There is good reason to believe that the length of the post-ovulatory phase is fairly constant, being about 14 days, and that variation in the length of the cycle is due mainly to variation in the pre-ovulatory phase (Zuckerman, 1937; Latz and Reiner, 1942; Corner, Hartman, and Bartelmez, 1945; Rock and Hertig, 1948; and Krohn, 1949). The period of amenorrhoea might therefore be expected to increase by one day for each additional day in the length of the cycle, even if the time between ovulation and birth were constant. In Table IV the period between ovulation and birth has been estimated by subtracting the interval between

TABLE IV.—Period Between Ovulation and Birth Related to Length of Cycle

Mean Length of Cycle (Days)	Period of Amenorrhoea (Days)	Assumed Interval between Onset of Menstruation and Ovulation (Days)	Estimated Period between Ovulation and Birth (Days)
23	274.8	9	265.8
24	274.0	10	264.0
25	276.0	11	265.0
26	278.0	12	266.0
27	279.9	13	266.9
28	279.1	14	265.1
29	280.7	15	265.7
30	282.2	16	266.2
31	286.1	17	269.1
32	281.8	18	263.8
33	281.7	19	262.7
34	285.8	20	265.8
35	285.1	21	264.1

the onset of menstruation and ovulation (assumed to be 14 days for women with 28-day cycles, and adjusted according to length of cycle) from the periods of amenorrhoea recorded in Table III. The estimated periods between ovulation and birth obtained in this way are all reasonably close to the mean of 266 days, based on 716 births.

It is concluded that variation in the period of amenorrhoea according to the length of the menstrual cycle is probably determined by variation in the interval between the onset of menstruation and ovulation. If this is so, the period between ovulation and birth seems to be independent of the length of the cycle.

It is perhaps necessary to stress that the observation that the period of amenorrhoea increases by about a day for each additional day in the length of the cycle is based on mean values derived from a large number of cases. The mean duration of gestation is of course associated with many other variables, and it seems unlikely that its association with the mean length of cycle can be used in individual cases to give an estimate of the expected date of delivery more accurate than the conventional one.

Summary

The association between the period of gestation and the length of the menstrual cycle has been investigated in 1,227 women whose menstrual history was recorded for one year after the birth of a child. The data were considered adequate for 716 women with regular cycles.

It is shown that the period of amenorrhoea (from the onset of menstruation to birth) increases by about a day for each additional day in the length of the cycle.

It is suggested that variation in the period of amenorrhoea according to the length of the menstrual cycle is determined by variation in the interval between the onset of menstruation and ovulation. If this is so, the period between ovulation and birth seems to be independent of the length of the cycle.

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THE ACUTE HYPOXIC EPISODE*

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"Anoxia not only stops the machine, but wrecks the machinery."—HALDANE.

A good deal has been written on the subject of hypoxia, and great stress has been laid upon its deleterious effects on certain systems and organs, and on the organism as a whole. All authors stress the importance of avoiding hypoxia and of promptly terminating it should it occur.

Courville (1939) has examined the pathological findings associated with acute hypoxia in nitrous oxide anaesthesia. Although it is more than 10 years old his classification of the pathological findings, based on the severity of the hypoxic episode and the length of survival time, retains as much of its value to-day as it did when it was first published.

Many conditions, both medical and surgical, may be accompanied by hypoxia, but the surgeon encounters it in its most dramatic form—that is, as acute cardiac failure, arrest, or standstill. It is generally recognized that in these cases the immediate concern is to re-establish efficient pulmonary ventilation by artificial respiration combined with oxygen, and to restore the circulation to the vital centres by manual systole. Efficient manual systole must be accomplished within four minutes from the time that heart action has ceased, and more quickly if possible. If chronic hypoxia has preceded the acute episode, then the period within which circulation to the vital centres must be restored may be very much shorter than four minutes. There are many cases on record in which recovery has followed cardiac arrest lasting longer than four minutes, but as the minutes pass the chances of full, and later of partial,

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recovery become progressively less. Once the circulation has been restored, the various manoeuvres designed to induce spontaneous resumption of cardiac activity may be carried out in a deliberate and somewhat more leisurely way; or else they may not be needed at all, as not infrequently the heart will resume beating under the stimulus of manual systole alone.

