Aids to Beauty

For the benefit of the ladies, whose presence I welcomed at the outset of my address, I venture to make a few remarks which are kindly meant. I refer to the practice of plucking the eyebrows, which presumably is intended to have a beautifying effect. Let me remind you that Nature provided the eyebrows for a specific purpose—namely, to divert the drops of perspiration which course down the forehead from entering the eyes. It would be just as reasonable to tear down the guttering from the roof of a building and allow the rain water to cascade over the window-panes. The natural corollary would be that those of the gentler sex who resort to this practice do not work hard enough to perspire.

Another beauty aid extensively employed in high society is the application of pigments of various kinds to the eyelashes, perhaps not quite so reprehensible an embellishment. This form of toilet is not without risk, and I have seen at least one "pair of sparkling eyes" rendered permanently glazed and blinded as the result of innocent preparation for a social function.

Conclusion

Ophthalmology is perhaps the cleanest and most congenial of all the specialties, its practice attended by a minimum of blood and pus and the unpleasantness of working in obnoxious cavities. Nevertheless it is apt to be monotonous and tiring, especially when one is cooped up in darkened rooms for the greater part of the week. To find that mental relaxation so essential for the human machine it has been my habit for the past few years to spend part of the week-end in the company of a few friends walking and climbing on Table Mountain, the mountain so beloved by my fellow countryman and that great statesman, the late Field-Marshal Smuts. It was on the summit of Table Mountain that he delivered perhaps the finest of all his many inspiring addresses, on the occasion in May, 1923, when he unveiled the Mountain Club War Memorial to those of its members who fell in the 1914-18 war. He spoke of the Religion of the Mountain, and I hope you will pardon me if I quote a few sentences of his address:

"What is that religion? When we reach the mountain summits we leave behind us all the things that weigh heavily down below on our body and soul. We leave behind a feeling of weakness and depression. . . . We feel a great joy. The religion of the mountain is in reality the religion of joy. Not only on the mountain summits of life, not only on the heights of success and achievement, but down in the deep valleys of drudgery, of anxiety and defeat, we must cultivate this great spirit of joyous freedom and uplift of the soul. We must practise the religion of the mountain down in the valleys also."

Not to all of us comes the opportunity to scale mountain heights where we may experience for ourselves the exhilaration of spirit so beautifully described by Field-Marshal Smuts; but to each of us performing our daily round and common task, despondent and worried by the troublous times in which we live and the cares of practice, it is possible to look up to something higher than ourselves. Someone to whom we can turn for help and guidance. Though I am not one who parades my religion, I can give you an assurance that if you practise this uplift of the soul from day to day you will not be disappointed. On what more appropriate note can I end this ophthalmological address than by reminding you of the words of the Psalmist, "I will lift up mine eyes unto the hills, from whence cometh my help."

ASPECTS OF THE CIRCULATION'S ECONOMY*

BY

K. J. FRANKLIN, D.M., D.Sc., F.R.C.P.

Professor of Physiology, St. Bartholomew's Hospital Medical College

It is obviously pertinent now to ask how the order of blood-flow reductions found in experiments upon animals corresponds with experience in human circulatory failure. *A priori*, I think, it might be expected to correspond where the conditions are sufficiently similar, but otherwise it would show divergences, though with analysis of the clinical and other experience available it should be possible to classify the various types of blood-flow redistribution, and of exitus through the progression of certain of them to the stage of irreversibility. I propose to give a number of instances of blood redistribution in man; many of them are in line with the order of sacrifice which I have detailed, but certain are not, for the conditions were different. I shall pass then to consideration of the blood flows in diving mammals, in the foetus *in utero*, and in obstetric shock, and shall show points of similarity which emerge, in particular the preferential treatment of the brain.

Circulatory Effect of Cold

In the first place, the symptom of coldness due to contraction of skin vessels is so common an early symptom in various disorders that it needs no emphasis. In the case of the limbs it may be followed by pain in ischaemic muscles; this was so with the late King Gustav of Sweden on October 28, 1950, the day after his collapse. At the time, however, his brain was clear and he was able to receive several members of his family. The bulletin issued in the evening, no important change having occurred in the interim, stated that the heart's activity was comparatively good. Let us turn to a second instance. When the great eighteenth-century physiologist, Albrecht von Haller, was dying he exhibited a fine professional interest in his own circulatory failure (Cushing, 1901). For a while he found that he could still feel his pulse; thereafter it was imperceptible. Here then, the arm circulation had been markedly reduced while that to the brain remained competent.

