BRITISH MEDICAL JOURNAL

LONDON SATURDAY APRIL 4 1953

THE SURGEON AND ISCHAEMIA*

BY

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I am very conscious of the honour which the Horsley Trustees have done me in inviting me to deliver this Horsley Memorial Lecture. I have always regarded Victor Horsley as an Olympian. Indeed, I have a curious second-hand knowledge of him, for on more than one occasion the late Sir Charles Ballance, who assisted Horsley at the operation, recounted to me the dramatic story of the first removal of a tumour of the spinal cord. When I began to practise neurological surgery, many years ago, this led me to peruse Horsley's account of the operation, which was and is a model of orderly reasoning from physiological principles to practical therapeutics: to-day I can think of no better intellectual exercise for a student in the transitional period from preclinical to clinical work than a study of Horsley's procedure on that occasion, and of his reflections upon his own diagnostic problem and upon the technique which he used. That report exemplifies the aspect of Horsley's outlook and life's work which has always appealed to me most: his insistence that physiological hypotheses, and so far as possible operative procedures, should be tested experimentally before being incorporated into surgical techniques. How characteristic of him is the comment in his report that the choice between stitching the spinal dura and leaving it open is one which "requires experimental investigation at the present time." Here was a problem: it must be attacked—and when Horsley was concerned attacked is the right word—without any delay.

I deprecate any tendency to consider Horsley's great contributions to medicine as twofold—the physiological and the surgical. There was no dividing-line between the two. He passed from laboratory problem to clinical problem, and from clinical problem to laboratory problem, with the confident ease of one who was equally talented and equally skilled in both spheres. Possibly the only matters to which he did not apply the rigorous tests of the experimental method were certain of his own passionately cherished beliefs. That is the way of crusaders; and Horsley died, as he might well have chosen, in the midst of a crusade.

Perhaps it would have been more appropriate if I could have selected as the subject of this lecture some neurological topic. On the other hand, it seemed to me that Horsley would not have disapproved of my choosing to speak of some practical aspects of the vascular supply of tissues, to the clarifying of which contributions have been made from laboratory, ward, and operating theatre. It seemed to me also that I might most conveniently approach my subject by considering first that ischaemia which is desirable.

*Victor Horsley Memorial Lecture delivered at B.M.A. House on December 11, 1952.

DESIRABLE ISCHAEMIA

The objective of checking bleeding from injured tissues is quite understandably older than any attempt to provide the surgeon with a bloodless field for a planned intervention, and efforts to secure it did not necessarily depend upon a knowledge of the circulation of the blood. About the second century A.D., Heliodorus applied a bandage above the level of an amputation for gangrene in order to compress the vessels of the limb. This innovation could not have been based on pathological principles, for at the time the accepted technique was to amputate through the gangrenous and therefore presumably bloodless part of the limb. Probably about the beginning of the sixteenth century the site of amputation of a gangrenous extremity was moved to be proximal to the line of demarcation, a change in technique which soon produced the first of the special tourniquets (designed by Fabry) for use at amputations, and this original tourniquet has had many ingenious mechanical successors.

However, until the middle of the nineteenth century the tourniquet was merely a constricting band, and sometimes a destructive one at that. In order to provide a field in which the surgeon could operate upon an extremity unhampered by bleeding, in the eighteen-fifties Esmarch introduced his method of forcing the blood out of a limb by the centripetal application of an elastic bandage and the application of a second similar bandage at the root of the limb before the first was removed. This was, of course, a highly effective method of providing a bloodless field; but it was a purely mechanical one. An alternative method based on physiological principles deduced from both animal and hominal experiments was introduced about the same time by Lister (1879). Lister showed that on elevation of a limb its veins emptied by gravity and that after a few minutes its arteries underwent reflex contraction, so that the volume of blood entering the extremity was minimal; a tourniquet was then applied to the root of the limb. This was the kind of preliminary physiological investigation of a problem, carried out both in man and in animals, which finds many parallels in Horsley's investigations.

