HÆMODYNAMIC BASIS OF ACUTE PRESSOR REACTIONS AND HYPERTENSION*

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To be the first Haile Selassie lecturer is a unique privilege. My pleasure at having been chosen for this task has two further causes. The first is that we have in our country a great admiration for the gallant people of Abyssinia and their noble representative H.M. the Emperor Haile Selassie ever since their heroic fight for independence and liberty. The second is being allowed to give this lecture under the auspices of the Institute of Cardiology. Dr. Paul Wood has in his kind introductory words mentioned our long association in military hospitals in Africa and Italy. What he did not say was that under primitive conditions in the Algerian desert and in the wild Italian mountains he created a model medical unit which attained a level of clinical work that could have matched the work of any medical department of a first class teaching hospital. It was thanks to his interest and support that I was even able to do original research work. It is, therefore, with a feeling of great indebtedness and gratitude that I begin this lecture.

I am going to summarize work that I have been carrying out with my colleagues Dr. Fencl, Hejl, and Jirka over the past eight years when we have been interested in the question of the relation between acute rises of blood pressure during pressor reactions of various kind and the permanent rise of blood pressure forming the basis of essential hypertension. Hines (1940) and others have claimed that some subjects with a normal pressure respond to a standardized cold stimulus by an exaggerated and protracted blood pressure rise and that the incidence of later essential hypertension is much more frequent among these hyper-reactors than among normal subjects. Although the far-reaching conclusions of Hines were disproved by further investigations (Hoobler, 1961; our own unpublished data), there is no doubt that many candidates for later permanent hypertension react to various pressor stimuli in the way suggested by Hines, but the connexion between these temporary rises of blood pressure and permanent hypertension was not established. The question naturally arose whether these transient exaggerated pressor responses could not actually be already an early phase of hypertension, the permanent blood pressure elevation being produced by fusion of the protracted acute rises.

If this were so, it would be expected that the blood pressure would be increased both acutely and in essential hypertension by the same hæmodynamic mechanism. It is today generally accepted that in essential hypertension this increase is due to a rise of the total peripheral vascular resistance, while cardiac output remains normal. Data are scarce on the hæmodynamic basis of acute blood pressure elevations, but Stead *et al.* (1945) have shown that during anxiety accompanying cardiac catheterization, blood pressure is increased by an increase in cardiac output, while total peripheral vascular resistance is unchanged or low. Thus it appears that there is no link between the acute and chronic blood pressure rise.

However, if we study carefully the data of Goldring and Chasis (1944), Bolomey *et al.* (1949), and

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Werkö and Lagerlöf (1949), on which the statement about the normal cardiac output and increased total peripheral vascular resistance in essential hypertension is based, we find very high figures for the cardiac output and values of the total peripheral vascular resistance within normal limits in a considerable proportion of their hypertensive patients. In addition the average cardiac output values of their control subjects are above the usual range of values under basic conditions, suggesting that at least some of the subjects were investigated during emotional tension. On the other hand Wolf and Wolff (1951) claimed on the basis of ballistocardiographic measurements that while most subjects with normal pressure respond to an unpleasant emotion by a rise of cardiac output, hypertensive subjects tend to produce their acute pressor responses by an increase in total peripheral vascular resistance. Ballistocardiography is, of course, no longer accepted as a method that can afford adequate information about changes in cardiac output. It seemed, therefore, important to repeat this work with more precise methods.

This was done by my colleague Dr. Hejl (1957) who measured cardiac output by the dye-dilution technique while blood pressure was estimated sphygmomanometrically, mean blood pressure being calculated as diastolic +40 per cent of pulse pressure. Two pressor stimuli were used. The first consisted of the immersion of one leg into water at 4°C. for two minutes, the other in mental arithmetic, asking the subject to subtract every two seconds a difficult figure, e.g.17, from the previous result starting from, e.g. 1963. The important thing about this mental stimulus is that the task itself should not be outside the scope of the subject, but the rate at which the performance is demanded is such that he should find it difficult. It may be seen from Fig. 1 that during this mental stimulus,

