It could be pushed back, but on the release of pressure again emerged for this small distance, very slowly, as if levered up by an elastic body beneath. Next day the tube projected about ½ in.; it was again replaced, and pressure applied over it by a small pad under the dressings.

On the fifth day, finding it impossible to keep the tube in position, it was removed, and an inspection made. The membrane was completely hidden by the edge of the skin of the posterior meatal wall, where this skin had been out across just distal to the growths; The skin could not be replaced in position, being pushed forwards from behind, presumably by blood-clot.