Tourniquet Paralysis

The occasional occurrence of paralysis after the application of tourniquets became too high a price for a proportion of the patients to pay for the surgeon's bloodless field, and posed the problem of the causation of the paralysis. The time during which it is possible to occlude the circulation to a limb without pathological consequences in the tissues distal to the constricting band might appear to be a figure which could be determined by a series of experimental observations on normal individuals; and indeed much work has been done on the subject. The times recorded by different workers, under different conditions, have been so variable that this is a problem to which the experimental method has not as yet provided a uniform solution.

In most of the reported cases of tourniquet paralysis the arm has been the site of application, at a level where the radial nerve is unusually exposed to pressure, and the pressure had often been concentrated by the use of too narrow a constricting band, which introduced the possibility of direct physical trauma to the underlying nerves. It seems to me of great significance that in those cases of tourniquet paralysis which have been investigated by surgical exploration the band employed has been narrow and unyielding, and that the operations have disclosed neuromata at the site of pressure (e.g., Speigel and Lewin, 1945).

Lewis stated that a nerve could withstand total ischaemia for at least 12 hours and possibly even for 20 hours, a period much in excess of that required for any operative procedure on the limbs; and I have seen complete recovery of the nerves of the lower limbs after acute aortic obstruction had existed for nine hours. It might be surmised that nerves which possessed an arteria comitans (median, sciatic) would be particularly vulnerable to ischaemia, and, indeed, in the arm Sinclair (1948) found the sensory territory of the median nerve to be first affected; but tourniquet paralysis of the sciatic nerve is rare, possibly owing to the diffuse pad provided for it by the overlying muscles. After the release of the cuff of a sphygmomanometer which has been inflated to above systolic pressure for periods up to at least 30 minutes, return of function in the nerves of the arm is usually rapid (within a minute or so); but, as I have said, there are considerable differences between patients in the effect of ischaemia upon nerves, so that individual susceptibilities, which cannot be assessed in advance, may lead to considerable divergences from this average figure.

Reactive Hyperaemia

There is a practical objection to the use of any tourniquet. After its release, and, as shown by Lister, whether the limb is elevated or not, there ensues in the distal part of the limb a period of reactive hyperaemia during which free bleeding occurs from innumerable tiny dilated vessels which do not lend themselves to forcipressure or ligation. Thus, at the end of an operation during which a tourniquet has been constantly applied, time must be allowed for this reaction to disappear, and for the effect of such simple haemostatic measures as the gentle pressure of warm moist packs. Because of the possibility of ischaemic lesions after the application of tourniquets, it is natural that techniques have been suggested by which the cessation of circulation in a limb is made intermittent by the timed removal and reapplication of the constricting band. But there are then a series of episodes of reactive hyperaemia, and a further serious objection to this method is provided by the observation of Barlow and Pochin (1948) that a second subsequent period of ischaemia induced by reapplication of a tourniquet appears to interfere (even after a short—25 minutes—period) with the complete recovery of conduction in the nerves under the band.

Another objection to interrupting the time during which a limb is constricted by a tourniquet is one which has given me some thought. It is that at ordinary temperatures adequate metabolic exchange is maintained in a part only while flow is occurring in its capillaries. Temporary release of a tourniquet can be effective in supplying only one physiological requirement—the removal of accumulated metabolites; these must reaccumulate as the haemoglobin brought by the second and subsequent releases is reduced. I have come to hold the view that if the possibility of local trauma to nerves can be eliminated by the selection of a suitable tourniquet it is best to complete an operative procedure without releasing it, provided that at the termination of the operation time is allowed for the disappearance of reactionary hyperaemia before haemostasis is considered to be satisfactory and the wound is closed. The broad, soft segment of compression provided by the cuff of a sphygmomanometer is the method of choice. My experience leads me to believe that, provided that the tourniquet be properly selected and provided that the patient's arteries are normal, any undesirable after-effects of its use are due to ischaemia. They will occur only if the survival time for any tissue cut off from its blood supply is exceeded, and therefore should not happen after operations upon the limbs. In many peripheral operations a tourniquet is extremely useful, and sometimes it is indispensable.