The part played by the peripheral constriction in maintaining higher cerebral activity is also exemplified in the late Sir Joseph Barcroft's exposures of himself to severe cold. On two occasions he lay down naked in a freezing-room, and carried on until an assistant, seeing unconsciousness to be imminent, came to the rescue with warm blankets and hot drinks. In each experiment "J.B." at first lay shivering, with his limbs flexed in a sort of effort to huddle up, and he was very conscious of the cold. During this stage his nervous system, in an effort to fight the adverse circumstances and to preserve the body's heat, was constricting his cutaneous vessels and keeping the blood in the internal parts; because of the cold he had to suppress, by an effort of will, his instinct to be up and about. Suddenly thereafter his nervous system gave up the struggle; he stretched out his legs, and the sense of coldness was succeeded by a beautiful feeling of warmth as his skin vessels relaxed—he lay "basking" in the cold. At this

*The second Oliver-Sharpey Lecture, given at the Royal College of Physicians of London on March 15, 1951. The first lecture appeared in last week's issue.

point his initiative had gone and he was completely acquiescent while his body temperature, no longer kept up by cutaneous vasoconstriction,* was falling. His natural modesty, also, changed to "Well, I don't know what," and he no longer worried about what some person alien to the experiment would think if that person came in and found him stark naked.

It is obvious from this account that in the earlier part of "J. B.'s" exposure sacrifice of the cutaneous blood supply (and doubtless of that to the musculature) was part of the circulatory readjustment which conserved the blood flow to the highest nervous centres and kept them active; with such sacrifice reversed, these centres went out of action and less modest ones took over, while even these latter would quickly have followed the first but for the attendant's intervention with the warm blankets and hot drinks.

Reduced Blood Flow in Conditions of Shock

In obstetric shock in human patients Sheehan (1949) found that the blood flows were reduced, without a complete shut-down occurring anywhere, in the order: (1) that to the skin, the capillaries being affected less than the other minute vessels, and the superficial veins being markedly contracted; (2) that to the muscles; (3) and (4) that through the portal system and liver, and that through the kidney—he was unable to say which first suffered; (5) that to the brain, which was more or less normal until the onset of dying.

Further details will be mentioned later. Meanwhile we can add that Sheehan thought that the same order of reduction of blood flows occurs in patients with severe haemorrhages, and that he found some evidence of a cardiac effect of the shock. The finding, said to occur also in experimental animals, was the occurrence of subendocardial haemorrhages over the distribution of the left atrio-ventricular bundle branch, with peculiarly swollen Purkinje fibres in the vicinity. It seems, therefore, that the coronary circulation itself may be included at times in the blood flows which are unduly reduced.

Though the above is the order in which, in man, parts of the body often have their blood flows cut, it is not the only one, nor is it sufficiently detailed about the brain supply. I have myself often attempted to picture the distribution of the blood flows which obtained in some exhausted infantrymen whom I saw during the Battle of Arras in 1917. They had made an attack, consolidated their positions, and then been relieved later than planned. When I saw them they were coming back in extended order across the open, but were fast asleep. By what mechanisms they managed to do this I do not know, but obviously the highest nervous centres were out of action while the limb muscles must have been receiving a good blood supply. I also remember a forced night march of 30 kilometres, suddenly ordered for our field artillery brigade on the French front in the summer of 1918. We had had a full day's activity before it, and in consequence, as we moved through the moonlit villages and countryside, many of us were sleeping at intervals though remaining in our saddles—dropping off in one sense but not in the other.

*Cf. cases of haemorrhagic shock at the front during the late war, when cutaneous vasoconstriction was so marked during the period of resistance to circulatory collapse that it was well-nigh impossible to make injections via these vessels; if thereafter they relaxed, the prognosis immediately worsened.

That the highest brain centres can be suddenly cut out is suggested—though here also no direct connexion with a blood-flow restriction is established—by the experience of Nor Hussain, sole survivor of the crew of 74 on the steamer *Indian Enterprise*, which with 580 tons of explosives aboard caught fire and blew up in the Red Sea on June 19, 1949. Asked at the subsequent public inquiry in London if he had smelt anything before the explosion, Hussain said: "When a man is about to die he does not remember very much. I have no recollection. I did not hear any alarm given." Psychologists may have an alternative explanation of this, and there may also be explanations other than purely circulatory ones of the sparing of the vital brain centres during many forms of successfully conducted general anaesthesia; in some of them, however, as also in alcoholic intoxication, depression of higher cerebral activity goes hand in hand with cutaneous and other vasodilatation.

Blood Flow in Diving Animals

I wish now to refer to diving animals and their adaptations, and in this connexion much that is pertinent to this discussion was included by Irving (1939) in his review. Cessation of circulation, he noted, affects the various tissues very differently. The arm or leg can endure tourniquet-produced anoxaemia for a quarter of an hour without undue discomfort and for nearly an hour without permanent damage ensuing. Nerve fibres also are quite resistant, but peripheral nerve endings are seldom at their best after even a few minutes' asphyxia, and the brain is particularly sensitive to it. Apparently, the brain as a whole will not operate during true anoxaemia, and the blood returning from it is seldom more than half desaturated.

