ASPECTS OF THE CIRCULATION'S ECONOMY*

BY

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Dr. Oliver's objects in founding these lectures in memory of Professor William Sharpey were "to promote physiological research by observation and experiment, and encourage the application of physiological knowledge to the prevention and cure of disease and the prolongation of life." With these objects I find myself to be in sympathy; they are, indeed, very much the basis of my own outlook, as they were of that of one of my heroes, Richard Lower (1631-91), Harvey's greatest follower in circulation studies in the seventeenth century. I would particularly stress physiological research by *observation*, much as I value and have indulged in its counterpart; for experiments too often disturb unduly the normal conditions and render difficult the assessment, from their results, of what *naturally* happens. Direct acquisition of knowledge by observation has been a feature of our science throughout the two millennia of its story, and it has become possible in recent times, as I shall describe more fully later, to extend such "zooscopy" (Franklin, 1933, 1949b) to many of the internal activities, including the blood's circulation, of the living body.

My choice of subject for these lectures would, I think, have appealed to both Sharpey and Oliver, for the latter's interest in the blood and its circulation is manifest in the titles of his book (Oliver, 1895) and of the papers which he published in the *Journal of Physiology* (Anon., 1928), while the former's main research contribution was on ciliary action, and the movement of mucus by cilia is part of the circulation in the extended connotation of that term which I shall mention below.†

Literature

The blood's circulation and the cardiovascular system within which it is effected have been my major research interests for nearly 30 years, and I have deemed it right to study the associated literature with some thoroughness, whatever the date of publication of any particular contribution may have been. This is not any purposeless devotion to medical history as such, but an attempt to "take out of the past all that is noble and good, and

to build on it for the future"; it is also an acknowledgment that the great men of earlier centuries can still, through their thoughts and attitude to our science, assist our progress to-day. In one instance in particular—namely, in connexion with our Oxford work on the foetal circulation and cardiovascular system (see Barclay *et al.*, 1944)—study of the literature produced not only the right outlook on certain vexed points, but also a list of queries and agenda which formed the basis of our next season's research. It also, in part, suggested my subsequent anatomico-physiological research upon the Eustachian valve (Franklin, 1948b).

Apart from the above particular indebtedness to historical studies, I should like to mention that they give one a correct perspective and thereby proper orientation. In the nineteenth century the main interest of the cardiovascular physiologist was in the heart and arteries; thereafter the small and the most minute vessels came more into the picture with the work of Ebbecke (1917), Dale *et al.*, Krogh,* and Lewis, the veins with the later work of Fleisch and Gollwitzer-Meier,† and arteriovenous anastomoses with that of Lewis and Grant and others. Experimental proof of the functional activity of blood depots, and of the consequent changes in circulating blood volume, dates essentially from Joseph Barcroft's work of 1922 and thereabouts.

More important, however, than this ever-expanding scope of blood-circulatory physiology is the realization that the blood circulation itself is but part of the vast continuous movement of the body fluids as a whole, a movement by means of which even the cell constituents are constantly being removed and replaced so that no individual remains exactly the same being from hour to hour, or even from minute to minute, however much he appears so to do to himself and to his fellows. I have recently (Franklin, 1951) written on this extended connotation of the circulation which we owe primarily to isotope researches carried out by the biochemists, so I will not say much more about it here. It has, however, corrected a progressive lack of balance between

*The first Oliver-Sharpey Lecture, given at the Royal College of Physicians of London on March 13, 1951.

†Carl Ludwig introduced the kymographic recording of blood pressure in 1847, and Sharpey used to show students and others how it was done by turning his top-hat round and imitating the movement of the float with a finger. The hat used to be preserved at University College, but I have not seen it since the recent war. My own copy of Harvey's *Opera omnia* (1766) has the inscription, "University College London. 1st May, 1840. To Mr. I. B. Carlill, in remembrance of the Session 1839-40. From W. Sharpey, M.D. Professor of Anatomy and Physiology." Sharpey (see Sharpey-Schafer, 1927, 17) studied classics at Edinburgh University before transferring to the Faculty of Medicine, and it is interesting that, from the Latin medical texts available in 1840, he chose Harvey's works for the presentation to his pupil, Mr. Carlill.

*Krogh's work on the capillaries is so neatly appraised by the words, *Ad augusta per angusta*, that I have no compunction in "lifting" the phrase from its original setting and context in Victor Hugo's *Hernani*.

†Sir James Barr in 1930 claimed some measure of priority in this new outlook. He wrote: "The objects of the circulation are to convey oxygen and nutritive material to the tissues, and remove carbonic acid and other waste products therefrom. I look upon the circulatory system as one unit, but although we have numerous books on diseases of the heart, it is only of recent years that much attention has been paid to the distributing tubes. When in 1906 I gave the address at the meeting of the British Medical Association in Toronto on the circulation viewed from the periphery it was generally considered that I had opened up a new vista. On many occasions I have dealt with the parts played by the arteries, arterioles, capillaries, and veins."

increasing knowledge of the activities of the blood-circulatory system and less rapidly increasing knowledge of the other fluid movements, and has led to a more integrated view of the whole.