Partial Ischaemia

The practice of securing *partial* ischaemia for operative procedures was sanctioned by Paré, who had the idea from Galen. Paré directed that vessels should be tied towards their "roots," and the technique was developed by various surgeons who had found that aneurysms could often be dealt with by tying the affected artery on the cardiac side of the aneurysm: in this matter surgical practice preceded physiological knowledge of the circulation of the blood. After the discovery of the collateral arterial circulation it was inevitable that attempts should be made to devise instruments which could compress percutaneously the artery feeding an aneurysm, without constricting the remainder of the extremity and so obstructing alternative arterial routes. This was obviously a technique which could be put to the test of experiment; and it was soon shown that local pressure exerted for four hours upon the radial artery of the horse led to the obliteration of the vessel by periarterial exudate.

This knowledge was applied to the treatment of aneurysms in man; but it has always been incomprehensible to me that it did not occur to anyone to test, on man, one very practical point—whether such concentrated local pressure could be endured. The literature abounds with reports of cases in which the method had to be abandoned because of the torture it occasioned. This is hardly surprising: one such instrument, employed by Sir William Blizzard, was supported on "the outer part of the knee and the great trochanter, a piece of steel passing from the one to the other; and to the middle of this a semicircular piece of iron was fixed, which projected over the femoral artery, having a pad at its end moved by a screw, by turning which the artery was readily compressed and the pulsation in the aneurysm stopped, without any interruption to the circulation in the smaller vessels. But, although this patient possessed unusual fortitude of mind and indifference to pain, he was incapable of supporting the pressure of the instrument longer than nine hours."

The method of proximal arterial occlusion by ligature or by clamp was subsequently adapted to the temporary control of arterial flow when a lesion requiring operation was so near the root of a limb that the application of a tourniquet was impossible; but as a method of providing a bloodless field it suffered from the considerable disadvan-

tage that, when a collateral circulation was well developed, even high temporary proximal arterial occlusion might not secure a worth-while diminution in total arterial flow: and it was in these very cases—for example, proximal arteriovenous fistulae in the limb—that a bloodless field was always desirable and indeed often indispensable. When a tourniquet could not be applied to a limb there was until recently only one satisfactory alternative method, and it was applicable only to the lower limbs: on several occasions in the treatment of both urgent and chronic vascular lesions I have used with complete success Macewen's method of compression of the abdominal aorta by the pressure of the closed fist of an assistant, a manœuvre which allows one to deal without haste with lesions involving the great vessels supplying the lower extremity.

Advantages of Induced Hypotension

It is not surprising that efforts have been made to secure ischaemic or partly ischaemic operative fields in the head and neck and in the trunk. My own experience has been confined to testing the usefulness of these efforts during operations on the trunk. It is obvious that in this region a relatively bloodless field can be produced only by some technique other than local—for example, by lowering the systemic blood pressure. Before describing briefly the technique evolved by my colleagues in anaesthesia, Dr. Gillies and his staff, I must first examine the question whether such hypotension is in the interests of the patient. There is no doubt that in the ischaemic field provided by induced hypotension the surgeon can perform an operation with great precision and speed, as a result of the ease with which structures can be displayed and identified. This is naturally for the good of the patient, who spends a shorter period with both *milieu intérieur* and *milieu extérieur* abnormal. Tissues can be disturbed with the maximum gentleness, and loss of blood is reduced to the minimum. On the other hand, before adopting any such hypotensive technique, the surgeon must be equally sure that certain hypothetical undesirable sequels will not occur.

First he must be certain that systemic hypotension of the duration proposed will not impair, temporarily or permanently, the function of any organ or any tissue, and particularly of any essential organ or tissue which is known to be unduly sensitive to ischaemia, such as the central nervous system, the heart, the liver, and the kidneys. Secondly, he must know that, after the period of hypotension is over, the return to normal of systemic blood pressure will not be followed by reactionary bleeding. It will be convenient to dispose of this second point by saying that in my experience the very bloodlessness of the field makes it easy to secure any vessel which may require occlusion, and that reactionary bleeding of sufficient degree to call for reintervention, or to complicate convalescence, has occurred in only 4 out of a total of 802 operations; in one case (haemorrhage from the middle sacral artery after excision of the rectum) it was fatal.

Thirdly—and Mr. Julian Taylor called my attention to this point—he must know that, especially in procedures which require large operative fields, sufficient circulation will be soon enough established after the wound is closed to provide adequate humoral defence-mechanisms against the multiplication and invasion of any stray organisms (whatever their origin) which may have gained access to it. In the method we use, the period of hypotension can be regulated by the anaesthetist, and can be shortened, if it be desirable, by the administration of such a drug as methylamphetamine hydrochloride. The total duration of the designed period has never exceeded three hours.

