quantities of air are introduced into the venous circulation the sudden drop in arterial pressure is due to mechanical obstruction to the venous flow through the pulmonary artery. The obstruction is soon overcome by an immediate process of breaking up of the air into small particles, so that the frothy blood passes to the lungs. It is remarkable how the pulmonary artery rapidly becomes free; post mortem it shows but few particles of air in the lumen either of the trunk or of the large branches. These appearances give little support to the view that the pulmonary factor is of importance in the mechanism of death.

Does anaemia of the bulbar centres account for the polypnoea? Not fully; polypnoea is sometimes developed when small amounts of air are introduced into the veins which are not sufficient, either in amount or in rate of entrance, to cause an appreciable lowering of arterial pressure. A reflex factor in the causation of the polypnoea is not unlikely, the afferent impulses arising within the cardiac area or in the carotid sinus, which, as shown by the work of Hering,⁵ Heymans,⁶ and others, is the seat of important reflex control of the vascular system in general, and of the encephalic blood pressure in particular.

In a paper on this subject read at a meeting of the Société de Biologie in Paris¹ I drew attention to apnoea as a prominent feature in the effects of injection of air. It is maintained in some cases for quite long periods before cardiac death. The respiratory centre fails, and the anomalous condition is seen of a heart beating, however slowly and irregularly, with no air entering or leaving the lungs, and a very low arterial pressure. The role of apnoea in the mechanism of death seems to be an important consideration, though it has not been given prominence as a factor in this. When sufficient air is injected to cause death apnoea is usually seen before the end, but it needs a larger amount of air to cause it than in deep anaesthesia. In animals with cut vagi the symptoms were like those of deep narcosis with intact vagi. Probably the vagus is an afferent path, not necessarily the only one, for the impulses to the respiratory centre, a path which is deleteriously affected in deep chloralose anaesthesia. In this condition and in vagotomized animals the polypnoeic disturbance is much less than in other cases, and the polypnoea is to be regarded as a mode of defence of the organism. Apnoea of short duration does not necessarily portend a fatal result. But if the apnoeic phase lasts more than half a minute or so it is a certain sign of failure of further resistance, and indicates a fatal termination.

B. Open Thorax.

When the chest is opened and artificial respiration performed the symptoms caused by the introduction of 50 to 100 c.cm. of air into the jugular vein are different from those mentioned in the case of natural respiration. The blood pressure falls as before, but of course there is no evidence of interference with the respiratory mechanism and no indication of the reactions of the respiratory centre in response to reflex or other influence. The heart is the organ which succumbs, and fibrillation is common in these conditions. In case of closed thorax the nervous centres die for lack of blood, consequent on the mechanical obstruction of the circulation, while the heart remains active for a time and is apparently capable of recovery if conditions can be made favourable. The duration of the period of starvation of the centres by deprivation of blood is a factor in causing the death of the centres. In some cases this period is fairly short.

How does the heart maintain its activity without an efficient coronary circulation and in conditions where one would expect serious anoxaemia? Probably a small supply of oxygen is sufficient to keep up the discharge of impulses from the sino-auricular node, and this supply may be available for a time by direct diffusion of oxygen from the arterial blood in the right auricle, which remains bright red for a long time. Removal of the products of combustion in the absence of a proper venous circulation may be also effected by diffusion, aided by contraction of the muscle.

Conclusions.

Dogs can recover from the effects of introducing about 100 c.cm. of air into the jugular vein.

Resistance to the effects is diminished in deep anaesthesia and after section of the vagi.

The heart in some conditions is the organ which fails in fatal cases, but failure of the respiratory centre is the cause of death in others. Apnoea is an important symptom indicating the loss of reaction in this centre. Ventricular fibrillation is not a common cause of death.

With regard to treatment, the inhalation of oxygen while the respiratory centre is active is indicated. Artificial respiration should be tried when it shows signs of failure. As for bleeding and aspiration, they inspire little faith. Animals in experiment exhibit marked powers of natural recovery, and one is very prone to attribute to some remedial measure an undue beneficial effect.

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THE TREATMENT OF DESPERATE CASES OF DIABETIC COMA.

BY

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MANY physicians must have had the disappointing experience of losing a certain proportion of cases of diabetic coma even since the introduction of insulin. From all countries records and statistics show a varying number of patients who die in spite of energetic treatment with insulin. Such has been my experience. It therefore seems worth emphasizing an aspect of the treatment by means of which recovery has followed in two desperate cases of coma—in-patients who I am sure would have died under my treatment of a year ago. The deciding factor in their recovery was, in my opinion, the administration of *extremely large* quantities of intravenous fluid, hypertonic saline and gum acacia solution.