Although literature on hypoxia is extensive, there are only scattered and inadequate references to the treatment of the post-hypoxic state. It is generally assumed that irreversible damage to the vital structures, and particularly to the brain and brain stem, occurs at the instant of the hypoxic episode and that treatment is futile on account of the irreversibility of the damage. We believe, and we hope to show in the following discussion, that the passive "wait-and-see" attitude which has hitherto prevailed is not justified, and that active treatment is not only possible but is vitally necessary if we are to save a number of those who in the past would have succumbed. We agree that any destruction of nervous elements at the time of the hypoxic incident is irreversible, but suggest that in many cases such total destruction is only of minor extent and that there are large areas of reversibly damaged tissue which is capable of recovery under suitable management. We believe that much of the fatal hypoxia and extensive cerebral damage occurs in the post-hypoxic period, and can thus be prevented.

The Role of Cerebral Oedema

One of the sequelae of acute hypoxia is the appearance of cerebral oedema. This is only to be expected, as oedema will appear anywhere in the body where oxygen want has interfered with the integrity of the capillary membrane. This oedema interposes a physical barrier between the oxygen-supplying blood capillaries and the cells. In the brain the oedema, affecting as it does a structure enclosed in a rigid bony case, has the further damaging effect of raising intracranial pressure and of thus interfering mechanically with cerebral circulation. Thus the initial hypoxia becomes potentiated, and with it the hypoxic damage mounts, completing a vicious circle of great detriment to the chances of the subject's recovery. It is of little avail at this stage that the original hypoxic episode has been controlled. The vicious cycle will continue even after, say, the heart has been restarted after cardiac arrest and efficient circulation has been re-established. It is necessary to break the vicious cycle—that is, to treat the existing or developing cerebral oedema. We believe that even the pre-terminal hyperpyrexia which is often seen in these cases may in at least some of them be explained on the basis of oedema involving the heat-regulating area. Therefore this sign need not be taken as necessarily pre-terminal, although it often precedes death. We take it to mean only that extensive damage is present which is extending into the hypothalamus.

Dehydration Therapy

With these considerations in mind, we have of late subjected patients who have had an acute hypoxic episode to a regimen of vigorous dehydration. The following case history is presented as an example of the method of treatment, and also because of the extreme severity of the hypoxia, which yet was followed by a quite unexpected return to apparent clinical normality.

A well-nourished man of 43 was to undergo thoracotomy for carcinoma of the left lung. His general condition before operation was good, and apart from his present illness there was no other major disorder. Bronchial obstruction due to the growth made it impossible to collapse the affected lung during operation, and after some manipulations cyanosis began to appear, and continued to increase in intensity. The cyanosis was not relieved by repeated tracheo-bronchial toilet, and only momentary improvement followed whenever a moderate amount of blood and

secretions was aspirated from the dependent lung. The lesion was found to be inoperable and the chest was closed; this was completed two hours and thirty-five minutes after induction. After closure the patient reacted, opened his eyes, but still his colour remained dusky as before. Bronchoscopy was done and much material was aspirated; while this procedure was still in progress cardiac arrest occurred.

The chest was immediately reopened and an asystolic flabby heart was found. Manual systole restored circulation to the extent that a carotid pulse could be felt; soon the heart resumed spontaneous action. An estimated four minutes had elapsed from the time the diagnosis of cardiac arrest had been made to the establishment of manual systole. Oxygen administration through an endotracheal tube had been carried out from the instant the heart had been known to have stopped. After efficient heart action had been observed for some 10 minutes, the chest was closed. The patient was breathing spontaneously and oxygen administration was continued, but he remained in deep coma with widely dilated pupils and all reflexes absent. The colour was improved but by no means satisfactory.