The first point—the general and local effects of hypotension—is of fundamental physiological importance. The integrity of any tissue depends upon its receiving an adequate quantitative and qualitative supply of blood. This is primarily a function of the cardiac output, which depends among other factors upon the maintenance of adequate total blood volume, a sufficient proportion of which reaches the heart through the great veins. Fortunately there is now a large body of evidence, derived from both laboratory and operating theatre, that, at least for the periods required for the completion of most ordinary procedures, the fall of blood pressure and reduction in cardiac output do not result in impairment of function of vital tissue, provided that full oxygenation is maintained: with the stipulation that one has—as I am fortunate to have—anaesthetists of physiological outlook and of great skill.

The Hypotensive Technique

In my unit the method employed by Dr. Gillies and his staff to secure hypotension has been the production of generalized vasodilatation by paralysing, with a spinal anaesthetic, the preganglionic fibres of the whole thoracolumbar sympathetic outflow; the precise details of the method have been recorded (Griffiths and Gillies, 1948; Gillies, 1950). This method has the advantages of combining analgesia and muscular relaxation with the hypotensive state.

The association of hypotension with extensive spinal anaesthesia was noted as long ago as 1928 by Koster, so that the method is not a new one, but one which, as so often happens, represents the application of an old technique refined by the methods so often used by Horsley—laboratory experiment and clinical trial. First, the effect on the experimental animal of ablation of the spinal cord, segment by segment from its caudal towards its cranial end, has been studied from the points of view of increase in local circulation in the limbs and of reduction in systemic blood pressure (Hermann *et al.*, 1936). The former occurs when the segments supplying preganglionic fibres for the respective limbs are removed, the latter when the destruction of these segments is nearing completion. Secondly, it is now known that preganglionic sympathetic fibres emerging from the spinal cord in its anterior roots can be blocked by a concentration of anaesthetic—for example, procaine—approximately one-tenth of that required to paralyse the motor fibres with which they mingle; thus it can be easily arranged that sympathetic paralysis is more extensive than the anaesthesia and muscular relaxation actually required for any given operation.

Peripheral circulation in the limbs and reduction in blood pressure have also been investigated in man by noting their values at suitable intervals while the level of analgesia induced by lumbar puncture was allowed to spread cranially (Sarnoff and Arrowood, 1946; personal observations). Sarnoff and Arrowood added the important observation that the fall in blood pressure was not increased by any procedure which paralysed the skeletal muscles. The fall in blood pressure is the result of vasodilatation, which affects both arteries and veins. Arteriolar vasodilatation reduces total peripheral resistance; venous vasodilatation increases venous capacity, reduces return flow to the right heart, and diminishes cardiac output (Shackman *et al.*, 1952). Whether this is of itself deleterious depends upon its effect upon the flow in the capillaries, which since Krogh's time has been recognized to be the essential nourishing and oxygenating stage in the circulation of the blood. When hypotension is not the result of loss of blood or of plasma—that is, when the blood volume remains at a normal level—it does not affect capillary circulation adversely: indeed, our anaesthetists find that the rapidity with which cutaneous capillary circulation is restored after local pressure is one reliable index of the general condition of the patient.

It has been shown in our unit that the oxygen requirements of the tissues are related to the state of unconsciousness, and not to the plane of anaesthesia, and that when the cardiac output is lowered during the period of hypotension it is still sufficient to provide an adequate supply of oxygen. Moreover, the dilatation of the smaller arteries and arterioles prevents the occurrence of the phenomenon termed by Krogh (1922) "plasma skimming," in which during contraction of the vessels their branches receive only the

peripheral flow of plasma, the erythrocytes as they pass in the axial stream escaping the mouths of lateral branches. Plasma skimming results in local anoxia.

The intracranial structures can be selectively protected from the effects of hypotension by maintaining a "head-down" position. The veins in the field of operation can be emptied by gravity by so placing the patient upon the operating table that this area is at a higher level than the rest of the body. A further diminution of blood pressure may be secured by arranging the patient in such a posture that blood is "pooled" in the legs: an advantage of this arrangement is that, if the need arises, by elevating the limbs some or all of this pooled blood can be rapidly returned to the circulating component of the blood volume.