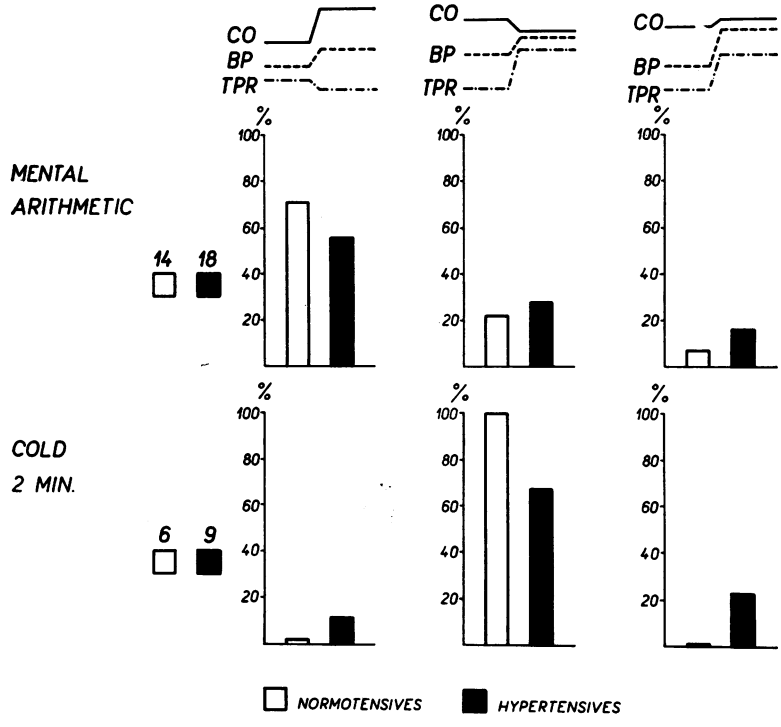

FIG. 1.—Incidence of the various types of the general hæmodynamic response to mental stress (mental arithmetic) and an immersion of a leg into 4°C. cold water for two minutes in controls with normal blood pressure and patients with essential hypertension. Diagrams at the top of the columns indicate the mechanism of the blood pressure rise. CO=cardiac output; BP=blood pressure; TPR=total peripheral vascular resistance (Hejl, 1957).

which is accompanied in almost all subjects by an unpleasant emotion, the rise in blood pressure may be produced by any of three possible pressor combinations of a change in cardiac output and total peripheral resistance: (1) increase in cardiac output with total peripheral vascular resistance unchanged or slightly decreased; (2) increase in total peripheral vascular resistance with cardiac output unchanged or decreasing; and (3) increase in both functions. While the first type is slightly more prevalent among normal subjects and the second and third type in hypertensive subjects, the separation is by no means a sharp one. Moreover, when changing from the mental to the cold stimulus, all the normal subjects responded by the second type of the overall hæmodynmic reaction.

This immediately raises the question of whether we are dealing with two or even three different types of hæmodynamic response, mobilized with different facility by different stimuli in different subjects. To find an answer, it was necessary to obtain information about the details of these various general hæmodynamic responses. While the cardiac output is a straightforward function, the total peripheral vascular resistance consists of many parallel resistances in the various vascular areas of the body. These resistances need not change all in the same direction, and so the change of the total peripheral vascular resistance might not give adequate information about the hæmodynamic changes in the various regions of the body.

METHODS

We have, therefore, worked out a method that enables us to follow simultaneously hæmodynamic alterations occurring in at least the most important regions of the vascular bed. The investigation of hæmodynamic changes produced by unpleasant emotion having been one of the aims, it was necessary that the procedure adopted be in itself as little traumatic and as physiological as possible. The details are shown schematically in Fig. 2. Under local anæsthesia the brachial artery and the antecubital vein on the right forearm were cannulated percutaneously by the Holmgren (1956) modification of the Seldinger (1953) technique with polyethylene catheters, the distal ends of which were inserted into a three-way stopcock. One arm of the venous stopcock served for the injection of the dye-indicator used for the estimation of the cardiac output, the other arm was connected with a micro-infusion pump delivering a sustaining inulin and *p*-aminohippurate (PAH) solution at the rate of 0·2 ml. per minute.

One arm of the arterial stopcock was connected with a capacitance manometer, with which blood pressure was recorded. The other arm was connected with a blood-sample fraction collector (2-second intervals) for the cardiac output estimation. In the earlier investigations congo red was used as dye-indicator*, but later it was replaced by rose bengal which has an added advantage of being extracted almost quantitatively by the liver. Its disappearance slope from the plasma is, therefore, an indicator of the hepatic (splanchnic) blood flow (Heonig, Schück, and Jirsa, 1954), if subsequent measurements are done at intervals not shorter than 15 to 20 minutes when a saturation effect might be observed with flattening of the disappearance curve. An indwelling catheter was used for urine sampling in the clearance measurements, the urethral mucosa having been anæsthetized beforehand by "nupercaine." Blood flow in the left forearm was measured by the occlusion plethysmograph of Barcroft and Swan (1953). Skin blood flow in the corresponding area of the right forearm was estimated in the earlier investigations by a thermocouple, later quantitatively