The most dangerous cases of coma requiring such treatment are easily differentiated by one or two simple clinical observations from the less severe cases which respond readily to adequate doses of insulin alone. Typical air hunger and varying degrees of unconsciousness are present in both types, and chemical tests show a large excess of sugar and ketone bodies in the urine and blood. In addition the desperate cases show evidence of dehydration, collapse, and circulatory failure. The pulse is rapid and feeble, the blood pressure very low, the veins are empty, the tissues drained of water, and the most striking sign is the *low eye tension*. This may be so extreme and the eyeball so flat that one has almost to lift the lid to make sure the eye has not previously been removed. There is a real "melting of the flesh into water"—an early description of diabetes—or, more exactly, a melting of the water from the flesh, dehydration. This dehydration is produced by the intense polyuria of the preceding period and the failure to absorb fluid because of vomiting and unconsciousness. The volume of the blood is reduced and the blood is concentrated, of which a raised haemoglobin content is evidence.

Another feature of these desperate cases is a very scanty secretion of urine, sometimes actual anuria. It has been suggested that kidney failure is the cause of death in such cases, and that death is really a uraemic one. In my opinion, however, oliguria or anuria is due to dehydration and a low blood pressure. An exactly similar

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condition is found in cholera—dehydration, collapse, and anuria. Certainly in all the cases of diabetic coma I have seen proteinuria, casts, and often blood cells have been found, but these have disappeared in a few days after recovery, and the oliguria within twelve to thirty-six hours after the re-establishment of the body fluid and circulation. This condition is accompanied by nitrogen accumulation in the blood and blood urea concentrations of 80 to 100 mg. per 100 c.cm. or even higher, due essentially to the dehydration. At the same time the blood chlorides are very much depleted, as in cholera.

The chemical findings in the blood in diabetic coma may be usefully divided into two groups, which may be called (1) the diabetic, and (2) the dehydration complex, all the features of the second being present also in cholera.

1. Diabetic Complex.

Hyperglycaemia.
Excess of ketone bodies.
Low alkali reserve.

2. Dehydration Complex.

Tissue depletion of water—for example, low eye tension.
Low blood volume and pressure.
Concentrated blood, high haemoglobin and specific gravity.
Nitrogen retention—high blood urea.
Low blood chlorides.

The first derangement is rectified by insulin, the second by abundance of fluid, which in desperate cases should be given in *large quantities* and preferably *intravenously*. The importance of the administration of fluid to coma cases has been known for years, and was recently brought out at a discussion at the Royal Society of Medicine; but the quantity of fluid necessary has not been emphasized or defined.

The following three cases are recorded, the first fatal, to illustrate the procedure and the amount of fluid that may be necessary in dealing with such cases. All were completely unconscious, and only such details are given as bear directly on the treatment.

CASE I.

Male, aged 52. Seen at noon: pulse 130, feeble; temperature 97° F.; very low eye tension. Urine: sugar + + + +, ketones, FeCl_4 +, blood sugar 1.531 per cent., alkali reserve 13 per cent. Insulin 40 units was administered intravenously, and 60 units subcutaneously. Between 1 and 2.30 p.m. 2 pints of normal saline were given subcutaneously and $1\frac{1}{2}$ pints by the rectum, all completely absorbed. As this seemed a large amount I unfortunately did not give intravenous fluid. At 2.30 p.m. 3 ounces of urine were obtained, containing less ketone bodies; albumin, trace; casts, granular. At 3.30 p.m. the blood sugar was 1.30 per cent., the pulse 132 and slightly fuller, and 100 units were given. At 6.30 p.m. a few cubic centimetres of urine were collected, loaded with sugar, but with much less acetone—a negative FeCl_4 . Blood sugar 1.020 per cent., temperature 102° F. Shortly after, the pulse collapsed almost entirely, but the patient was partially revived by adrenaline, 3 minims intravenously. Camphor and ether was administered, and a pint of hypertonic saline was being given to the moribund man when he died. No post-mortem examination was obtained. (It is interesting to note that the blood urea was 153 mg. per cent., and the chlorides (whole blood) 290 mg. per 100 c.cm.—extremely low. The increase in the osmotic pressure of the blood produced by the extreme hyperglycaemia (1.53 per cent.) was balanced by an exactly corresponding diminution of the sodium chloride.)