The orthodox view is that filling of the coronary arteries is maintained at a pressure which is the mean of systolic and diastolic pressures. In the hypotensive stage, in which we aim at a systolic pressure of approximately 60 mm. of mercury, the pressure available to fill the coronary arteries is greatly reduced; and, when atropine is not given before operation, paralysis of their sympathetic innervation exposes them to the unopposed constrictor action of the vagus nerves. Nevertheless, we have never found any clinical evidence at or after operation that, at least after periods of hypotension lasting up to three hours, the myocardium suffers any damage. Nor have we seen clinical evidence of hepatic damage; we realize that it is difficult to be sure of this, and consequently have seldom used the hypotensive technique in cases of known or suspected hepatic insufficiency. On four occasions we have encountered oliguria for 36 hours, after which normal urinary output was restored. We encountered four fatal cerebrovascular complications in a series of 16 patients who were operated upon for malignant hypertension; these operations were undertaken as a last resort. It is quite possible and even probable that the hypotension contributed to this complication, but not absolutely certain; we have had a similar complication appear in cases operated upon under a different technique of anaesthesia, by which every care was taken to maintain the blood pressure during operation at its preoperative level.

Other Ways of Producing the Hypotensive State

The hypotensive state may be induced by certain other methods. Hypotension follows the administration of suitable doses of ganglion-blocking drugs such as hexamethonium (Paton, 1952); the state produced is somewhat similar to that after the spinal blockade of preganglionic fibres, in that the blood volume is not reduced. In ganglion-blockade hypotension the blood pressure may be influenced by changes in posture and by the administration of sympatheticomimetic drugs such as *nor*adrenaline; obviously, additional provision must be made for analgesia and for adequate muscular relaxation. According to another technique, blood is removed by arteriotomy and returned to the circulation by intra-arterial transfusion as and when required (Gardner, 1946). In this method bleeding in the field of operation is reduced as a result of the general vasoconstriction which follows the abstraction of large quantities of blood from the circulation; in my view intense general vasoconstriction increases anoxia as a result of plasma skimming by the terminal arterioles.

The production of an ischaemic field in the trunk by the employment of a hypotensive technique should not be routine even when both anaesthetist and surgeon are familiar with it, although it provides conditions so favourable that I for one must regularly remind myself of this. It is unsuitable for the elderly and for those suffering from organic cardiac disease. The surgeon must take the greatest care to control what bleeding there is, and must remember that any loss of blood is badly borne by patients in the hypotensive state, especially if it be a rapid loss consequent on some unforeseen operative complication. Any such loss should be at once replaced by transfusion: usually transfusion is not required, and indeed one advantage of the method is that it reduces demands upon the transfusion service. I regard hypotensive anaesthesia, when used with judgment, as a major contribution comparable to the introduction of the safe tourniquet.

Cooling Technique

Earlier I emphasized that in ordinary conditions and at ordinary temperatures each tissue had a minimum requirement of oxygen. This oxygen requirement is not always a fixed one: thus in man it can be lowered by producing a state of unconsciousness, and in many other animals it is drastically reduced during states of hibernation. It would be of great physiological interest, and possibly of clinical importance, if methods could be devised by which an organism could be brought into a condition in which its requirements of oxygen were reduced to a level so low that its tissues would withstand abnormally long periods of ischaemia without any subsequent interference with function. The first stages of an investigation of this speculative kind must obviously be carried out in the experimental laboratory; and a possible approach is the application of the knowledge that the speed at which physico-chemical reactions (and therefore metabolic processes) are completed is retarded by reducing the temperature at which they are occurring. Much highly important fundamental work on these lines has been originated in Toronto by Bigelow and his co-workers (1950), who have subjected dogs to surface cooling; they found that their animals did not develop an oxygen debt.