On the other hand, the respiratory centre, some spinal cord centres, and some sympathetic ganglia are quite resistant, continue to discharge rhythmic trains of nervous impulses during the first quarter of an hour of asphyxia, and may be revived after even longer periods. The different duration of survival of some parts of the nervous system indicates a varying sensitivity to anoxia, "but the integrated whole which is necessary to conscious activity is apparently much more delicate than some of its components." The heart as a whole is rapidly affected by anoxia; oxygen lack, as we learn from other sources (Hilton and Eichholtz, 1925), is by far the most powerful dilator of the coronary vessels, and heart failure sets in when they have dilated to 500% without relief of the musculature.

To return to Irving—newborn animals are more asphyxia-resistant than adults. It seems likely that the sensitivity of the brain to the condition is common to all mammals, and that any special arrangements which preserve the divers must keep up a proper oxygen supply for the brain and probably also for the heart. The other tissues are less sensitive to asphyxia and also less indispensable for life. Addition of carbon dioxide in appropriate amount to the inspired air causes in man, the cat, the dog, the rabbit, the musk-rat, and the beaver an increase in the flow to the brain and decrease in that to the muscles; the reduction in the flow to the latter during apnoea is effected through the sympathetic nerves. Irving concluded his survey by stating: "It is interesting that the principal physiological adjustments of divers differ only quantitatively from those of land animals."

Circulation in the Foetus

Passing to the circulation in the foetus (Barclay *et al.*, 1944; Franklin *et al.*, 1946), we note first that the blood returning from the placenta is not very fully saturated with oxygen, and that the only part to which even that blood is distributed without adulteration is the "umbilical" portion (the left two-thirds in the sheep foetus) of the liver. The anterior caval inflow into the heart is less oxygenated than the joint umbilical, portal, and abdominal caval blood streams which arrive by the thoracic posterior vena cava, and the orientation of the parts ensures that it is the bulk of this joint blood which, together with the pulmonary venous return, passes to the arch of the aorta for distribution via the coronary arteries to the heart, and via the other offshoot or offshoots of the arch to the head and forelimbs. In the foetus, then, the heart and brain, after the "umbilical" part of the liver, get as good an oxygen supply as possible.*

Intrauterine State and Obstetric Shock

Let us compare this intrauterine state with that found by Sheehan (1949) in cases of obstetric shock. He wrote:

"The reduction of the rate of blood-flow to most of the body is naturally associated with a reduction of metabolic activity by the body in general, as is evidenced by the fall of body temperature and the reduced rate of oxygen usage by the body as a whole. It is, however, important not to exaggerate the slowness of the blood-flow through the abdomen and limbs. It is a slowness of flow, not a complete arrest. Some blood certainly flows down the abdominal aorta even in very severe shock. This is easily shown by manual compression of the upper abdominal aorta, which produces a definite rise of blood pressure in the upper parts of the body, even in moribund patients. In addition, the blood-flow to the various parts of the body is sufficient to maintain the life of the tissues; there is no necrosis, apart from one special exception to be mentioned later. Human beings do not develop the necrosis of intestinal mucosa which is found after prolonged experimental shock in certain types of animals.

"In contrast to this evidence suggesting a very considerable reduction in the blood-flow to most of the body, there is the very significant fact that the patient remains quite conscious until the terminal stages of shock. This can only mean that the blood-flow to the brain remains relatively good.

"Thus the actual condition of the circulation through the vascular bed in shock seems to be as follows:

"The blood going from the heart each minute passes into one or other of two functionally distinct circuits which have very different circulation times, though the rates have not been measured. (a) A high proportion of it goes to the brain and passes rapidly through the cerebral circulation back to the right heart. The rate of blood flow through this circuit may well be almost normal, except in dying patients. (b) The remainder (a much lower proportion than normal) is distributed to the rest of the body and circulates very slowly through the vessels until it reaches the right heart and mixes with the rapid current of blood returning from the cerebral circuit.

"In patients who have severe haemorrhage, the circulatory changes are probably very similar and form a beneficial defence mechanism to maintain an adequate blood supply to the brain in the presence of a sudden reduction of blood volume. In shock the same mechanism appears to come into action, but without any obviously useful purpose. As

*The ductus venosus blood in the sheep foetus is 60 to 70% saturated with oxygen, the left ventricular blood 40 to 50%, the umbilical arterial blood about 30%.

will be shown later, there is some evidence of sympathetic over-activity in shock, and it is possible that this may be responsible for the vasomotor disturbance of shock."

We have, then, in obstetric shock, haemorrhage, and in the underwater physiology of diving mammals evidence of circulatory adjustments which ensure that the heart and the brain remain well supplied with blood, in general surprisingly so, while other parts of the body have their supplies cut, some of them severely. In the foetus there is no circulatory readjustment, but the normal mechanisms ensure the same effect. In all the cases mentioned, the various organs appear to have places in the order of restriction corresponding, in the main, with their capacity to withstand anoxia. Anoxia, however, is probably but one of many alterations brought about by diminution of blood flow, and we should probably think also in terms of other changes and of any particular organ's indispensability to life.