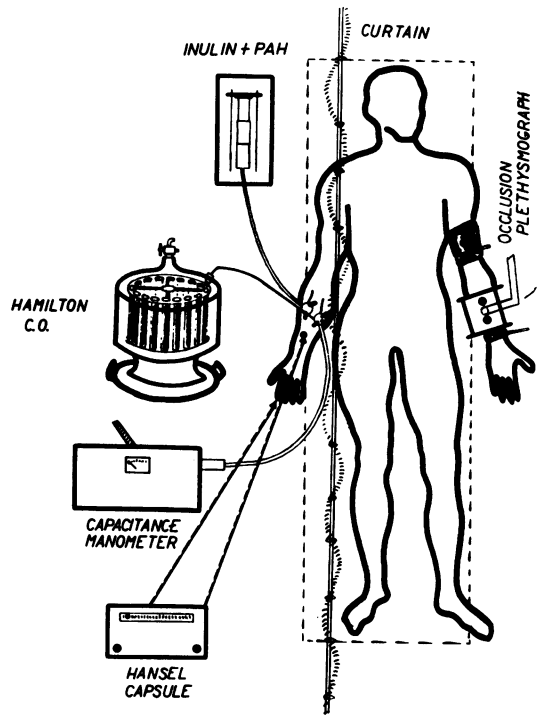

FIG. 2.—Schematic representation of the experimental set-up. For details see text.

* We found Evan's blue unsuitable for repeated estimations because of the blue discoloration of the skin lasting for several days. With the polethylene cannulas there was never hæmolysis in the samples of blood so that a red dye could safely be used. No side-effects were ever observed.

by the *Wärmeleitmesser* of Hensel and Bender (1956). Muscle blood flow in the forearm could then be obtained as a difference between total forearm and skin blood flow, skin being estimated as 8·6 per cent of the total forearm (Cooper, Edholm, and Mottram, 1955).

An important detail of the procedure was the placing of a curtain to the right side of the subject, through which his arm with the cannulas protruded, so that he was unable to notice any turning of the stopcocks and start of any measurement. This was further supplemented by several sham cardiac output measurements with a saline injection, so that any sensation of fluid injected through the venous cannula would be deprived of an emotional element. Actually all the subjects adapted themselves very well to the procedure and were co-operative and relaxed throughout the investigation.

This arrangement made it possible to estimate simultaneously cardiac output, systolic, diastolic, and mean blood pressure (by planimetry or by an integrator), to calculate from these values the total peripheral vascular resistance in arbitrary units $\left(\frac{\text{mean BP}}{\text{cardiac output}}\right)$, to estimate renal blood flow from the PAH-clearance, to obtain information about splanchnic blood flow, and to assess blood flow in skin and muscle. Regional vascular resistances were calculated in arbitrary units in an analogous manner as total vascular resistance.

Reactions to Stress

The course of events during stressful mental arithmetic in a healthy subject is shown in Fig. 3. The mental stress produced a rise of both systolic and diastolic blood pressure by 25 mm. Hg. This rise was due to an increase in cardiac output from a control level of 5·5 litres to 9 litres, while total peripheral vascular resistance slightly decreased. Thus, the overall hæmodynamic reaction was type I of Hejl. At the same time renal vascular resistance rose and a drop in skin temperature suggested vasoconstriction in the latter area. On the other hand there was an eightfold increase in forearm blood flow (from 2 to 17 ml./min./100 g. forearm) with a large fall in the flow resistance, suggesting an extensive vasodilatation in muscle. The vascular resistance in the whole extrarenal vascular area, calculated from the difference of the reciprocal values of the total and renal vascular resistances, also decreased, but the drop was much less than in muscle (which is part of the extrarenal area) as evidenced from the rise of the ratio of extrarenal vascular resistance to forearm vascular resistance, suggesting that some other part of the extrarenal vascular bed did not participate in the vasodilatation and might even have been constricted.

Fig. 4 is a typical example of pressor response of the second overall hæmodynamic type. The pressure rise was produced by immersion of the right leg in 4°C. cold water for two minutes and the blood pressure rose as a consequence of an increase in total peripheral vascular resistance, while cardiac output fell slightly. The renal and cutaneous vascular bed contracted and the increase in forearm flow again suggested a vasodilatation in muscle. The only difference from Fig. 3 was in the rise of the extrarenal resistance, pointing now definitely to vasoconstriction in some other large extrarenal vascular area, overbalancing the vasodilatation in muscle.