Total fluid: 2 pints subcutaneously, $1\frac{1}{2}$ rectally = $3\frac{1}{2}$ pints = 2 litres.

CASE II.

Female, aged 53; admitted to King's College Hospital at 3.30 a.m. Temperature 97° F., pulse 86 and very feeble; intense dehydration; eyeball hardly palpable. Urine: sugar + + +, acetone FeCl_4 +, albumin +, casts granular and blood. Blood sugar 0.600 per cent. She was given 120 units of insulin and 2 litres ($3\frac{1}{2}$ pints) of hypertonic saline from 4.30 to 5.30 a.m., and strophanthin $1\frac{1}{2}$ 250 grain. 6.30 a.m.: Temperature 97.4°, pulse 112 and feeble. 10.30 a.m.: Urine (only a few cubic centimetres by catheter), sugar + + +, FeCl_4 +. Blood sugar 0.520 per cent. Insulin 100 units intravenously. From 11 a.m. to 3 p.m. $3\frac{1}{2}$ pints of normal saline subcutaneously. 4 p.m.: Urine (a few c.cm.), sugar + + +, FeCl_4 0, Rothera +; blood sugar 0.328 per cent. Dehydration obviously less; eye tension higher; temperature 98.7° F., pulse 124, still very feeble. She was given 1 pint of gum acacia plus 6 ounces bicarbonate solution (20 grams), and adrenaline 6 minims intravenously, which caused an immediate improvement of pulse and colour. Insulin 20 units and glucose 20 grams by mouth were now given four-hourly. At 10.30 p.m. the pulse (120) became less full, and $1\frac{1}{2}$ pint of gum

acacia with $1\frac{1}{2}$ pint (200 c.cm.) of 5 per cent. glucose, 20 units of insulin, and 4 minims of adrenaline were given intravenously. After this the pulse remained satisfactory, the eye tension was practically normal, and consciousness was partially recovered during the night. (It is interesting to note that the plantar reflex was extensor during unconsciousness, but became flexor next day.)

Total fluid: 9 pints 6 oz. (5.3 litres); 7 pints (4 litres) intravenously in ten hours.

CASE III.

Female, aged 54. Admitted 9.30 a.m. Very dehydrated, moderately low eye tension, pulse hardly felt, air hunger giving way to feeble, intermittent gasps: Urine: sugar + + +, FeCl_4 + + +, albumin +, and granular casts. Intravenous injection started immediately, and from 9.30 to 11 a.m. 2.3 litres (4 pints) of hypertonic saline and finally 1 pint of gum acacia solution were given, the first litre containing 100 units of insulin, 5 minims of adrenaline, and 20 grams of sodium bicarbonate (5 drachms). At the end of this the pulse had considerably recovered, and the blood sugar was 0.356 per cent. No blood could be obtained before the injections on account of her desperate condition. From 11 a.m. to 1 p.m. she received 2 pints of normal saline subcutaneously, containing 30 grams of glucose, and by 2 p.m. the pulse was satisfactory (rate 115) and the eye tension higher. A small quantity of urine was obtained by catheter at 1 p.m., and the secretion was well established by 7 p.m. She became conscious enough to swallow, and was given 20 units of insulin and 20 grams of glucose four-hourly by the mouth, with abundance of fluid.

Total fluid: 7 pints (4 litres) in four hours; 5 pints intravenously in $1\frac{1}{2}$ hours.

DISCUSSION.

It will be noticed that in Case i the patient, who died, received only $3\frac{1}{2}$ pints of fluid and none intravenously until he was almost moribund. The other two patients, who recovered, received much more fluid, largely intravenously, at the beginning of treatment. One required $9\frac{1}{4}$ pints, the other 7 pints before the circulation seemed satisfactory. There is no proof that the first patient would have recovered with more intravenous fluid, or that the others would have died with less; but this is my strong impression, and certainly the circulatory condition of the first (fatal) patient was better when first seen than that of the others.

The following points in the treatment merit a fuller discussion.

Technique of Injection.

