ADVENTURES IN PHYSIOLOGY AT QUEEN'S UNIVERSITY, BELFAST, IN WORLD WAR II

by

PROFESSOR HENRY BARCROFT, M.D., F.R.C.P., F.R.S.

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IN the autumn of 1939 William McKee Bonnar, a young medical graduate of exceptional ability, joined the Physiology Department to do research for an M.D. thesis. We discussed what he should do. Research was needed to see if the sympathetic supplied and maintained vasoconstrictor tone in the arteries in human muscles. It did in animals but was said not to in man. I said to Bonnar how nice it would be if one could record the blood flow through a human muscle, then cut its motor nerve supply and see if that increased the rate of the blood flow through the muscle. If so one could conclude that human muscle did have a sympathetic

![Diagram](image)

**FIG. 1. Apparatus for the measurement of forearm blood flow by plethysmography.**
innervation which mediated vasoconstrictor tone. Could this be done? Muscle blood flow could be measured in a segment of the human forearm by the plethysmographic method (Fig. 1). The motor nerve supply could be severed, functionally, by blocking the nerves with local anaesthesia. But then we saw a difficulty. Supposing the nerve blocks were followed by hyperaemia in the forearm. This might be because of release of sympathetic vasoconstrictor tone in the cutaneous vessels — only 65 per cent of the tissue contained in the segment of the forearm in the plethysmograph is muscle. Bonnar went away and thought about it. A day or two later he returned. He had looked up the anatomy of the forearm. Just above the elbow the nerve supply to the forearm muscles was in the radial, median and ulnar nerves (which would contain the sympathetic fibres, if any), these nerves did not supply the forearm skin. So Bonnar said: “If we block the deep nerves above the elbow, we should be blocking the nerve supply to the muscle vessels, not to the skin vessels, and if the blocks caused increase in forearm blood flow it would prove that the sympathetic nervous system did supply human muscle vessels and maintain sympathetic vasoconstrictor tone in human muscle.”

Bonnar’s idea sparked off research by himself, Edholm, Effron and myself. Edholm was Lecturer in Physiology; Effron an American qualifying at Q.U.B. It occurred to us that the blood flow in the forearm segment might be increased because of the emotional stress of the minor surgical operation of injecting local anaesthetic round the radial, median and ulnar nerves. Increase in forearm blood flow following the nerve blocks need not necessarily be due to paralysis of sympathetic nerve fibres. It would be better to record the blood flows in both right and left forearms simultaneously, at any given moment the effect of emotional stress would cause similar changes in blood flow in each limb. If the blood flow through the forearm with nerves blocked exceeded that in the opposite normal forearm, one could safely attribute the fact to the effect of the nerve blocks. A preliminary series of experiments was performed on six subjects in which the forearm blood flow were recorded for 35 minutes. The averaged results, expressed in ml blood flow per 100 ml forearm per minute, are shown in Fig. 2 (top right). One sees a gradual increase in flow, perhaps because the forearms were warming up. However the point is that at any given moment the blood flow (per 100 ml forearm) is the same in one forearm as in the other and that the blood flow in one forearm can be used as a control for the effect of a test procedure in opposite one.

Mr. Loughridge very kindly showed us how to infiltrate local anaesthetic round the radial, median and ulnar nerves. Novocaine was used in those days; to be effective a little adrenaline had to be added to keep the anaesthetic localized. Bonnar soon became an adept at doing the nerve blocks. When successful the muscles of the wrist and hand were paralysed for half an hour or more. Fig. 2 (top left) shows the averaged results of experiments on twenty-five subjects. Note that the rate of the blood flow through the nerve blocked forearm averaged about double that in the opposite control forearm segment. One such experiment was given as a Demonstration before a meeting of the Physiological Society at Cambridge in October, 1941.