That this vasoconstriction took place in the splanchnic area was suggested from the flattening of the rose bengal disappearance curves during the pressor reactions in the later investigations and also from the vasoconstriction in the exposed intestinal mucosa of the anus præternaturalis in two subjects, evidenced by a drop of the temperature of the mucosa during the pressor stimuli (Fig. 5).

Skin blood flow having been assessed indirectly in the earlier investigations from changes of skin temperature, a larger series of measurements of skin and muscle blood flow has been carried out separately when the Hensel-Bender method was introduced. The result is summarized in Fig. 6, proving that the increase in forearm blood flow during the pressor reaction is localized in muscle and not in the skin (Fencl *et al.*, 1959).

The results of all our investigations of hæmodynamic changes during a pressor response are summarized in Fig. 8. The division of the data into three columns has been made according to the general hæmodynamic change and corresponds to the division in Fig. 1. It may be seen, however, that irrespective of the general hæmodynamic response, the regional vascular resistance always changes in the same direction—there is always vasoconstriction in the kidneys, skin, and the splanchnic area (increase in the ratio extrarenal vascular resistance/forearm vascular resistance) and a vasodilatation in the muscles. Although the extrarenal vascular resistance itself behaved

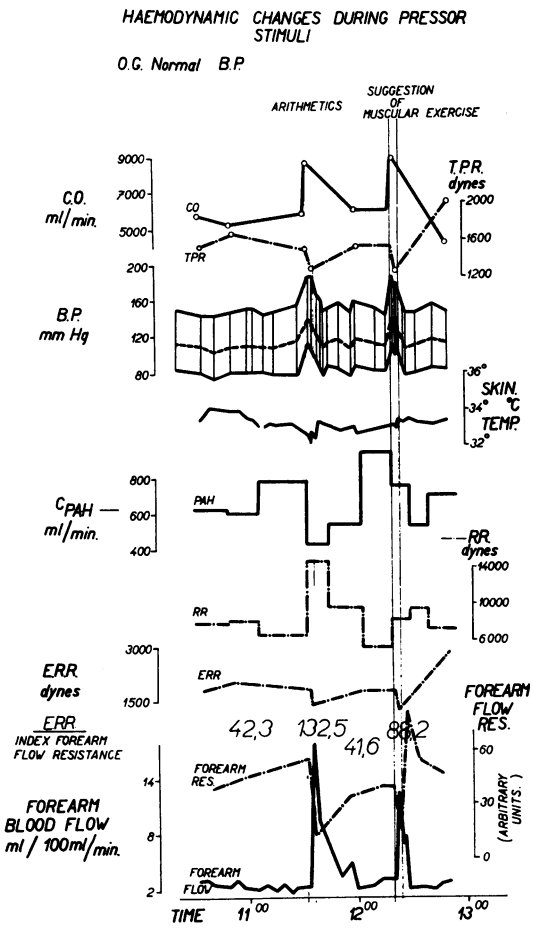

FIG. 3.—General and regional hæmodynamic changes during mental stress (mental arithmetic) and during verbal suggestion of heavy muscular work (riding a bicycle at top speed up-hill) in a healthy subject (Brod *et al.*, 1959).

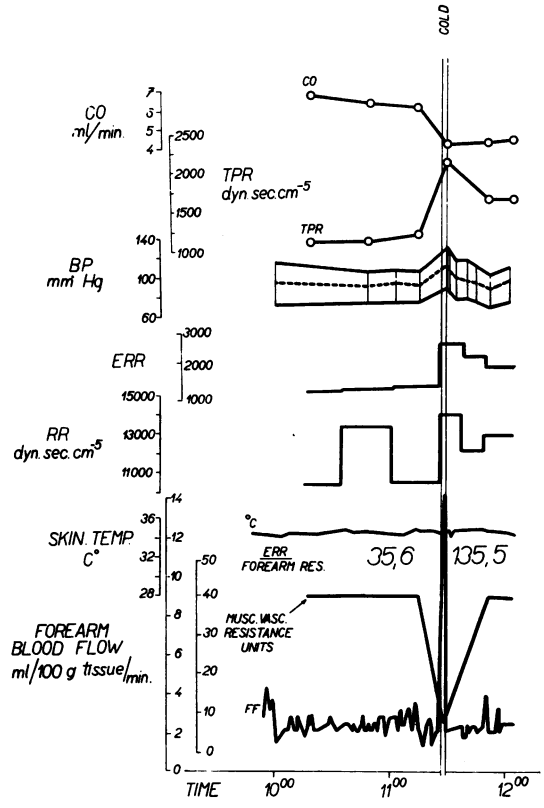

FIG. 4.—General and regional hæmodynamic changes during an immersion of a leg into 4°C. cold water in a subject with normal blood pressure (Brod *et al.*, 1959).

divergently in the three subgroups, it is to be remembered that this is a composite function and that it consists of vascular changes in the opposite direction (muscle versus splanchnic area and skin). In the same way the change of the total peripheral vascular resistance depends on the mutual balance of the vasoconstrictor and vasodilator component: it decreases if the vasodilatation has the upper hand, it rises if vasoconstriction is of greater degree than the opposing vasodilatation.