In the Wilkie Surgical Research Laboratory in Edinburgh, Dr. Delorme (1952) has cooled dogs by passing arterial blood through an extracorporeal cooling system and returning the cooled blood to a vein. By this procedure the temperatures of the animals were stabilized at between 22 and 26° C., the normal temperature of the dog being 38° C. At temperatures of this order he found that tissues such as those of the central nervous system and the viscera could be completely deprived of their blood supply, as by a tourniquet, for periods in excess of those lethal at normal temperatures, and that without any transient or permanent evidence of loss of function. As Delorme remarks, a combination of the hypotensive and cooling techniques has many possibilities in facilitating and extending surgical procedures, particularly perhaps those employed in cardiac surgery. This work is continuing: there are some technical problems and clearly many physiological problems still to be investigated.

These, then, are some aspects of desirable ischaemia. Some are long-established as useful, some only recently so: still others have to prove their applicability to practical surgery. All have lent themselves to the combination of investigation and trial in both laboratory and clinic which was so faithfully pursued by Horsley throughout his professional life.

UNDESIRABLE ISCHAEMIA

For the remainder of this lecture I shall deal with certain aspects of ischaemia which are known or suspected clinically, and about the genesis of which fundamental information is almost completely lacking. Any observations I make must therefore be highly speculative, and confined to generalities.

It is well known that the local reaction of any tissue to noxious stimuli—which include incisions made by the surgeon's knife—is made up of two main components (Lewis, 1927). These are: (1) at the site of application of the stimulus, dilatation of minute vessels and swelling which results from the outpouring of plasma from capillaries; and (2), in the vicinity of the site of the stimulus, a "flare" which results from dilatation of the neighbouring arterioles, a dilatation mediated through an axon reflex involving local sensory nerve fibres. Both these components are factors in the humoral mechanism of tissue-defence and tissue-repair. When the lower sensory neurones supplying an area have been interrupted—or, to be more accurate, after they have

undergone Wallerian degeneration—the flare no longer occurs when a stimulus is applied to the denervated area. Thus even when the blood supply to such an area is intact its tissues may be regarded as relatively ischaemic so far as local defence and local repair are concerned*; and this is the minimum degree of ischaemia which can be recognized clinically.

This lack of completeness of the local vascular reaction no doubt accounts for the indolent appearance so characteristic of the small cutaneous lesions which may occur in an area of anaesthesia resulting from the division of a peripheral nerve. The same appearance is seen in the ulcers of the face which may occur after section of the posterior root of the trigeminal nerve, although in such circumstances the peripheral sensory axones are still in continuity with their parent cells in the Gasserian ganglion: it would seem that, in these circumstances also, the functional capacity of peripheral axones is seriously impaired, if not abolished (N. M. Dott, 1952, personal communication). Professor Dott has found that the appearance of such facial ulcers may be prevented by preliminary cervical sympathectomy, and that, if one is present, rapid and permanent healing is assured after cervical sympathectomy. In such cases the primary operation of posterior root section does not interrupt the vasoconstrictor fibres destined for the face. which reach the skin supplied by the trigeminal nerve by way of the periarterial plexuses round the branches of the external carotid artery. On the other hand, when a peripheral nerve is divided, the vasoconstrictor fibres which are ultimately distributed by way of its sensory branches are interrupted: the denervated part remains warm until Wallerian degeneration has occurred, and thereafter is consistently colder than normally (Richards, 1951).

This peripheral sympathectomy does not seem to reduce the incidence of cutaneous lesions in the denervated area or to favour their repair. In such an anaesthetic area, what modification, if any, occurs in the healing of lesions, accidental or made by the surgeon, as a result of the curtailing of the vascular response to injury? From a not inconsiderable experience of such cases I agree with the view that the process of repair is retarded. A somewhat similar problem is posed when amputation becomes necessary in a lower limb, the distal parts of which are anaesthetic as a consequence of congenital lesions of the cauda equina. In such cases it is, I believe, wise not to include anaesthetic skin in the flaps. I do not base this view on the inevitable instability of the anaesthetic skin when it is ultimately sheathed in a prosthesis. Even when complete protection is afforded to the original wound by encasing the stump in plaster-of-Paris, its union is slower than normally, and its edges are more apt to show localized patches of necrosis in the neighbourhood of stitches. Lumbar sympathectomy will improve the blood supply to such anaesthetic areas, because their vasoconstrictor fibres join the peripheral nerves which supply them distal to the level of interruption of their sensory fibres.