So far so good. But did the result necessarily prove that the blood vessels to human muscle had a sympathetic vasoconstrictor innervation? Was there no other
possible explanation? There was one. Under certain conditions muscular contraction, by compressing the blood vessels within the muscle substance, opposes the passage of blood through the muscle. Now blocking the radial, median and ulnar nerves abolished 'tone' in the skeletal muscles of the forearm; was the hyperaemia following nerve blocks due to abolition of the restriction to flow caused by muscle 'tone'? This could be tested by recording the effect on forearm blood flow of blocking the deep nerves in a sympathectomized subject. Only the motor nerves would be blocked. If the blocks had no effect on forearm blood flow then the increase in flow seen in a normal subject after blocking must be because of blocking of their sympathetic fibres. The difficulty was that there were very few sympathectomized subjects available. Eventually we got the name and address of an elderly man living at Limavady—Mr. Samuel Anderson. He had had a unilateral sympathectomy for causalgia due to a wound in World War I. Bonnar and I went to Limavady and knocked at his door, which opened. As I diffidently strove to explain the object of our visit the door began to close. Just as he was about to disappear it opened a little. "Do you mean to come to Belfast for Research?" "Yes" I admitted. "Oh! I thought you'd come about my pension. Of course I will." Another unilateral sympathectomy patient, Mr. Frank McLaughlin, volunteered too. Blocking the
motor nerves in the two sympathectomized forearms did not increase forearm blood flow to above that in the opposite control forearms, as is shown in Fig. 2 (bottom left). That is to say removal of ‘tone’ by paralysis of the forearm muscles made no difference to muscle blood flow. It looked as if doubling of forearm blood flow after deep nerve blocks in normal subject could be due to release of sympathetic vasoconstrictor tone.

Once again so far so good. One doubtful point still had to be settled. Sometimes the local anaesthetic seeped outwards and anaesthetized one or more of the cutaneous nerves supplying the forearm skin. Could we be absolutely certain that the increase in flow after blocking was not due to release of sympathetic vasoconstrictor tone in the forearm skin? If we had been experimenting on an animal this question could have been settled by skinning the limb. If increase in limb segment flow followed nerve blocks in the skinned limb it would have been because of the removal of sympathetic vasoconstrictor tone from the arterial tree in the skeletal muscles. Impossible in man of course. Now, Professor D. C. Harrison, who had kindly been a subject for a nerve block experiment, suggested to us a way for ‘functionally’ skinning the human forearm. Namely by the electrophoresis of adrenaline into its skin to arrest the cutaneous circulation. The idea had come to him when reading an American article advocating the treatment of asthma by the electrophoresis of adrenaline into a large area of skin on the back. The electrophoresed skin looked white, and did not regain its normal colour for some hours; evidently adrenaline was absorbed slowly into the body, the author considered this way of administering adrenaline was better than by subcutaneous injection. Be that as it may, at any rate, so far as Prof. Harrison’s suggestion was concerned it served our purpose well. Fig. 3 shows the white skin of the forearm after adrenaline electrophoresis. Fig. 2 (bottom right) shows the averaged results of two experiments, in which the blood flow in the ‘functionally skinned’ forearm is compared with that in the opposite control forearm. Blood flow was doubled after nerve blocks in the functionally skinned limb. We believed that we had now proved that human

![Fig. 3. Blanching of the forearm skin after adrenaline electrophoresis.](image)
Muscle vessels did have a sympathetic innervation, and that the sympathetic in man mediated vasoconstrictor tone in our muscle vessels (Barcroft, Bonnar, Edholm and Effron 1943).

Professor G. W. Pickering (now Emeritus Professor Sir George Pickering, F.R.S.) was external examiner for Bonnar's thesis including these and other researches. Bonnar was awarded the M.D. with Gold Medal. But it ended tragically; Bonnar joined the R.A.F. and died in a flying accident in Asia.