"Fixity of Internal Environment"

Claude Bernard (1813-78), the greatest of the French physiologists and one of the greatest of all physiologists, began the better understanding with his concept, expressed in somewhat varying phrases over a number of years (see Olmsted, 1939), of the constancy of the internal environment of the body; one form of the idea was contained in the sentence, "*La fixité du milieu intérieur est la condition de la vie libre.*" Doubtless Bernard was originally thinking of the *blood* as the internal environment; but with the passage of time and increase in knowledge of tissue fluid and its movements—indeed, nowadays with the progress of isotope investigations of intracellular circulation itself—the term "internal environment" has acquired a more special connotation, even if the blood composition and flow remain closely connected with that environment's homeostasis or homoeostasis.

In his time Claude Bernard's concept was not fully appreciated, and after his death, like many of his more subtle contributions to our science, it fell rather into the limbo of forgotten things. In succession, however, in more recent times Haldane, Henderson, Cannon, and Barcroft have resuscitated, examined, and extended it; and Barcroft in particular, in 1934, really got to grips with the problems raised. In his final discussion he wrote: "Authors of great distinction have emphasized the importance of the statement*; they have stressed the fixity of the environment, but there is a curious silence about the freedom of the life. What has the organism gained by constancy of temperature, constancy of hydrogen-ion concentration, constancy of water, constancy of sugar, constancy of calcium, and the rest? Is not the poikilothermic animal a very good animal? The bass or the perch with a blood on the acid side of normal—what fault is to be found with its muscular contraction or its heart-beat? You may take other organs of the body and subject them to a concentration of oxygen far below that necessary for man as a whole and they will function excellently. What, then, is this free life of which the fixity of internal environment is the condition?"

Mental Activity

After reviewing the effects of cold, heat, change in hydrogen-ion concentration, and acute and chronic oxygen lack and oxygen excess, many of them from

*"The fixity of internal environment is the condition of a free life."

personal experience, Barcroft came to the conclusion that the fixity of internal environment is controlled by the upper part of the central nervous system. As a general rule it is this part of the body which suffers if the environment is altered beyond physiological limits ; in other words, the fixity of the internal environment is the condition of mental activity. The processes of the mind require a medium of great constancy in which to attain to ordered development. "To look for a high intellectual development in a *milieu* whose properties have not become stabilized is to seek music amongst the crashings of a rudimentary wireless or the ripple-patterns on the surface of the stormy Atlantic . . . by degrees throughout the ages the constancy of the internal *milieu* became controlled with ever-increasing nicety till ultimately this control was perfected up to the point at which man's faculties could develop and he could attain to an understanding in terms of abstract knowledge of the world around him. . . . Of that intellectual ascendancy, 'la fixité du milieu intérieur' appears to be the, or at least a, condition ; of that intellectual ascendancy 'la vie libre' is no inapt description."

Fortunately for our efforts at interpretation, Carl Schmidt and his colleagues (see Schmidt, 1950) have measured the total cerebral blood flow, A-V oxygen difference, and vascular resistance in normal human subjects during active and passive overventilation of the lungs, and inhalation of high (85-100%) and low (10%) oxygen-containing and high (5-7%) carbon-dioxide-containing atmospheres. Except for the passive over-ventilation, these correspond with four out of the six conditions mentioned by Barcroft, and in Schmidt's five the cerebral blood flows were respectively 36, 32, 45, 73, and 95 ml. per 100 g. of brain tissue a minute, compared with the normal of 54 ml. Obviously there is nothing in common between them except considerable departure from this normal, and even that is not constant in direction or of anything like the same order throughout the series. In respect of total cerebral oxygen consumption, however, three of the five conditions gave the normal figure of 33 ml. per 100 g. of brain tissue a minute, and in a fourth the amount was 32 ml. ; in the fifth alone—namely, active overventilation—was there a marked change, and Schmidt thought that the rise here to 38 ml. was related to the extra mental activity associated with the excessive voluntary respiratory efforts.

Mental disorder, on the other hand, can be present without departures from normal in total cerebral blood flow, A-V oxygen difference, and vascular resistance. Kety *et al.* (1948), for instance, found no change in schizophrenic subjects, either before or during their beneficial treatment with amylobarbitone or thiopentone, and Kety and Schmidt (1948) wrote: "The higher psychic functions are associated with biochemical changes so smooth and complex as to render any attempts to describe them in terms of mere oxygen utilization no more adequate than to predict the fidelity of a radio by its power requirements."