At this stage, half an hour after successful restoration of circulation, 50 ml. of 50% glucose was injected intravenously, and within one minute signs of lightening of the coma were observed, such as roving eyeballs and involuntary incoordinated movements of the extremities. This improvement persisted for a little over half an hour, when coma again deepened without, however, reaching the depth that had obtained prior to the glucose medication. Some four hours later the temperature began to rise rapidly, and the injection of glucose was repeated. This time the patient made attempts at sitting up and even of getting out of bed, but he was still unconscious. Later the coma again deepened, but the level did not reach to where it had been before the second injection. The temperature began to fall and during the night a slow intravenous drip of 1,000 ml. of 25% glucose was given. He remained in light coma during the following day, but regained consciousness on the third post-operative day, and thereafter made an uneventful although slow recovery. He had no residual neurological symptoms and presented no evidence of kidney damage from the hypertonic solution when he was discharged from hospital 10 days later.

This was a case in which total hypoxia of at least four minutes, superimposed as it was upon prolonged severe hypoxia, made it likely that the patient would succumb; yet after vigorous dehydration therapy he recovered with no apparent residual damage. This would indicate that the nervous elements destroyed beyond recovery by the original hypoxia must have been relatively few. It was striking how after each administration of hypertonic glucose the coma markedly lightened and never quite returned to its previous depth, and how by the same measure it was possible to check hyperpyrexia. That the result was not permanent after each administration is not surprising, as we know that oedema recurs after the drug has ceased its dehydrating action. This has been sometimes called "rebound oedema." The improvement observed was not due to the glucose itself, as it has been shown that glucose is ineffective in increasing cortical survival time, at least in rabbits exposed to hypoxia (Noell and Chinn, 1950); nor does it increase resistance to hypoxia in dogs (Snapp, Adler, and Kramer, 1948). The same has incidentally been shown also in rabbits for glutamate, pyruvate, succinate, and fumarate (Noell and Chinn, 1950).

It would appear that concentrated human serum albumin, which has been recommended as a substitute for hypertonic glucose in the control of oedema (Cole, 1951), is also useful in these cases, and it has been employed by one of us in a recent case. Another substance which is worth trying, especially because of its universal availability, is double or quadruple concentrated plasma. This may be obtained by reconstituting dried plasma with half or one-quarter the quantity of water usually employed. On theoretical grounds plasma expanders, such as dextran and polyvinylpyrrolidone would also seem to be indicated, but there is as yet not enough information to allow of their evaluation as dehydration agents. Serum or plasma has proved as effective as hypertonic glucose and may actually be preferable, as the latter, if administered for any length of time, may lead to renal damage. However, this should not be a deterrent to its use in the absence of a more suitable agent, for the con-

dition of the patient is desperate. It may be advantageous to give a diuretic agent at the same time as the hypertonic solutions, in order to maintain kidney function during this critical period. Efficient kidney function is probably a very important factor in the control of the oedema. Recurrence of oedema will be prevented largely by a rigid control of fluid and electrolyte administration, but the effectiveness of such control depends much upon adequate renal function.

Adequate Oxygenation

Oxygen is administered continuously throughout the post-hypoxic period, and a mask or nasopharyngeal catheter is preferred to a tent on account of its greater efficiency. A scrupulously clear air-way is maintained at all times and secretions are often aspirated through an endotracheal tube. A slight head-down tilt of the bed at approximately 7 degrees assists the drainage of secretions without interfering unduly with cardio-respiratory function or causing congestion of the head. There should be no hesitation to perform a tracheotomy in order to ensure an unobstructed air-way or to facilitate the removal of secretions. Tracheotomy is also advisable if coma is prolonged, as it is unwise to keep an endotracheal tube in position for longer than 24 to 36 hours.

While a clear air-way is of the first importance, the adequacy of tidal exchange must not be overlooked. These patients may remain in a state of chronic hypoxia if adequate ventilation is not ensured. If necessary they can be placed in a Drinker respirator or a similar device. We recently observed a case in which post-operative hypoxia occurred when the patient was returned to her bed. Ten hours later she was still unconscious with only leg reflexes remaining; under a regimen of endotracheal tube, Drinker respirator, and concentrated albumin, she revived sufficiently in three hours to respond to instructions. Anaesthetic drugs have no place in the treatment of the post-hypoxic respiratory depression, having been shown in rabbits to be actually harmful (Noell, 1948).