It was now 1941, London was being bombed heavily. There were many casualties. Edholm happened to be on a visit to London at the time and to meet Professor McMichael, a member of the Medical Research Council's Shock Committee. McMichael and Sharpey-Schafer were about to begin a study of the effect of haemorrhage on the circulation in man. Cardiac output would be measured by cardiac catheterization, which they were the first to perform in this country, and they were to study the effect on cardiac output of bleeding the subject a large amount of blood, namely two bottles. Edholm then told McMichael about the finding at Q.U.B. of sympathetic control of the blood vessel in human muscle. As a result Edholm and I were invited to join McMichael and Schafer at the British Postgraduate Medical School during the Summer vacation to work with them and study the effect of massive haemorrhage on the forearm blood flow. Sir Edward Mellanby, the Secretary of the Medical Research Council, suggested that the Friends Ambulance be approached to see if their members would be willing to act as subjects for the catheter and to be bled two bottles of blood. About twenty volunteered. The experiments were done in the afternoon. After recording the effect of bleeding 2 bottles of blood on the cardiac output and forearm blood flow the blood was put back into the volunteer who stayed in hospital overnight and went home the next morning. The results recorded on the first two subjects showed nothing of much interest. And then it happened. During massive bleeding the third subject fainted. There he lay exsanguinated, unconscious, beads of sweat on his forehead, lips ashed grey—he looked like death—I was very frightened, I thought 'we've done it this time.' Not so Otto Edholm, he is made of sterner stuff, he just went on measuring the forearm blood flow. And just because he was (and is) such a skilled experimentalist, his attention was not to be distracted from the ritual of turning several glass taps in proper sequence, a ritual repeated every half minute for forearm blood flow determinations. The subject soon recovered. After the experiment calculations of the forearm blood flow showed a truly remarkable and totally unexpected finding. Forearm blood flow during the faint had increased. Now fainting is accompanied by a precipitous fall in arterial blood pressure as was well known. Fall in blood pressure accompanied by increase in forearm blood flow could only be explained on the basis of a marked vasodilatation of the forearm blood vessels. The existence of such vasodilation was quite a new finding. Was the vasodilation in the forearm an indication of a widespread vasodilatation in other parts of the body, so widespread as to explain the precipitate drop in arterial blood pressure?

We then searched the literature to see how the fall in arterial pressure during fainting had been explained. The drop in blood pressure is accompanied by marked bradycardia, as had been known for many years. Michael Foster, towards the end
of the last century, attributed the drop in blood pressure to sudden vagal slowing of the heart which he believed would be accompanied by marked reduction in cardiac output. Sir Thomas Lewis did not agree. He quoted experiments by Starling, on the dog, showing that slowing the heart to half its normal rate did not reduce cardiac output because the output per beat became doubled. Chance gave Lewis the opportunity to put the matter to the test. In World War I he had a clinic for the medical examination of recruits, and a number of them fainted when venous blood was taken for blood tests. As soon as he saw a recruit beginning to faint he injected atropine to stop the bradycardia. Preventing the slowing of the heart did not prevent the fall in blood pressure. Since the fall in blood pressure could not have been due to decrease in cardiac output, then it must have been due to peripheral vasodilatation. It was because of this that Lewis had introduced the now well known name ‘vasovagal syndrome’ for the faint, to denote vasodilatation and vagal inhibition of the heart occurring simultaneously, but not in a cause and effect relationship. Lewis left it at that. Beyond saying that fall in blood pressure was due to peripheral vasodilatation he did not go.

After reading Lewis’s work it occurred to us that the vasodilatation we had observed in the forearm in the faint was quite in accordance with Lewis’s postulated peripheral vasodilation.

It was not until the sixth experiment that another subject fainted. Again, the faint was accompanied by precipitate drop in arterial pressure, bradycardia and increase in forearm blood flow, unmistakable sign of vasodilatation in the limb segment. We were coming to believe that these faints, although very alarming, were not dangerous. Blood from enormous numbers of blood donors was being taken, dried and sent to the army in North Africa—about 4 tons of it. The incidence of fainting while giving blood was known approximately and a very rough calculation showed that some 25,000 blood donors must have fainted, without any fatalities so far as we were aware. Now it seemed clear that our most interesting findings were going to be the changes in the circulation during the faint. But the summer vacation was slipping away and for a subject when bled to faint was exceptional. Fortunately Sharpey-Schafer thought of a way of increasing the incidence of fainting. Wide pneumatic cuffs were placed round the upper part of both thighs and inflated to diastolic pressure for half an hour, a procedure that trapped about 750 ml of blood in the distended leg veins, a small venesection then induced fainting. The method had the considerable advantage, too, that releasing the cuffs returned the blood to the subject, obviating the tiresome sterile precautions needed for the transfusion of blood withdrawn by venesection. Fig. 4 shows results obtained in a typical faint. The averaged changes in forearm blood flow in nine subjects before and during and after fainting are shown in Fig. 5 (top left). The work at the Postgraduate School was presented by Sharpey-Schafer at a meeting of the Medical Research Society at University College Hospital and published in the Lancet (Barcroft, Edholm, McMichael and Sharpey-Schafer, 1944).