Circulation of the Blood

Having stated that, and having duly stressed its outstanding importance for the proper appreciation of the functioning of the body in both health and disease, I may, perhaps, be allowed to confine my further remarks to aspects of the economy of one particular part of the whole fluid movements—namely, the circulation of the blood. The scope of such circulatory physiology (Franklin, 1948a) can be divided into four parts, concerned respectively with: (1) the blood flow in the embryo and foetus, and the changes which occur at birth; (2) the post-natal blood flow; (3) the blood flow, artificially transferred from one subject to another; and (4) the blood flow in tumours.

With item 3 above I shall not specifically deal. With respect to item 4, I had hoped, a few years ago, that it would be possible to study the circulation in tumours and to discover means by which it could be influenced so as to produce regression of the tumours without any serious disadvantage to the hosts. Dr. R. W. E. Watts and I subsequently discussed the literature and the problem with Professor A. Haddow and Dr. Eric Horning, of the Chester-Beatty Institute, and Dr. Watts made a very determined effort, with the use of two or three techniques, to get the answers. Unfortunately, the techniques proved inadequate and the problem remains. But I hope that some time, with fresh methods, this potentially important research may be resumed, and that it will "encourage the application of physiological knowledge to the prevention and cure of disease, and the prolongation of life."

Studies of the circulation of the blood have as their primary objective the acquisition of knowledge about the intact and unanaesthetized human being and lower animals at various stages of their lives, under all conditions from rest to full bodily activity, and over a wide range of variations in external environment. The knowledge required is as follows: (1) How, in what amount, at what speed, and at what pressure the blood is distributed to the various parts. (2) The various details relating to its passage through the tissues or to its by-passing of them. (3) Data about its return from the periphery (tissues, by-passes, and blood depots where such are present) and the reaction of the heart to such return.

As subsidiary objectives of medical and veterinary importance, we may add the above, as affected by: (1) disordered conditions of the body, (2) narcotics and/or anaesthetics, (3) the administration of other substances by various routes, (4) haemorrhage at varying rates and of various total amount, and (5) the transfusion of blood or of blood components.

The objectives in question, it must be admitted, have to date been only very imperfectly attained. On the other hand, study of the circulation was somewhat sporadic until little over a century ago, so the total research period has been relatively short; in addition, it is only during the last three decades or so that the number of those engaged in such research, the range of techniques, and the necessary financial support have increased to an extent at all commensurate with the vastness of the problems to be solved.

Another criticism which can justly be levelled at our present knowledge of the blood circulation is that it is, on the whole, too piecemeal—that is, that there are too few records of the conditions *simultaneously obtaining* in a large number of parts of the functioning cardiovascular system; the great majority of researches have dealt with isolated sections such as the coronary, pulmonary, and cerebral blood flows. It is true that Rein (1931), by applying thermistomuhurs to many blood vessels within each of a number of animals, made a step in the right direction; it is true also that Silfverskiöld (1938) made important contributions to knowledge of the blood volume and its distribution in a variety of conditions, and that certain other studies have given relatively extensive pictures of the circulation. Their total number, however, is as yet all too small, and additions to them are an urgent need.

Radiography and Cineradiography

This particular aspect of research is one which has especially appealed to me over a number of years. About 1931, when I was seeking for a method which would allow study of circulatory happenings without too extensive departures from the normal, produced by operative procedures, I noted in a reprint given me by my friend, Dr. H. M. Carleton, that the thoracic posterior vena cava of the cat was visible in radiographs (Carleton, 1929). That was before the effective introduction of radiopaque media, such as thorotrast, for intravascular injection, and for a while I made progress rather laboriously by a combination of radiography and anatomical dissection. By 1933, however, the contrast media were coming into use, and in that year I co-operated for the first time, indirectly, with Professor Robert Janker, of Bonn, who was the effective pioneer in cineradiographic studies of animal physiology and pathology. In January, 1934, I went to work with him, and few scientific experiences have been so exciting for me as my first view, upon the dazzlingly bright fluorescent screen of his apparatus, of the passage of the radiopaque medium from the point of its injection round through the blood vessels and the heart.

That was the first of many visits to Bonn, but in some ways it was the most important, for it led to the establishment within the West Wing of the Nuffield Institute for Medical Research, Oxford, of a centre in which, it was planned, all available radiographic and photographic techniques should be applied to medical research. I still have my original list* of the techniques I envisaged we might use; many have been employed in the Institute since its opening in 1935, even if one at least waited for a decade. Another has not been used in the Institute, but has recently been a success in the hands of Dr. D. A. McDonald and Dr. J. M. Potter in my department at Bart's.† Still others remain as yet unused, though potentially informative.

The point which I wish to make here is that cineradiography in its direct and indirect forms, and radiography as indicated, combined with intravascular or intracardiac injection of suitable contrast media, are for many circulation researches the techniques of choice, for they allow observation or recording with the minimum of

*It owed much to the help of Mr. P. Betton Done and Mr. W. Buckstone, of Messrs. Kodak Ltd., and of my technician, Mr. M. S. Tuckey.