Although we may attribute them to relative ischaemia, we are quite ignorant of the ultimate cause of these variations in healing, and even of the stage or stages at which the delay in healing occurs. Thus it may be that the initiation of the process of repair is delayed, or that the ultimate production of collagen fibrils and the return of fibroblasts to the resting phase is postponed. It is true that in man (although not in many other animals) the end-stage of repair of many tissues is often fibrosis; but in the majority of clinical cases this is the direct result of impairment of blood supply from organic arterial disease, whereas in the conditions to which I have been referring the vascular tree is normal, although its response to a demand for tissue repair is incomplete. Defects in a process so species-specific should obviously be studied by observations on man.

*Nevertheless accurate measurements of the temperature of the skin around such lesions (Doupe and Cullen, 1943) have shown that the purely local reaction leads to increased warmth.

Some Problems

There are many gaps in our knowledge of the more common problems which may confront surgeons in those forms of ischaemia which are due to definitive lesions of arteries—problems so numerous that I shall have to select some which have interested me most. First let me consider one aspect of acute diminutions of arterial supply. It has seemed to me that when there is no organic disease of the arterial tree the most striking recoveries after surgical relief from potentially dangerous situations have occurred in patients who have not ceased to grow, or have only lately ceased to grow: and in addition I should place in this favourable group young women who have recently borne children. This is a personal view, and a clinical view at that, and I realize that I cannot offer you scientific proof of it. Nevertheless I believe that it is not outside the bounds of possibility that these patients have something—call it what you will—circulating in their blood which potentiates the recovery and repair of ischaemic tissues to a degree not found in other groups: including, for example, the reduction of loss of tissue to an unexpected minimum and the taking of skin grafts placed upon indubitably ischaemic areas. This is the sort of hypothesis that might come to trial; and, if it prove to be soundly based, might be found to depend upon some asset of a general biological nature common to animals—including man—at these stages of life.

When I come to consider chronic and acute-on-chronic ischaemia I must confess that again we lack much fundamental information. In most situations man is so overarteried that arterial obstruction may progress unnoticed until—and perhaps suddenly—the supply of blood is reduced below minimal requirements. The results of this reduction range widely from death of the individual to death of a small block of tissue. We are still two stages distant from having complete knowledge of the whole process.

The penultimate stage is the ability to recognize ischaemia before it is clinically evident. It is true that in the case of the limbs, which are the most accessible for such measurements, we now have instruments of precision such as plethysmographs which greatly increase the delicacy of estimations of the blood flow. Yet we have still to apply to the problem the method of mass observation, introduced to the profession by Jenner, in which a sufficient sample of the population would be observed over a sufficient length of time in order to determine the earliest change measurable by the apparatus at present available.

The ultimate stage, which may and probably does follow the penultimate after a considerable interval, is the determination of the pathological physiology which initiates obliterative processes in the arterial tree, the established morphological details of which are well enough known. As Leriche has said, the initial changes are so minute that they are probably of an order at present undetectable. Indeed, the search must be to some extent a blind one, for we do not really know what to look for. Any investigation on these lines must also take cognizance of many variables—for example, the appearance of degenerative processes in infancy, the beginnings of which must be during intrauterine life; and the strange immunity to degenerative changes possessed by certain vessels, such as the peroneal artery of the leg and the interosseous arteries of the forearm, whose ageing, if ageing it be, is so much slower than that of arteries running within a centimetre or two of them. When we acquire this information, our next objective should be to find some way of preventing the changes in the walls of arteries which sooner or later lead to the presentation to blood, as it circulates, of mural areas which favour thrombosis, with all its possible disastrous sequels—loss of intellect and power, loss of cardiac muscle, loss of limb.

Although this must remain the correct objective, if we were able to detect pre-ischaemia, and if we had the opportunity of looking for examples of it in the population, we might possibly reduce the number of clinically evident cases,

and mitigate the severity of those which do occur, by by-passing the morphological issue and, as an expedient, raising to prophylactic levels the amount of anticoagulant substance derived from humoral sources normally circulating in the blood. At the present time this is possible experimentally: when introduced into the portal circulation, curare increases the output of heparin from the liver. Unfortunately, even if a suitable pharmacological preparation were available, therapy of this kind would need to be continuous, for we do not know whether a tendency to clotting—"pre-clotting"—precedes episodes of thrombosis by a long period or a short one. Moreover, investigation along such lines might not commend itself, because on occasion clotting is a valuable protective mechanism, and to suggest its abolition transgresses a clinical precept which is usually sound enough—that one must never try to correct one pathological process by substituting another; although in this particular problem I should not subscribe to that view.