It seems to me, therefore, that the successive diminution of blood flows to parts other than the central nervous system, which we have mentioned as occurring in a number of conditions, has not as its primary or basic effect, though it often has as a highly important secondary one, the preservation of the highest mental activity. Rather, I imagine, may the conservation of the vital nervous centres be the more essential thing ; for while they retain the necessary conditions for their

activity ways are left open for the subsequent full restoration of higher brain functions if these have undergone temporary reduction or suppression as in the cases mentioned by Barcroft, as in sleep, and as in various other circumstances. In so far as the conditions in the mature foetus are parallel, they can be remembered also, for in that foetus the highest nervous functions have not yet appeared. Further, in a small number of post-natal human subjects they never do develop, or only imperfectly, and in others, at varying stages and to varying degrees in later years, higher mental activities deteriorate or disappear without apparently altering the order of successive restriction of blood flows in haemorrhage, etc.

Reactivity of Cerebral Blood Flow

It remains to substantiate this idea by demonstrating preferential homoeostasis of the blood supply to the vital centres of the brain stem and spinal cord, and some fairly close correspondence between their use of the blood constituents and the preservation of their activities. At the outset I shall frankly admit that the evidence is far from adequate ; on the other hand, such as it is, it does not seem directly opposed to the hypothesis which I have advanced.

Schmidt (1950), to begin with, reported sympathetic vasoconstrictor effects in the hypothalamus of the cat, and in the parietal cortex of that animal and the monkey, while the medulla, pons, and occipital cortex of the cat were irresponsive. With regard to the rabbit, which was not in Schmidt's list, the first point to be noted is that the internal carotid arteries supply the greater part of the cerebrum, while the vertebrals supply the occipital cortex, cerebellum, brain stem, and (in part) the spinal cord ; the brain-flows of these major arteries under normal conditions are strictly unilateral, and the two vertebral flows remain functionally separate (as shown by Drs. D. A. McDonald and J. M. Potter in their beautiful colour film*) even while proceeding farther in the single basilar artery formed by their union.

In unanaesthetized rabbits Lubsen (1941) found that the cervical sympathetic innervation was basically constrictor to both the external and the internal ipsilateral carotid arteries, but to the former more powerfully than to the latter ; it was also constrictor to the contralateral internal artery. With weak unilateral stimulation the constriction of the external carotid resulted in increased cerebral flow through both hemispheres ; with medium stimulation there was increased ipsilateral and decreased contralateral cerebral flow ; with strong stimulation there was bilateral decrease, the contralateral one predominating over and lasting longer than the ipsilateral one. Adrenaline, in the dosage of 10 μ g., caused rise of blood pressure and increased cerebral flow ; in the dosage of 50 μ g. there was an initial decrease of cerebral flow before the increase in about half the cases, and in the dosage of 200 μ g. the drop was more marked. In a proportion of cases of 50 μ g. there was a second fall in flow after the rise. Bilateral ganglionectomy increased sensitivity to adrenaline, the peak being reached at 10 days ; at this stage 50 μ g. decreased the cerebral blood flow despite the rise in blood pressure. Unilateral ganglionectomy predisposed to increased cerebral flow

*"Blood Streams in the Basilar Artery." A 16-mm. silent colour film, 245 ft., photography by Douglas Fisher ; rate of projection 24 frames a second. Published 1950. London: The Wellcome Foundation Ltd. Research Record No. 1.

on the operated side, and decrease on the contralateral side.

All this evidence of reactivity of the cerebral blood flows is complemented by the finding of Poupa (1948) that application of a tight tourniquet to the root of the rabbit's thigh over a period of four to five hours resulted in constriction of the internal carotid artery during, and after, the application up to the time at which premortal dilatation occurred. Control experiments showed that a marked fall of blood pressure could be produced by injection of cold saline or of acetylcholine into a jugular vein without affecting the calibre of the internal carotid artery. While one wishes that the reproductions of Poupa's radiographs had been better, one cannot help thinking that Lubsen's evidence, added to that of Poupa, shows an appreciable degree of reactivity in respect of the rabbit's cerebral blood flow.

Unfortunately, neither author studied the vertebral arterial flows, and the only pertinent findings that I can quote are those by my various colleagues and myself on the differential reactivity of the vessels to adrenaline. Nor do they give a really satisfactory answer, for it is not easy to make studies of the vertebral arteries where they pass through bony canals or are overlaid by veins. My general impression is that they and their offshoots are somewhat less reactive to adrenaline than the internal carotid arteries, but much further work needs to be done to substantiate or otherwise the hypothesis that the vital centres, in even this one species, can remain homeostatic in respect of their blood flow while most of the higher centres, supplied by the internal carotid arteries, are less so in respect of theirs. If the hypothesis is not substantiated in the rabbit and other mammals, including man, that will not, I think, invalidate the suggested late position of the brain as a whole in the order of sacrifice, but it will leave many problems to be solved. In other words, the preferential preservation of the brain's blood flow may be but one of the factors concerned, and biochemistry—defined by Young (1951) as "the study of the structure and function of living matter on a molecular basis"—may be the ultimate solver of the problems propounded.