†The use of the technique in question—namely, ultra-high-speed cinematography—was their own idea for recording features of the blood flow in the rabbit's basilar artery. At the Institute I had thought of using the method on studies of the origin of the mammalian heart-beat.

departure, through operative procedures, from the normal.*

From 1936, when the leading British research radiologist, the late Dr. A. E. Barclay, came to the Institute in an honorary capacity, we had the use of all the cine-radiographic and radiographic techniques to which I have referred† and circulatory studies, *inter alia*, profited, the first major one being that on the foetal circulation and the changes which occur during, and shortly after, birth (Barclay *et al.*, 1944). Its origin was to some extent fortuitous. I had been to Bonn on yet another visit, and had brought back with me a section of film, made in co-operation with Professor Janker, showing the passage of radiopaque blood through the dog's heart. I offered to project this as an extra demonstration at a meeting of the Physiological Society, and it there followed an ordinary film, made by Sir Joseph Barcroft and Dr. D. H. Barron, of the intrauterine foetal movements. At the time these Cambridge workers were trying to establish the moment of occlusion of the ductus arteriosus, and the accidental juxtaposition of our films in the Society's programme suggested to Dr. Barron that cineradiography might solve their problem. In the outcome the research not only did that, but also gave the larger story of which the functional closure of the by-pass in question forms but a part.‡

The next major circulatory research, which resulted in our *Studies of the Renal Circulation* (Trueta *et al.*, 1947), had as its curtain-raiser the preliminary studies of Barnes and Trueta, carried out in 1941 in relation to war injuries, but not then completed because of the suddenly increased wartime demands made upon surgeons' time. The later research was discussed by Drs. Trueta and Barclay and myself one Sunday night in Oriol Senior Common Room, and was planned to be a comprehensive study of direct, central, and reflex nervous effects upon all radiographically accessible parts of the functioning cardiovascular system (Trueta, 1945). Before it became diverted to the renal circulation in particular, it yielded information about the events occurring simultaneously within the greater part of the rabbit's circulatory system—that is, it gave the sort of wider picture to which I have above referred. Some of its renal results are mentioned later. Meanwhile, I would add that, as before, the radiographic studies were reinforced by related anatomical, though this time microscopical rather than macroscopical, ones.

After leaving Oxford in 1947 for Bart's, I was without the techniques which I had enjoyed at the Nuffield Institute, but I still wished to study the circulation as a whole as well as piecemeal. It seemed to me that I might possibly accomplish the former, though gaining only one picture per animal used, if I could inject intravenously a dye which did not diffuse at all rapidly from the blood, could therefore inject a coagulant which would not seriously alter the blood distribution,

*It is rather like what happened in a dream experienced by Professor U. Ebbecke, of the Physiological Institute, Bonn. In a field he saw a girl with an animal which was transparent; the blood vessels were all visible and he could see the blood go "whoof" round the various organs. He thought he would like to have such an animal (it was a sort of marmot) for himself, so he asked the girl where she had got it (as she said her father would not let her part with that one), and ordered one for himself. But, when his animal came, it was of the common variety, and his disappointment was not ordinary.

†He brought the direct apparatus invented by himself, and while at the Institute devised and made an indirect one.

‡History and comparative anatomy made not inconsiderable contributions to the research, and we were greatly indebted to Dr. (now Professor) E. C. Amoroso for his great and disinterested help in respect of the structural studies.

and, finally, could fix the specimen and prevent further change. With 5% Evans blue in the dosage of 1.5 ml. per kg. as the dye, "stypven" (Russell viper venom) in the dosage of 1 mg. per kg. as the coagulant, and 5 or 10%* formol as the fixative, this has proved a useful technique for a number of purposes, especially to corroborate or expand results obtained by other means, but it is not yet perfect; in particular, the dye tends to diffuse *post mortem*.† Fast thrombin, another coagulant which I have used, is less satisfactory because it can provoke vascular reflexes.

Differential Distribution of Available Blood Volume

After that long but necessary introduction I pass to a major theme—namely, the differential distribution of the available blood volume under a variety of circumstances, and the mechanisms by which such differential distribution is effected. Gollwitzer-Meier (1931) wrote that the regulation of the blood flow serves to adapt the blood supply of the organs to their needs; similarly, Fleisch (1935) wrote that its object is to ensure that each tissue has brought to it in each moment of time the exact amount of blood necessary for its activity. With certain qualifications‡ this view is acceptable for physiological conditions, but in a number of pathological ones parts of the body may have their blood supplies severely reduced while others continue to receive more or less their normal allowance.

Before, however, proceeding farther along this line, I have to note that the differential distribution of the available blood volume has been envisaged in two senses. In one of these it is the anatomical allocation of the blood volumes between the heart and the various vascular territories, in the other it is the physiological apportioning of the total cardiac output as *blood flows* to the different tissues. The anatomical picture is to some extent linked up with the physiological one, but a particular vascular area can obviously be fairly full of blood without the flow through it being marked, and vice versa. Unfortunately, measurement of flow is technically difficult, and objection can be taken to many of the procedures as introducing unphysiological conditions. Indeed, despite certain drawbacks, the answers given by timing the cineradiographically recorded progress of contrast media, and multiplying the distances travelled by the cross-sections of the vessels determined (on the assumption that they are circular) from their calibres, are often preferable to the answers given by thermostromuhrs and other measuring devices.