Conclusion

I fear that, by selecting so vast a subject as ischaemia to be the topic of this Memorial Lecture, I have been constrained to be so eclectic that it may seem to lack continuity. If that be so, the fault is mine.

While I was engaged in preparing the address, more than once I had the feeling that here was a matter on which I should have liked to enlist Horsley's advice and help. I venture to repeat that the lecture has been designed to illustrate that oneness of the laboratory, the ward, and the operating theatre so well exemplified by Horsley's life's work. Indeed, there is something more than oneness. For there is holism in surgery as well as in philosophy—the tendency for the final accomplishment to be greater than the sum of the contributions from each of these three arbitrary divisions of our efforts.

To few in our profession have been given those twin gifts without price: the genius to produce ideas, and the steadfastness of purpose to pursue their ideas as ideals. Such a one was Victor Horsley.

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Two new American journals were published in January, —*Applied Microbiology* and the *Journal of Histochemistry and Cytochemistry*. The agents in this country are Messrs. Baillière, Tindall and Cox, and orders for the journals may be sent direct to them or placed with any bookseller. Annual subscription for *Applied Microbiology* is 63s. post free, and the journal will be published bi-monthly. The other journal is the official organ of the Histochemical Society of America, costs 60s. per annum, and will also appear bi-monthly. The *American Surgeon* is the new name given to the *Southern Surgeon*, official publication of the South-eastern Surgical Congress of America, to mark its widened scope as a general surgical journal. It is published monthly, annual subscription 82s. Messrs. Baillière, Tindall and Cox are the British agents.

HEALTH OF PREMATURE CHILDREN FROM BIRTH TO FOUR YEARS*

BY

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AND

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This paper describes the health of a national sample of premature children who have been observed during the first four years of their lives and compared with a carefully chosen group of "controls." Details of their growth and development will be published in subsequent papers.

Some 40,000 of the babies born each year in Great Britain weigh at birth 5½ lb. (2.5 kg.) or less, and by international agreement are classed for statistical purposes as premature. Approximately a quarter of them die before they are a month old, and it has been claimed that many of the survivors, as a consequence of prematurity itself or of the antenatal conditions leading to it, are sickly, stunted, or mentally retarded. It is probable that in the future we will be able to save the lives of more of these babies, and it is important to know how large a proportion will be handicapped in later life and what institutional or other special care they will need.

At first sight it seems that these questions could be easily and directly answered by tracing in later life children who had been prematurely born. Many studies of this type have in fact been made, the majority being concerned with growth and development rather than with health. But the results have been conflicting. Some reveal prematurity as a major cause of mental backwardness and dwarfed growth, whereas others show premature children as retarded only to the extent that they were born before term.

The difficulties of tracing children after a lapse of years are great, and few investigators have found more than half the survivors for whom they were looking. Moreover, depending on the channels through which they have had to work, some appear to have been more successful in tracing the abnormal children and others in tracing the normal ones. They have also, in general, been content to compare the health and development of premature children with "national averages," often obtained many years earlier from highly selected groups and by methods differing widely from those used in their own inquiries. A few have compared premature children with a random sample of children born at term during the period of their inquiry, and others have compared each premature child with its sibs. None of these methods is satisfactory, because prematurity is not distributed at random in a series of births. Premature children tend to be female, to be first-born, to come from the poorer classes, and to have mothers who are above the average age for child-bearing. And unless they are

*This follow-up survey of premature children is being made by a joint committee of the Institute of Child Health (University of London), the Society of Medical Officers of Health, and the Population Investigation Committee. The chairman of the Committee is Professor James Young, the vice-chairman Professor A. A. Moncrieff, and the secretary Professor D. V. Glass. The Nuffield Foundation has financed this inquiry during the pre-school years, and a grant for continuing it in the primary school period has been made by the Board of the Hospital for Sick Children, Great Ormond Street, through the Institute of Child Health.