Assuming that vasodilatation like that in the forearm muscles occurred in all the muscles throughout the body in haemorrhagic fainting Sharpey-Schafer concluded that the total decrease in peripheral resistance would be large enough to explain the marked fall in arterial blood pressure.
Back in Q.U.B. at the beginning of the October term there was still much to be found out. Was the vasodilatation in the forearm during the faint in the muscle or in the skin? If in the muscle was it mediated by the sympathetic nerve supply to human muscle vessels or by a circulation vasodilator substance? And now the B.M.S.A. came to our assistance. Having explained the nature of the research and its importance to the Officers, and our need for volunteers to be subjects, they gave the matter careful consideration, and most generously offered to be subjected themselves and to make our needs more widely known.

Research continued as follows. After loosing the equivalent of 2 bottles of blood and fainting, the skin of the subject, including that of his forearm looks extremely pale. But it was just conceivable that vasodilation in the forearm in the faint could be in the invisible deeper layers of the skin. Now the forearm is mainly muscle but the hand is mainly skin. What happened in the circulation in the hand during fainting? Fig. 5 (top right) shows the averaged results of 6 experiments showing decrease in the rate of the blood flow in the hand in the faint. From this we concluded that the vasodilatation in the forearm was much more likely to be in the forearm muscles.

![Diagram](image_url)

**Fig. 4.** Results recorded before, during and after a typical haemorrhagic faint. Shaded rectangle: cuffs on thighs inflated to diastolic pressure. Open rectangle: venesection. Vertical broken line: faint fully developed.
than in the forearm skin. We then turned to the mechanism of the vasodilatation in the forearm. Was it nervous—mediated by the sympathetic to the forearm vessels? Or hormonal, due possibly to the release of adrenaline which was known to vasodilate the vessels in skeletal muscles. An answer could be got by observing the behaviour of the forearm circulation in the faint in sympathectomized subjects. Few of them were available. Mr. Samuel Anderson kindly volunteered. And so did Edna Mack (now Mrs. Brownlow) a girl of 16 who had been to the Physiology Department for various experiments on more than forty occasions. She and her parents approved the project. Mr. Patrick Fitzgerald, now Professor of Surgery in the National University of Ireland, a friend of Dr. Edholm’s had sympathectomized patients in Dublin, who volunteered. Fig. 5 (bottom left) shows the averaged results of the forearm blood flows of six sympathectomized subjects during fainting. Blood flow decreased during these faints, so we concluded that the vasodilatation seen in normal subjects must have been mediated by the sympathetic nerves to the skeletal muscle blood vessels—that is to say mediated by the sympathetic nerves whose existence had previously been proved by following Mr. Bonnar’s suggestion.
Now attention turned to a new question. Animal experiments had shown that the sympathetic had two sorts of fibres to skeletal muscle vessels—vasoconstrictor fibres and vasodilator fibres. Was the vasodilatation in the forearm in the faint due to inhibition of the vasoconstrictor—release of the vessels from vasoconstrictor impulses, or did the opening of the vessels involve active stimuli for vasodilatation via vasodilator fibres? This could be tested by recording blood flows in both forearms, blocking the radial, median and ulnar nerves on one forearm and inducing fainting. If, during the faint, blood flow in the normal forearm exceeded that in the nerve blocked forearm that would be because of the action of vasodilator nerve fibres. Fig. 5 (bottom right) shows the averaged results of the forearm blood flows in six such experiments. Note that blood flow in the nerve blocked forearm is about double that in the opposite normally innervated one. This is explained by the removal of sympathetic vasoconstrictor tone in the muscle vessels by local anaesthetics of the sympathetic fibres in the motor nerves. The forearm blood flows in the nerve blocked forearms have been superimposed on those in the normal forearms in Fig. 6. Note too that in the faint blood flow in the normally innervated
forearm exceeded that in the nerve-blocked forearm. Vasodilatation in the innervated limb exceeded that in the functionally denervated limb. Why? Probably because of the presence of sympathetic vasodilator fibres mediating impulses during fainting, impulses that excited active vasodilatation in the skeletal muscle vessels.