Blood Depots

Be that as it may, we can begin by examining what I have called the anatomical blood distribution; and first I would mention the content of blood found or estimated to be in the blood depots (see Franklin, 1937). In the dog the only unconditional one—namely, the spleen—can contain the equivalent of up to 20% of the total blood volume, but in other laboratory species the percentage is lower, and in some very small indeed. In the dog, Grab, Janssen, and Rein (1929) considered that the liver's contribution (released through the activity of the hepatic venous sluices) could exceed

*5% for macroscopical, 10% for microscopical, purposes.

†In the earlier researches I had the co-operation of my friend Professor E. C. Amoroso, and I should like here to acknowledge his help. I was also indebted to various members of my departmental staff for investigations of particular points, and am likewise grateful to them.

‡I am thinking here mainly of the capacities of some tissues for accumulating a temporary oxygen debt.

that of the spleen, but Silfverskiöld (1938) found this idea unacceptable; he was also unable to accept earlier estimates of the capacity of the splanchnic area. Barcroft gave the maximum content of all the depots in the dog, were they simultaneously full, as 46% of the total blood volume, but this was the result of an addition sum rather than a direct experimental determination of their combined simultaneous storage capacity.

With regard to man, the depots which have been mentioned have been chiefly the spleen, the subpapillary venous plexus of the skin, and the hepatic venous portion of the liver vasculature. Belief in this last as a possible blood depot is based solely upon anatomical evidence of "sluice mechanisms," similar to the dog's but much more rudimentary, at the exits from the hepatic veins into the vena cava. The subpapillary venous plexus over the whole extent of the skin would not, in Barcroft's view, contain more than 0.5 litre of blood. The spleen, according to the same authority (personal communication), could discharge up to 0.5 litre of concentrated corpuscles,* that is, double what Eppinger and Hueck estimated. Finally, Barcroft regarded 1,800 ml. (Wollheim's estimate of the skin depot's capacity alone) as being a maximum for the capacity of all the human depots together.

Since those statements were made, other evidence has been advanced suggesting that in man there are *no* appreciable reserves of blood or blood cells subject to emergency mobilization. Parson *et al.* (1948), who quoted four references in support of the changed outlook, themselves found no significant change in the plasma or red-cell volumes, as directly measured by the T-1824 or ³²P techniques, after subcutaneous injection of 1 mg. of adrenaline. I imagine their conclusions affect only one's belief in the human spleen as a potential blood donor of consequence; and even in respect of that organ one would like to see them repeat, with their more modern techniques, the temperature-change experiments described by Barcroft in 1925.

With regard to mammals other than man, the account given above is derived from separate studies of individual depot functionings, and against it we have to set the findings of Silfverskiöld (1938), who studied the anatomical blood distribution *as a whole*, his main subject being the mouse, his subsidiary ones the guinea-pig and rabbit. He regarded the mouse body as consisting of a cranial portion and a caudal portion, with the diaphragm separating them. The cranial portion was subdivided into head and fore-part, the caudal portion into a middle part and a hind-part. As will be observed from his table, the head was found to contain about 10% of the blood volume at rest and during excitement, and 12% during muscular work. During excitement there was a transfer of 14% from the abdomen; this amount went mainly to the fore-part, but also to some extent to the hind-part, of the animal. Under the action of adrenaline the addition to the lungs was 3% and to the fore-part as a whole 11%; in consequence, more blood was in the portion cranial to the diaphragm than in the rest of the body together. Silfverskiöld's findings as a whole showed that the heart and its associated great vessels have the power to accommodate greatly increased amounts of blood under various conditions, while, on the other hand, being the parts

Silfverskiöld's Survey of Relative Distribution of the Blood Pigment Per Cent.

	Rest	Excitement	Work	Narcosis and Laparotomy	Ether Collapse	Adrenaline	Peritonitis
Head ..	10	10	12	14	8	—	13
Fore-part of body ..	35	44	—	36	37	46	24
— Lungs ..	—	—	—	6	4	9	—
Middle part of body ..	43	29	—	36	45	—	19
— Liver ..	—	—	—	14	25	—	—
— Intestine ..	—	—	—	5	3	—	—
Hind-part of body ..	13	17	18	16	10	—	15

mainly responsible for constrictive adaptations to haemorrhage. They also showed that the previously reported great variations in content of the intestinal vessels are largely mythical. With respect to the muscles, it was found that during activity the increase of blood in the two hind-parts, though these included half the musculature of the body, represented only 5% of the total. In the rabbit, despite the relative increase in the dimensions of the abdominal part of the alimentary canal, the blood content of the intestinal vessels was still not more than 9–10% of the total, with this latter reckoned as 6% of the animal's body weight. The findings as a whole are most interesting, though it would be useful if corresponding studies were available for carnivores.