Antagonistic Mechanisms

I think that is as far as I should go with the occurrence of the orderly differential restriction of blood flows as a whole, but I wish to consider the mechanisms through which, on occasion, this generally protective series of events is invalidated, and, in consequence, is followed by death. For Dr. Oliver's secondary object was to "encourage the application of physiological knowledge to the prevention and cure of disease and the prolongation of life."

I have already mentioned instances (Barcroft's experience in the cold, and cases of wound shock in the recent war) in which cutaneous vessels have given up their constrictor activity and the general body condition has promptly deteriorated. Such giving way of the constrictor efforts in the skin could conceivably initiate the regressive stage—for example, the cutaneous vessels might have their innervation paralysed by severe cold—but such evidence as we have indicates, I think, that anoxia of the liver is more probably the general villain of the piece. From my own experience, which is in line with much in the literature, I should say that the renal cortex tends to have its blood supply restricted or cut before the liver does, but Delorme (1951) in his very interesting article appears to put the liver in the prior

position. Maybe some of the many hepatic functions are embarrassed sooner than others, and both views may contain some of the truth. But let us examine part of the story in greater detail.

Enzyme and Vasotropic Factors

In the anoxic renal cortex, if we may take the simplest account, are produced (i) an enzyme, renin, and (ii) a vasotropic factor, "vaso-excitor material" ("V.E.M."). Renin acts upon a pseudoglobulin, hypertensinogen (or angiotonin precursor, or hypertensin precursor), which is formed in the liver, and the product is hypertensin or angiotonin, a vasoconstrictor agent which apparently acts mainly upon the arterioles, may perhaps be a factor in the normal regulation of arterial blood pressure, and is certainly concerned with hypertensive states. It is inactivated by an enzyme, hypertensinase or angiotonase, present in the healthy kidney, also to some extent in the intestinal mucosa, pancreas, and red cells, and to a minimal amount in the liver and in serum. V.E.M., which has to date been physiologically detected rather than chemically identified, is one of two vasotropic factors brought to recognition and to a wide measure of acceptance during the past 12 years, mainly through the work of the group which includes Zweifach, Chambers, and Shorr. This vasotropic factor is inactivated by the renal cortex (and perhaps, also, to a lesser degree by the liver) when that part of the kidney is once again adequately supplied with oxygen.

The other vasotropic factor, "vaso-depressor material" ("V.D.M."), has been chemically identified by Mazur and Shorr (1950) as ferritin or apoferritin. It is produced pre-eminently by the liver, but also by skeletal muscle and the spleen, under anoxic conditions. It is inactivated by the liver alone, and to perform this task the viscus must be adequately supplied with oxygen; further, too long-continued anoxaemia of the organ irreversibly depresses this faculty.

In the compensatory phase of shock, according to Zweifach, Chambers, and Shorr, the relative reductions in the renal cortical and hepatic blood flows are such that the renal cortex is rendered anoxic before the liver is affected. So production of V.E.M., but not of V.D.M., takes place. In the decompensatory phase, V.E.M. is produced, but the renal cortical blood flow is too scanty to carry it away into the general circulation. On the other hand, the further reduction in the oxygen supply to the liver results in the anoxic production of V.D.M. So in the first phase of shock V.E.M. predominates, and in the second phase V.D.M.

The part of the vascular system upon which these particular vasotropic factors exert their influences lies between the arterioles and the venules, and our knowledge of the functional anatomy of this region has been developed mainly by Zweifach with his delicate and fascinating micromanipulative techniques. V.E.M. ensures a brisk and effective, if perhaps somewhat in the nature of a bare maintenance, blood flow through this region. It enhances the frequency and amplitude of the rhythmic constrictor activity (vasomotion) of the metarterioles and pre-capillary sphincters, and very greatly enhances their reactivity to the topical application of adrenaline, as tested in the mesocaecum of the rat and omentum of the dog. It therefore produces a favourable reaction to a reduced circulating blood volume by confining the peripheral blood flow to the thoroughfare channels and ensuring an adequate venous return. V.D.M., on the other hand, progressively

depresses the reactivity of the metarteriolar musculature and pre-capillary sphincters, diverts blood to the true capillaries, and causes venular stagnation and inadequate venous return. With consequent progressive fall of oxygen in the blood supplied to the liver, the natural mechanism for the production of V.D.M. comes ever more into play, and that for its inactivation the opposite. So the shock becomes irreversible, and death ensues.