Other Measures

Another problem in these cases which requires mention is that of gastric dilatation. This condition is combated by early passage of a stomach tube; the tube may be left *in situ* to ensure against recurrence of dilatation, and may later be used for feeding purposes if coma is prolonged.

Meanwhile general supportive measures are carried out vigorously. Nutrition of the patient must be ensured, and may be carried out via a stomach tube, as described; intravenous protein hydrolysates are administered if necessary. Vitamins of the B complex and vitamin C are of advantage. Blood is transfused, and in this one must be guided by the actual amount lost. Overtransfusion is very harmful in these cases, but so is any deficiency of the oxygen-carrying elements of the blood. The blood pressure must be maintained, and for this vasopressors are preferred to intravenous fluids over and above the minimum requirements, so as not to interfere with the dehydration regimen. For the same reason electrolytes, particularly sodium, are omitted from such solutions as must be given. It must always be borne in mind, however, that along with the brain the whole body is being dehydrated; this necessitates a careful watch on the patient's electrolyte balance during the period of this therapy. If the blood pressure proves difficult to maintain, vasopressors are administered. Schmidt (1950) has shown that intracranial vessels are relatively insensitive to all drugs that constrict blood vessels elsewhere, and hence any of the innumerable vasopressors available may be employed. We personally prefer *noradrenaline* in a continuous drip for a period of time, or, failing this, phenylephrine hydrochloride ("neosynephrine").

Antibiotics are administered, and the stir-up regimen is followed—this consisting in turning the patient frequently from one side to the other; and carbon dioxide inhalations for short periods may also be indicated. This not only

improves pulmonary ventilation but also has a potent cerebrovascular dilating effect. The important point to remember is that under no circumstances must these patients be left flat on their back for any length of time. As the coma lightens, they may become very restless. If this occurs the temptation to over-sedate must be resisted, else the central depression and consequently reduced tidal volume will precipitate further hypoxia.

In an attempt to increase cerebral circulation, stellate ganglion block has been recommended and is widely employed, but it is still controversial whether the smaller cerebral vessels possess muscular constricting elements, and no final agreement has been reached on their extrinsic innervation (Schmidt, 1950). However, we are not too much concerned with these small blood vessels, but rather with the larger stems and the named vessels. It may be argued that these too should already be in a state of maximum dilatation; but that they are capable of further dilatation when the stellate ganglion is blocked can be inferred by use of the flicker photometer, and that they actually do dilate under conditions of hypoxia after a stellate block can be observed directly on retinoscopy. In the absence of localizing signs, the ganglion to be blocked is the one opposite to the side of the patient's usual preponderance. If, however, no result is obtained we would not hesitate to carry out a bilateral block despite dangers which have been ascribed to this procedure. We have seen no ill effects from it. Various drugs have also been recommended and tried in order to improve cerebral circulation, but they appear to be of little value.

Conclusion

Our therapeutic resources against the effects of acute hypoxia are few. They must ensure adequate oxygenation of the vital tissues of the body and suppress cerebral oedema with its potentiating effect on the hypoxic damage to the central nervous system. We believe that a dehydration regimen combined with the administration of oxygen, maintenance of an adequate tidal exchange, and general supportive measures afford the best means of achieving these ends. However, even when this line of treatment is adopted, it is still quite impossible to prognosticate on the outcome in individual cases. We have seen patients who immediately after the acute hypoxic episode looked fairly well deteriorate rapidly within a matter of hours, probably owing to rapidly developing and poorly controlled cerebral oedema, while others even after many days of coma regain consciousness without showing residual damage. Hence, we must not abandon hope in even those cases which seem hopeless at the onset; once an acute hypoxic episode has taken place, the patient's chances of recovery depend largely on our acting quickly, thoroughly, and completely.

Summary

A line of treatment is presented to combat the sequelae of acute hypoxia. This is based on the assumption that much of the damage is due to cerebral oedema which supervenes after the acute hypoxia has been relieved. Vigorous dehydration, combined with the administration of oxygen, maintenance of adequate tidal exchange, and general supportive measures are the mainstay of treatment.

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