Cardiovascular Blood Distribution

Changes in the anatomical blood distribution within the various parts of the cardiovascular system, including intravisceral changes, are due in the main to nervously and/or humorally intermediated cardiomotor and vaso-motor effects. Among the more marked intravascular changes are those in the veins, which are not the passive, lifeless vessels they were commonly stated to be half a century ago, but in many instances extremely reactive tubes, often much more so than the corresponding arteries.

The intravisceral changes in anatomical blood distribution, where not caused by back pressure in the veins draining the organs, are due not only to contraction or dilatation of the supplying arteries before these have entered the organs, but also, in many cases, to altered apportioning of the blood flow within the viscera themselves. In many there are potential by-passes or short-circuits or short-cuts, and this is no novel concept, for Stirling (1891) used the term "short-cut" in respect of the intrarenal vascular system and circulation, and doubtless one could find much earlier examples of this trend of thought.

Locations of By-passes

Among the organs in which by-passes are stated to occur are the following:

1. *The Skin*.—The occurrence of arteriovenous anastomoses here is so well known that I need not give details.

2. *The Lungs*.—Von Hayek (1940) found, in the human subject, that there were numerous connexions between contractile branches of the pulmonary arteries and the bronchial venous network, and that in consequence there was ample provision for the by-passing of capillaries. In resting laboratory animals Sjöstrand (1934, 1935) reported a patchy lung distribution of intravenously injected indian ink, and I have myself found similar patchy distribution of Evans blue, etc., except when artificially induced asphyxia or hypoxia was necessitating full use of all parts of the lungs. As the

*The evidence was provided during the radiological screening of a patient in, if my memory serves, Cairo. At one point something went wrong, there was a sudden noise and/or flash behind him, and his spleen promptly contracted to an extent which was estimated at 0.5 litre. One would like further details, but the opportunity is, unfortunately, past for acquiring such.

distribution of the injected dyes is variable, one can presume that there are intrinsic mechanisms regulating the tours of duty of the different alveolar regions.

3. *The Stomach*.—Barclay and Bentley (1949) found, in the human subject, that arteriovenous anastomoses in the region of the submucous vascular plexus caused diversion of the blood flow away from the mucous membrane when the sympathetic nerve supply was active: mere handling of the viscus at operation could effect this. Walder (1951) injected glass spheres of 60–180 μ diameter into the fluid perfusing human stomachs removed at operation, and showed that, under various conditions, anastomoses many times wider than the capillary vessels were open. Barlow (1950), finally, by double injection techniques, demonstrated direct type anastomoses in the submucous connective tissue of human stomachs removed at operation or necropsy. Their calibres in fixed specimens were normally 40–60 μ .

4. *The Intestine*.—The villi theoretically need a good blood supply during digestion but not at other times, and mechanisms exist, as Spanner (1931, 1932) showed, for by-passing the capillaries as need arises. In one group, which includes man, the rabbit, rat, mouse, and bat, the arteriovenous anastomoses are within the villi themselves; there are interesting specific variations in the anatomical arrangements within the group. In the second group, which includes the cat, dog, pig, and horse, the anastomoses lie in the submucosa, and again there are specific variations within the group in respect of details. The overall functional implications are presumably similar in man and all the other mammals mentioned.

5. *The Liver*.—Daniel and Prichard (1951) gave a preliminary account of their findings in a number of species, and from it, while awaiting the fuller story, we may extract the following. "The angiographic studies," they wrote, "have indicated that generally the portal venous blood flow is distributed throughout the liver and passes through all the many pathways which exist from hilum to periphery. They have also indicated that on occasion this blood flow is short-circuited, and that in these circumstances the shorter of the intrahepatic pathways, situated in the more central and hilar regions of the liver, transmit the greater part or even all of the flow, whilst little or no portal blood circulates through the longer pathways at the periphery."

6. *The Kidney*.—In the mammalian organ, under a variety of conditions, there can be diversion of part or of the whole of the renal cortical blood flow (Trueta *et al.*, 1946, 1947), and the diversion has been noted in all the mammalian species investigated. During it a varying number of layers of cortical glomeruli, beginning with the outermost, are temporarily shut off from the renal blood flow, and simultaneously there is a variable degree of constriction of the main renal artery in its course from the aorta to the kidney. The conditions of occurrence include acute asphyxia of the subject, when the exclusion of glomeruli is nervously inter-mediated (Franklin, McGee, and Ullmann, 1949, 1951). The blood which would otherwise have gone to these cortical destinations may be diverted in its entirety to other parts of the body without entering the renal artery at all, for in some asphyxia experiments, simultaneously with the cortical paling, there has also been a reduction in the normal vascularity of the medulla, though some circulation was continuing through it and the renal artery was not fully constricted (Franklin, 1950). On the other hand, the vascularity of the medulla may on occasion be markedly increased (see Fig. 71, and cf. Figs. 22 and 23 in Trueta *et al.*, 1947) during diversion of blood from the cortex, and such findings led to the idea that the basal glomeruli, with their afferent and efferent vessels and the vasa recta into which these latter discharge, could be regarded as by-passing routes. Various other possible by-passes, differing from the above in short-circuiting capillary networks of any kind, have been described by anatomists (see Franklin, 1949a, 1950).