The intravenous injections were given in all cases with a Juhé blood transfusion syringe. This is by far the simplest and most easily controlled method. Quite a small needle (size 12–14) can be used, and it has not been necessary to cut down on a vein, although they have all been collapsed. A small piece of rubber tubing (boiled) leads from the syringe and dips into the jug containing the infusion. It is my practice to add insulin, adrenaline, or any other stimulant (caffeine or digitaline, etc.) to the fluid in the jug. Also it is not easy with a small Juhé syringe to introduce the fluid too fast, and yet, as it can be injected under pressure, there is no risk of blockage or failure as with gravitation methods. The pressure and rate of injection are under perfect control. The fluid has been given at the rate of a litre in half to three-quarters of an hour, never faster. Such a syringe is invaluable, and can be used for aspirating as well as injecting fluids.

Nature of Intravenous Injections.

Double-strength physiological saline (1.8 per cent. sodium chloride) has been used for the first infusion in these and other less desperate cases. This strength was chosen arbitrarily in a hurry, because I did not know what strength of hypertonic saline was usually given. I subsequently found that 1.2 per cent. saline is given in the treatment of cholera (Rogers), and perhaps this would be better. Hypertonic saline was given because the available evidence shows that the body is depleted of sodium chloride and the blood chlorides are low (see Case i). It is an open question whether hypertonic has any practical advantage over isotonic saline (0.9 per cent.), but it is theoretically preferable. Gum acacia solution (7 per cent.) has been given after the saline because it is a fluid which remains in the vessels. I believe that much of the saline rapidly leaves the blood and goes to the dehydrated tissues, which can be observed to fill up during an infusion. It has been clearly noted in these cases that the effect of the pint of gum solution has been to amplify and fill the pulse more than the preceding larger volume of saline.

Volume of Fluid.

This paper advises the administration of very large quantities of intravenous fluid, much larger than has been advocated elsewhere, except in the treatment of cholera. In neither case, nor in other less severe cases, has there been any untoward sign of cardiac embarrassment or dilatation, or of general or pulmonary oedema, although the tissues visibly filled out during the infusions. The absence of such signs may seem remarkable in Case ii, where $9\frac{1}{4}$ pints (7 intravenously) were given in eighteen hours and only a few ounces of urine were secreted in twenty-four hours. The dehydrated tissues must be able to absorb such quantities without any surfeit of fluid. It is impossible to state dogmatically the ideal amount of fluid to give, as this must vary in every case with the body weight and degree of dehydration. The following theoretical considerations may be of interest.

If we knew the weight of the patient a few days previously and were able to weigh the patient when first seen in coma, some idea of the water loss could be obtained. This was impossible in the above cases. But recently another patient, not completely unconscious, was weighed on admission to hospital and again twenty-four hours later after treatment with insulin and fluid. The patient gained 12 lb. in weight without any oedema—a gain in weight which did not fall on succeeding days. In that twenty-four hours she received only 3 pints intravenously, but abundance of fluids (not measured) by mouth, and only 60 grams of carbohydrate as food. This 12 lb. is equal to 16 per cent. of her body weight, and is about 10 pints of water. It may be taken as her amount of fluid loss, and she was not by any means an extreme case of dehydration, as the eye tension was only slightly reduced. In some cases the percentage loss of water and the total loss must be much greater. When we consider that the body of a man of average weight contains over 40 litres of water, there is no doubt that over 4 litres, and probably 6 or 8 or more, must be lost in extreme dehydration (7 to 14 pints). It is not surprising, therefore, that in Case ii, the most extreme, the patient showed no evidence of excessive administration of fluid when $9\frac{1}{4}$ pints had been given. Judging from the relatively poor condition of the pulse after 7 pints had been given, and its immediate improvement after only one pint of gum (the eighth), it seems probable that most of the intravenous fluid leaves the circulation for the tissues.

It is interesting to note the quantity of intravenous hypertonic saline given in the treatment of cholera. Rogers* advocates 3 to 6 pints of 1.2 per cent. saline given at the rate of 4 oz. a minute—that is, 1 pint in five minutes (I have never given it so quickly in diabetic coma). Cox of Shanghai advises continuous intravenous isotonic saline for several hours, until collapse is overcome, at the rate of 2 oz. per minute. That is, 1 pint in ten minutes or 6 pints in the first hour—very comparable to the amounts I have given, but far exceeding my dosage when carried on for several hours. The conditions, however, are different, for the loss of fluid will continue in cholera while the diarrhoea lasts, whereas the loss in diabetes gives way to oliguria or anuria.