To the above summary we can add the findings that V.D.M. has an antidiuretic effect; that the intact adrenal cortex appears to be necessary for the proper functioning of the V.E.M. mechanism; that V.E.M. differs from renin in being heat-stable and dialysable, as well as in its more physiological aspects; and that it also differs from hypertensin and similar pressor agents, which produce *acute* changes in blood pressure by their constrictor effects on more proximal vessels—namely, the larger arterioles. It may be worth adding that the initial reaction in various kinds of shock, and one which will provide the anoxic conditions necessary for the production of V.E.M., may be a nervously intermediated one such as Trueta *et al.* (1947), for instance, found in their tourniquet experiments. I would not, however, rule out humoral mechanisms after a particular experience by Dr. A. M. Miles and myself.* For an anaesthetized rabbit gave birth during the experiment, and our observations suggested a liberation of posterior pituitary hormone in concentration sufficient to cause cortical paling in both the innervated and the denervated kidney; that was during the uterine contraction and parturition. Then, while the uterus was accommodating itself to the absence of the foetus, there was further, but reflex, cortical paling in the innervated kidney only.

Before leaving this summary of the work of Shorr and his colleagues, I should like to make some reference to the hypothesis which they have been developing and which brings their vasotropic factors into the physiological as well as the pathological field. This hypothesis is that the "vaso-excitor and vaso-depressor principles are oppositely acting components of a homeostatic mechanism participating in the regulation of peripheral blood flow and blood pressure" (Shorr, Zweifach, and Furchgott, 1948). While the articles written by these authors and their colleagues deal in the main with the drastic disturbances of equilibrium produced by experimental shock, they suggest that "under more normal circumstances circulatory homeostasis would undoubtedly be accomplished by more subtle alterations in the equilibrium between these vasotropic principles."

Damage to Parenchymatous Organs

Delorme (1951) began his very interesting contribution to the subject of shock by noting that "in the higher organism, when life is threatened, by a reduction in the effectively circulating blood volume, the blood-flow to tissues of immediate importance to survival is maintained by selective vasoconstriction elsewhere in the body (Malcolm, 1910, Mann, 1915)." He then went on to state that, while bone, muscle, and skin can remain anoxic for considerable periods without harm, compensatory circulatory adjustments can cause serious damage to parenchymatous organs such as the kidney and liver, and that the importance of this in the case of the kidney had become well recognized since 1942.

*I think one may reasonably cite evidence from a single experiment when, as in this instance, the chance of a recurrence of similar activity in further experiments is naturally remote and cannot be greatly increased by the most careful planning.

"That earlier and graver injury," he went on, "to the liver may occur in vasoconstrictive states has been neither so well recognized nor so intensively studied."

It is this point about the injury to the liver occurring earlier than that to the kidney which I cannot find demonstrated either in Delorme's own experiments or in his abstracts from the literature; and, as my own experience leads me to believe that the renal cortex in many circumstances suffers before the liver as a whole; further, as Van Slyke (1948) wrote that the renal function shows signs of failure before the hepatic in just the kind of shock—haemorrhagic—which Delorme chose for study; finally, as Shorr *et al.*'s schema, based on much careful study, depends on the vasoconstriction developing in the order kidney first, then liver, Delorme's contention needs to be thoroughly investigated. On the other hand, his proof that increase in the oxygenation of the portal vein blood in dogs increases resistance to haemorrhagic shock is a fine addition to our knowledge, and all can subscribe to the view, which he has further established, "that a gradient loss of liver function occurs under anoxic conditions and that peripheral vascular responses are directly or indirectly influenced by this failure."

Here I should like to say that I still wonder if the "umbilical vein portion" of the mature foetal liver is particularly dependent for its functioning upon getting the best-oxygenated blood that is available—that is, if there is a "purpose" in the anatomico-physiological arrangement of the parts. In one of the war years, when the performance of such research had to be carefully weighed against loss of food supplies, Dr. E. C. Amoroso arranged for a sow near term to be transported 40 miles to the Nuffield Institute for Medical Research so that, in conjunction with Mr. J. R. O'Brien, we could investigate *inter alia* the differential biochemistry of the umbilical and portal vein portions of the foetal liver. Unfortunately, the sow took avoiding action by commencing parturition as soon as she was on board the lorry, and the research has never been done. The point here is that some hepatic functions, after birth as well as before birth, may be more dependent than others upon oxygenation of the organ's blood supply, and in that case more detailed mention of the liver will be required from any future lecturer on my present subject.

Oxygen Treatment in Shock

I cannot proceed to my final remarks without first referring to something which leaps to the mind in reading Delorme's paper, apart from constantly obtruding upon the thoughts at other times. I refer to the possibility of oxygen therapy in shock; and I should particularly like to mention a communication on the subject produced by W. T. L. Ohlsson in 1949. Beginning with the statement that, "irrespective of its cause, shock is always attended by a slowing of the circulation and by unsatisfactory oxygenation throughout the body," he went on to show that the improvement effected by oxygen therapy was even greater than could at present be explained, and—a most important point—that, whereas the healthy subject can be adversely affected by inhalation of pure oxygen, the shocked patient (unless his shock is associated with a tendency to haemorrhage after damage to the lungs) can breathe such an atmosphere without harm and with all the benefits. "To sum up," ended Ohlsson, "oxygen is of great value in the treatment of shock, not only for

the suppression of the hypoxia but also for its good effect upon the circulation, similar to that of a transfusion. There is no time-limit for treatment with 100% oxygen; it can safely continue so long as the shock continues."