7. *The Uterus*.—Schlegel (1945–6) found "arteriovenous anastomoses" joining arterioles and venous lakes in the stratum functionale of the human endometrium; they were

present in increased number with advance in the menstrual cycle, so not unnaturally the author discussed their possible role in menstruation. According to Bartelmez (1947), however, they are non-existent in *Macacus rhesus*, so the basic mechanisms of menstruation cannot be dependent upon them (see also Reynolds, 1947).

The above list of locations of by-passes is far from comprehensive if one can rely upon the discoveries of arteriovenous anastomoses* reported *passim* in the literature. It does, however, detail some of the more important and better-documented ones, and it provides sufficient examples for my present purpose, which is to demonstrate that there are routes available for short-circuiting the blood flow to tissues which are temporarily inactive or for other reasons can, in the interest of the body as a whole, be rendered ischaemic over a period of time.

The one with which I have myself had much to do is the renal cortical by-passing, which can be brought into action in circumstances of stress in various mammals,† man probably included (Franklin, 1950), and which would provide the anoxic conditions necessary for the production of renin (Cruz-Coke, 1946; and personal communication, 1947) and of the vasotropic factor V.E.M., to which reference will later be made.

"Orders of Sacrifice"

In the Oxford studies (Trueta *et al.*, 1946, 1947), which led to the idea of a renal cortical by-passing, certain experimental procedures practised upon anaesthetized rabbits led to constriction of the femoral artery, abdominal aorta, and renal artery‡ in that descending order of severity, while the mesenteric artery remained unchanged in calibre or was slightly dilated. Haemorrhage, on the other hand, led to constriction of all the vessels studied, including the mesenteric artery, while a massive dose of adrenaline cut off all the parts supplied by the distal portion of the aorta, increased markedly the size of the heart, and caused widening, lengthening, and serpentine bending of the unconstricted portion of the aorta (see Fig. 13 in Trueta *et al.*, 1947).

These and other findings§ suggested to me in 1946–7 the idea of an order of sacrifice||—that is, of differential reduction of the blood supply to various tissues and organs in a number of circumstances. It also seemed to me that the incomplete order of sacrifice (skin, limb

*Either in Clara's (1939, p. 2) stricter sense (direct, regularly present communications between the arterial high-pressure and the venous low-pressure systems which by-pass the capillary circulation, and are characterized anatomically by their very specialized structure, and physiologically by their capacity for complete occlusion) or in the looser one employed by some writers (direct communications between the arterial and venous systems outside the capillary circulation). Schlegel (1945–6), for instance, used the term with the latter connotation.

†Professor E. C. Amoroso (personal communication, 1950) added the seal to those already known—the monkey, dog, cat, rabbit, rat, mouse, and guinea-pig—that is, all the laboratory animals so far tested.

‡In control subjects with the splanchnic nerves divided, the renal artery showed no constriction and the renal cortex remained throughout fuller of blood than normally, while the medulla was paler. The other vessels reacted as before.

§For example, those of Rous and Gilding (1929), who found in rabbits and cats that severe haemorrhage resulted in the skin, most of the skeletal muscles, the spleen, the omentum, and the bladder being largely deprived of their blood supply; on the other hand, the muscles used in respiration and in swallowing, the gut, the gall-bladder and liver, the pancreas, the red bone-marrow, and the pregnant uterus were adequately supplied. The authors attempted no detailed study of the kidney.

||This term contains a suggestion of teleology, so I should like to quote—via Professor Otto Loewi and Dr. W. Feldberg—from E. von Brücke the passage, "Teleology is a lady without whom no biologist can live. Yet he is ashamed to show himself with her in public."

muscles, renal cortex, central nervous system, and last of all the heart) which I then formulated* was perhaps the reverse of the order in which the parts developed their major demands for blood supply (gauged by their degrees of functional activity) during intrauterine and immediate post-natal life. The heart is busy from very early stages and, during the second half of mammalian gestation, is the only obviously active part in the otherwise lifeless-appearing foetus. The central nervous system, according to the findings of Barcroft and Barron in the sheep (résumé in Barclay *et al.*, 1944) attains functional activity progressively from below upwards; the demonstrable onset occurs about a fifth or more of the way towards full term, the nervous influences changing from excitatory to inhibitory, in respect of muscular movement, at about half-term. The renal cortex in many species is still not fully formed at birth,† and before birth excretory functions are subserved mainly by the placenta. Skeletal muscle, after its long period of intrauterine nervously induced quiescence, becomes visibly active at birth, and spikes appear for the first time in the electrical records. Finally, within a few days after birth the skin has settled down to its new duties; *in utero* it has no concern with temperature regulation, etc., and presumably its vessels are also compressed by the surrounding fluid.