The Q.U.B. studies in post-haemorrhagic fainting were published (Barcroft & Edholm, 1945) and were presented by Dr. Edholm in the second of two Arris and Gale Lectures given at the Royal College of Surgeons in London.

Other questions came. The R.A.F. wanted more research on the reason why airmen went unconscious at high altitudes. Discussions Dr. Edholm had in London led to the arrival at Q.U.B. of a Royal Canadian Airforce Medical Officer, G. W. Manning, and to a great number of experiments on the circulatory changes accompanying hypoxia—that is to say the breathing of oxygen nitrogen mixtures containing 6—10 per cent oxygen. Suffice it to say that the subjects who went unconscious breathing a low percentage of oxygen could be divided into two groups, most, about four out of five, went unconscious, much as during N₂O anaesthesia, with cyanosis, rapid strong pulse, and raised blood pressure, these were the "non-fainters". The fainters, about one in five, went unconscious with a vago-vagal syndrome, pallor, sweating, bradycardia, precipitate drop in blood pressure and vasodilatation in the forearm. Averaged results are shown in Fig. 7.

The precipitate drop in arterial blood pressure and increase in forearm blood flow during hypoxic fainting were demonstrated at the King's College London Physiological Society Meeting on J. E. Reid, a Q.U.B. medical student and were

![Fig. 7. Averaged results recorded before, during and after breathing 7–9% oxygen in 'Fainters' and 'Non-fainters'.](image-url)
published (Anderson, Allen, Barcroft, Edholm and Manning, 1946).

Mr. President, Ladies and Gentlemen, thank you very much for having listened to me so patiently.

The following kindly volunteered to be subjects for the experiments described in this lecture: S. Anderson, J. Beckett, R. D. N. Blair, Eileen Bonnar, Dr. W. McK. Bonnar, M. Cullaghan, H. Cameron, Barry Crymble, W. Davey, Linde Davison, A. S. Effron, Dr. O. G. Edholm, T. H. Flewett, Dr. Q. H. Gibson, W. A. Gilmore, W. Goldberg, A. F. Griffiths, Professor D. C. Harrison, J. A. Howard, Dr. F. R. Johnson, C. de Largy, J. D. F. Leith, C. S. Lindsay, R. J. Livingstone, Mr. J. S. Loughridge, Dr. J. K. McCabe, H. McClatchey, R. L. McCorry, Miss Macdonald, Miss Edna Mack, Frank McLaughlin, T. A. McQuay, A. B. Morrison, R. A. Neely, J. B. Pyper, Miss Quinn, J. E. Reid, W. E. Stafford, Miss J. O. R. Stewart, G. K. Thomas, E. Trinick, D. H. Tweedie, A. L. Wells, R. F. Whelan and G. Wolfenden.

ADDENDUM

The existence of both a dilator and a constrictor innervation to skeletal muscle blood vessels has been confirmed. At rest the vessels are subjected to considerable constrictor tone and this is varied reflexly in the circulatory apparatus to a variety of stimuli, such as change in posture, exercise and changes in intrathoracic pressure. The vasodilator fibres are not active at rest but contribute to the vasodilatation in muscle in emotional stress (Roddie and Shepherd, 1963). Emotional fainting (from the sight of blood) is accompanied by vasodilatation in the forearm (Greenfield, 1951).

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