From the practical point of view, we may be guided by the following clinical considerations. Enough intravenous saline should be given as soon as possible to fill visibly the shrunken tissues and re-establish the fullness and strength of the pulse. This may require 3 to 5 or more pints of fluid, and I consider it wise to finish the infusion with a pint of gum acacia, a fluid which remains in the circulation, while much of the saline rapidly leaves the blood and enters the tissues. It is desirable on theoretical grounds to commence with hypertonic saline (1.2 to 1.8 per cent.), but I have no proof that this makes any practical difference. After the intravenous treatment, it would seem advisable to give continuous subcutaneous (or rectal) saline, unless this is remaining localized and is not being absorbed into the general circulation, an indication that the body is sufficiently supplied with fluid. If the pulse volume relapses, more intravenous saline and gum solution (1/2 to 1 pint) should be given.

* See Manson's *Tropical Diseases*, ninth edition, p. 374.

The complete recovery of the eye tension is a sign that sufficient fluid has been given, but it is noticeable that the eye tension (and the secretion of urine) is slow of recovery, even when dehydration of the rest of the tissues has been overcome. A series of estimations of the haemoglobin percentage of the blood might indicate when sufficient fluid had been given, but is open to fallacies. The heart should be watched for signs of dilatation, and the ankles and lungs for oedema. I have not observed such danger signals occur, and think the risk is extremely small. In any case this risk must be taken if these moribund patients are to have any chance of recovery.

It may be that the ketone poisons *per se* are an important factor in producing the circulatory collapse, but there is no proof of this. I have, at any rate, observed several fatal cases in past years in which the ketonuria and ketonaemia has been greatly reduced by insulin without recovery of the circulation; these patients died, in my opinion, because I failed to supply the necessary large quantities of fluid.

I do not propose here to discuss the dosage of insulin, the necessity of warmth, and treatment with cardiac stimulants, although I think it important in every collapsed case to give a few minims of adrenaline in the first infusion. This has a remarkable, if temporary, effect in stimulating the circulation. Nor shall I discuss the advisability of giving sodium bicarbonate to replace the depleted alkali reserve and abolish acidosis. It may be noted, however, in the latter respect, that the hypertonic saline can very quickly remove the main symptoms of acidosis—the air hunger. In the last patient I treated, a litre of hypertonic saline completely abolished the air hunger in half an hour, before the infusion was finished or the pulse had recovered satisfactorily.

SUMMARY.

Attention is drawn to dehydration as the immediate cause of death from circulatory failure of desperate cases of diabetic coma. They die, as do cholera patients, from depletion of tissue and blood fluids, and often in the anuric state. The condition is recognized clinically by a feeble, empty pulse, shrunken tissues, low eye tension, and oliguria or anuria. In addition to insulin they require immediately large quantities of fluid, preferably intravenous. A treatment with hypertonic saline and gum acacia solution is described.

Memoranda:**MEDICAL, SURGICAL, OBSTETRICAL.****BILIARY CIRRHOSIS IN AN ELDERLY WOMAN.**

BILIARY cirrhosis of the liver is said to be commoner in young adults of the male sex. The following case, therefore, occurring in an elderly woman, appears to be worthy of record.

About 11.30 a.m. on January 19th I was called to see Mrs. X, aged 67, who complained of severe pain in the pit of the stomach. The onset was sudden, six hours previously, when she vomited, on one occasion, some bile-stained fluid. She was pale and sallow, but not markedly emaciated. She looked ill, toxic, and exhausted, with cold clammy skin, subnormal temperature, and rapid pulse; the tongue was dry and covered with a brown fur. There was repeated retching, with gaseous eructations. The abdomen was flaccid and not distended; there was epigastric tenderness, the liver was slightly enlarged, and on percussion the lower border was found to be one fingerbreadth below the right costal margin. No other abnormality was found in the abdomen or chest, apart from an occasional rale at the base of the left lung. No urine or stools were available for examination.

From 11 p.m. (her relatives stated) until 5 a.m. the following morning she repeatedly vomited black, tarry material, over one pint in all, and died suddenly at 7 a.m.

Previously, she had had rheumatic fever in childhood, and, during the last few years, frequent attacks of bronchitis. She had had attacks of diarrhoea, off and on, for the last two or three years, and had suffered from this continuously for the last three months. She always had a yellowish complexion, but had been strictly temperate in her habits.

At the necropsy all the abdominal contents, particularly the stomach and greater omentum, were tinged with bile, and there