While the orders of sacrifice still need much further research in respect of details, I do not wish to stress unduly this order of development, which is at present more hypothetical. It will, however, be most interesting if it is substantiated, for the changes effected slowly at the beginning of the individual's life-span will be shown to correspond in reverse with those often occurring, though usually more slowly, at its end. This will not only help to integrate the full story of the circulation's economy, but will be a guide to further research, as well as the basis for judgment with regard to points which are not readily open to elucidation by direct investigation.

Differential Reactivity of Vessels to Adrenaline

One of my interests since 1947 has been to test further the first hypothesis, and, as a simple beginning, I have collected extra evidence about the differential sensitivity of a number of the rabbit's arteries *in situ* to intravenously injected adrenaline. The rabbit was chosen for the earlier experiments partly because it is easy in this animal to note superficial kidney colour changes, partly because it was at the time the only species of reasonable size that was available in quantity. In the later experiments it was deliberately chosen to avoid the complications introduced, in respect of many other species, by discoveries about the part played by *noradrenaline* (see, for example, Schmitterlöv, 1948; and others). The medulla of the rabbit's adrenal gland contains mainly or exclusively adrenaline (Holtz and Schümann, 1950; West, 1951); this substance is also more important than *noradrenaline* in the rabbit for the transmission of autonomic impulses (West, 1951); finally, it definitely appears to be the transmitter in the case of the rabbit's ear vessels (Gaddum, Jang, and Kwiatkowski, 1939; Gaddum and Kwiatkowski, 1939): with regard to the other vessels I have so far failed to find any information.

*Since that time I have thought in terms of orders rather than of a single order.

†Extra layers of glomeruli are still being added on the outside except in those species in which the newborn animal sees, feeds, and moves about actively.

In the earlier experiments, carried out with the stypven-Evans-blue technique which I have described, I had the co-operation of Professor E. C. Amoroso, but the findings were not published as the work was not complete; nevertheless, it gave useful information as a basis for further studies. Recently, Miss Lindop, Mr. Pearce, and I reported to the Physiological Society the microscopically observed and measured reactions of various arteries to graded doses of intravenously administered adrenaline, and at the same meeting Professor R. H. S. Thompson and Dr. Tickner (1951) provided a complementary story. For they had found that monoamine oxidase was present in varying amounts in the walls of different arteries in the rabbit, and the increase in enzyme activity in their series corresponded, in so far as they and we had studied the same vessels, with the decrease in sensitivity to adrenaline in our series. Finally, I have done some more experiments with the stypven-Evans-blue technique, which has the advantage of indicating, by absence or intensity of coloration, the degree of blood supply to tissues; direct microscopical studies of the reactions of individual arteries give only part of the picture.

With regard to the work carried out by Miss Lindop, Mr. Pearce, and myself, I have to begin by saying that the dosages of adrenaline used were high because in general we decided to take full vasoconstriction as the end-point. In brief, the findings were that the ear arteries required 10 $\mu\text{g. per kg.}$, body wall arteries 20 $\mu\text{g.}$, the femoral artery 25 $\mu\text{g.}$, splenic artery 40–45 $\mu\text{g.}$, renal artery 50 $\mu\text{g.}$, small gastric and intestinal branches usually 100–120 $\mu\text{g.}$, and internal carotid artery 100–120 $\mu\text{g.}$ The vertebral artery seemed to be in the same class as the internal carotid or to require somewhat higher dosage, and technical difficulties made it impossible to see if the blood flow was completely arrested. A posterior spinal artery was very refractory and remained incompletely closed, though its branches were fully constricted, with as much as 200 $\mu\text{g. per kg.}$ The coeliac axis and superior mesenteric artery gave the most varied reactions, dilating or remaining unaffected or constricting, the extremes being slight constriction of the mesenteric artery in one subject with only 5 $\mu\text{g. per kg.}$, and no effect upon either vessel in another subject with 300 $\mu\text{g. per kg.}$

Order of Reduction in Blood Flows

The new stypven-Evans-blue series has on the whole given comparable results, though in infinitely more detail, as the distribution and intensity of dye-staining throughout the body were noted. On the whole, the two different techniques indicated an order of reduction in blood flows in which the skin and the non-vital skeletal muscles were the first parts to suffer; later came the spleen and the renal cortex, and, very late, the brain and spinal cord. The different parts of the alimentary canal, however, as also a number of other viscera, showed considerable variations from animal to animal, and on occasion some were still within the circulation when the central nervous system was out. Control stypven-Evans-blue experiments without adrenaline showed that variations were possible in the differential staining of the alimentary canal and other organs, and one presumes that in respect of the former these variations can be correlated with degrees of digestive and absorptive activity.

In the human patient, however, as I shall mention later, there is not in general a preferential blood supply

to viscera while the central nervous system supply is reduced, and the anomalous findings mentioned must be ascribed to the fact that the experiments were done on healthy anaesthetized subjects. In other words, the problem put to the body as a whole—namely, how it would deal with a full blood volume when the skeletal musculature was generally inactive, and adrenaline, often in high dosage, was introduced was fundamentally an unfair one. As Rothlin (1920) and many since have shown, isolated or perfused mesenteric and several other visceral arteries react to adrenaline by constriction; that on several occasions in our experiments they were irresponsive or dilated must mean that they were nervously inhibited or, though this seems on other evidence less likely in the cases of certain vessels, that their natural tendency to contract was overcome by the raised blood pressure.