Conclusion

I have, in these lectures, attempted to make a composite story of some aspects of the circulation's economy in both health and disease—that is, I have collated the evidence available from the experience of many in an effort to show how things are progressing in a part of the total circulatory research field which I put before you, in schedule form, in the first lecture. We have seen how various mechanisms which help to integrate the blood circulation in health become adapted to a somewhat different pattern of performance in various circumstances of departure from the physiological normal, though in those adaptations certain principles present in health tend, so far as is possible, to be preserved, so that if the disorder is finally overcome the way is open to full restoration to normal, while, if it is merely halted, so much as possible is retained for the future. I have also indicated trends of thought about the events in cases associated with graver prognoses, and have included one suggestion for improvement in the therapy of such.

The gist of my survey is the following:

1. The blood-flows to many individual organs vary on occasion not only *per se* but also in respect of their differential distributions within those organs.
2. In a variety of circumstances, in addition, there is an orderly reduction of the blood-flows to the various parts of the body.
3. The order in which the flows are reduced results, in many instances, in preferential treatment of the central nervous system and of the heart.
4. Despite this, the total amount of blood delivered to the brain as a whole varies within wide limits.
5. Such variation can occur without the highest nervous functions being affected; on the other hand, a serious disorder such as schizophrenia can be present without the blood-flow to the whole brain showing any departure from the normal.
6. It is conceivable, though it is certainly not proved, that there is homeostasis of the vital nervous centres in respect of their blood supply. In certain experimental animals, at all events, the arteries concerned appear to be less responsive than the internal carotid arteries and their branches to vasoconstrictor influences.
7. If such homeostasis of the vital nervous centres is found through future research not to exist, the problem presented by the preferential treatment of the central nervous system mentioned in (3) above will remain for solution along other lines.

It is possible that the general field covered by these lectures was also covered by my late friend and colleague Dr. A. E. Barclay, but I have not seen the script of his posthumous book,* which is shortly to appear. The evidence which I have presented is illustrative of the economy with which the blood circulation is effected, and therefore a justification of the statements by Gollwitzer-Meier and by Fleisch which I quoted in my first lecture. At the same time it is an account of aspects of the circulation's economy in the older connotation of that word, and it was in this sense rather than the other that I formulated the title of these lectures.

*Micro-arteriography. Blackwell Scientific Publications, Ltd., Oxford. Published after these lectures went to press.

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SOME SUICIDE STATISTICS

BY

DOUGLAS SWINSCOW, M.B., B.S.

Assistant Editor, "British Medical Journal"

The causes of suicide are diverse and often too obscure to elucidate in individual cases. A leading article in the *British Medical Journal* (1947) pointed out that suicide has been described as "our most baffling social disease." The incidence of this manner of ending life doubtless depends in part on religious, philosophical, and cultural, as well as social, influences. Many studies, both individual and statistical, have been made of suicide, but it is hoped that the following contribution may draw attention to certain features of suicide statistics hitherto unconsidered, or add fresh evidence in confirmation of data already published.

The graphs and tables given below (referring only to civilians) are calculated from various national statistics, and some of them indicate certain factors influential in causing people to commit suicide. Among these are economic factors and the relation between our present society and old people. The suicide rate might be reduced, as the infant mortality rate and the incidence of some communicable diseases have been, with the help of appropriate social measures.

It is commonly believed that the suicide rate in England and Wales, while showing considerable fluctuations, is in general rising. For instance, Stengel (1950), in a recent review of the literature, says that the suicide rates in England and Wales have shown a steady increase in recent years after a marked decrease during the war, though they are still below the 1938 figures. But this is too broad a generalization, and Figs. 3 and 4 below reveal that the rates in different age groups and for the two sexes are now behaving differently.

The death rate in England and Wales for suicide per million males in four age groups is shown in Fig. 1 by decades from 1861 to the end of 1920. The upward trend in every age group until 1911 is clearly shown. In the decade that includes the 1914-18 war the rates

all fell, though precisely by how much is questionable because of the difficulty of estimating the civilian population during the war.

The death rates for suicide among women changed over these decades in a similar way, as Fig. 2 shows,

FIG. 1.—Suicide rates per million in males (civilian), England and Wales, in decades 1861-1920, by age groups: under 25, 25-44, 45-64, 65 and over.

FIG. 2.—Suicide rates per million in females (civilian), England and Wales, in decades 1861-1920, by age groups: under 25, 25-44, 45-64, 65 and over.