Studies of animals after haemorrhage and during shock of various kinds much more closely imitate the conditions met with in patients, and experiments already mentioned, as well as others described in the literature, show that during haemorrhage the arteries, with some exceptions, constrict; certainly the mesenteric ones do so. Further, the liver seems to come more definitely in place in respect of reduction of blood supply; it appears to follow after the renal cortex, in Van Slyke's (1948) view, for he found "that in the dog, the function of the kidney is abolished by haemorrhage before that of the liver." Delorme (1951), however, took the line that the liver may be earlier or more gravely damaged than the kidney in vasoconstrictive states. It is, he wrote, "more susceptible to anoxia than either muscle or kidney (Russell *et al.*, 1944); although less sensitive than the cerebral cortex, it does not possess the protective circulatory adjustments of the latter (Gellhorn, 1943); moreover, the liver is unique among body tissues in that it depends on venous blood for the larger part of its oxygen supply."

[The second lecture, with a list of references, will appear in our next issue.]

The 27th Annual Report of the British Empire Leprosy Relief Association (1950) announces that since January five more lay workers and two nurses have been sent overseas. Five years ago B.E.L.R.A. resolved to recruit six doctors for overseas work, but so far only one of them has been appointed; in more than one area the progress planned has been frustrated for lack of medical supervision. Especially in East Africa the field is open. B.E.L.R.A. is aiming to help to the utmost in the establishment and staffing of leprosaria planned at key points and in the development of those selected for expansion. Lay workers are available, but some of the schemes may well have to be further postponed unless doctors and nurses can be found. The organization has always aimed to save the children before leprosy destroys them, and at the end of 1949 there were 1,500 B.E.L.R.A. adoptees. Dr. Ross Innes (Inter-territorial Leprologist for Kenya, Uganda, and Tanganyika) has completed a massive survey and made recommendations; on the basis of an examination of 362,000 persons throughout the area he estimates an incidence of 80,000 cases in Uganda, 35,000 in Kenya, and 100,000 in Tanganyika, with an average of 10 per 1,000 in Kenya, and 18 in the other two territories. As yet only 6,850 of them are receiving treatment. The report also notes that in Britain the outstanding achievement was the collection of almost £13,000 from the appeal broadcast by a cured leper in January, 1949, and when an anniversary letter was sent the following year to all those who had responded to the appeal, over 25% again contributed.

LOW-SALT DIET IN TREATMENT OF CONGESTIVE HEART FAILURE*

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Up to the turn of the century a diet low in sodium chloride was used most successfully in the treatment of oedema and other symptoms of congestive heart failure (Karell, 1866; Strauss, 1903; Widai and Lemierre, 1903; Finsen, 1904). After the introduction of mercurial diuretics the low-salt diet was used much less because these diuretics were more dramatically effective and easier for the patient than the slow and complicated treatment by dieting. In the English-speaking world in particular (Lewis, 1933; Levine, 1940; White, 1947) it became usual to treat cardiac oedemas with only a moderate or casual salt restriction and with mersalyl ("salyrgan") and a restricted fluid intake. Although many German (e.g., Volhard) and French physicians continued to treat their patients with the low-salt diet, Allen (Allen and Sherill, 1922) seems to be the only American in recent times to have done so on a large scale, and his chief interest was the effect of the salt restriction on hypertension.

During and after the last war, however, the tide again changed, and now great importance is attached to the usefulness of a low-salt diet, and very intensive research is being carried out to investigate the importance of sodium chloride or sodium to the physiology of the organism. This new development began with the publication of a number of clinical reports by Schroeder (1941), Schemm (1942), and Kempner (1944). The results of their investigations have received universal recognition (White, *et al.*, 1946), and have been supported by physiological and pathological investigations on the pathogenesis of congestive heart failure by Warren and Stead (1944) among others.

Schroeder demonstrated in 23 cases of cardiac oedema that a decrease in the consumption of salt to an amount less than the salt content of the urine was always accompanied by a decrease of oedema. Furthermore, he showed clearly that the low-salt diets hitherto used were not sufficiently low in salt, and that a limitation to 1 g. in twenty-four hours was often necessary to achieve a decrease of oedema or merely to prevent its increase. He also demonstrated the very interesting point that a decrease in the amount of the fluid intake on such a low-salt diet had no effect in decreasing the oedema—in fact, in some cases oedema disappeared more readily when the patient was given more water. In 1944 Schemm's second report gave the results of eight years' treatment of 241 patients with oedema, 90% with cardiac oedema. He successfully used a low-salt, acid-ash diet together with a larger intake of water, if possible 3–4 litres a day. Finally, Kempner (1944) in his study of the effect on hypertension of a diet

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*This work was supported by a grant from the King Christian X Foundation.