Cardiac output increases in all instances where total peripheral vascular resistance drops. However, it has a rising tendency also in those subjects in whom, owing to a perfect balance between vasoconstriction and vasodilatation, total peripheral resistance does not change. There was even some increase in the cardiac output in the one normal subject (several hypertensive subjects behaved in the same way), in whom total peripheral resistance has slightly increased. This proves that the rise of the cardiac output is not a secondary consequence of the drop in total peripheral vascular resistance, but an integral component of the circulatory response to the pressor stimulus.

A drop of the cardiac output occurs only in those instances in which the increase in total

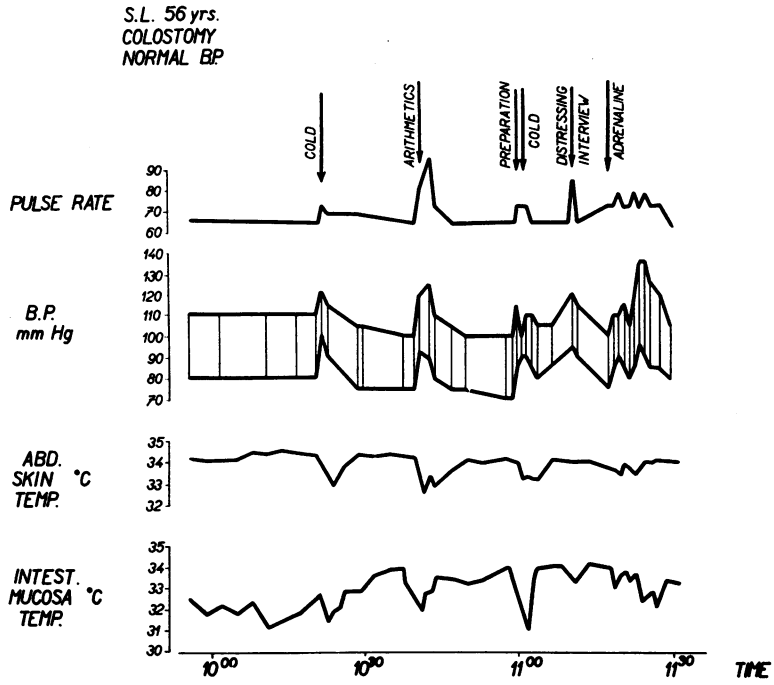

FIG. 5.—Changes of temperature of the exposed intestinal mucosa in the anus præternaturalis during various pressor stimuli. In the first of the measurements the mucosal temperature is not yet stabilized, although one might suspect that its rise towards the later level would have been smooth but for the drop during the first cold stimulus. When the level became stable, there can be no more doubt about the fall of the temperature during all the subsequent pressor stimuli (Brod *et al.*, 1959).

peripheral vascular resistance—due to an overwhelming vasoconstrictor component, unbalanced by a corresponding degree of vasodilatation in the muscles—exceeds some 20 per cent of its original value, perhaps as a consequence of the reflex connexions known to exist between the peripheral vascular bed and the heart (Warren and Stead, 1947, and others). The reaction in subjects with essential hypertension did not differ in quality from that in the normal controls. However, in accord with the data in Fig. 1, the degree of vasoconstriction in the kidneys, splanchnic region, and skin was usually more severe, and was not matched by a parallel increase in the degree of vasodilatation in muscle. Moreover, the duration of the pressor reaction differed: while in the normal subjects all the changes tended to revert to the control level within 4 to 5 minutes after the stimulus was stopped*, the reaction lasted in the hypertensive patients on the average 29 minutes beyond the cessation of the pressor stimulus, and in some the changes were still present when the investigation was terminated 45 minutes after the end of the pressor stimulus (Fig. 7).

HÆMODYNAMIC RESPONSE TO EXERCISE

The hæmodynamic response consisting of an increase in cardiac output and redistribution of blood from the viscera and the skin to muscle recalls the circulatory readjustment that occurs during muscular exercise. It seemed, therefore, of interest to examine this reaction with our complex technique and to investigate at the same time the question of the degree of exercise

* The renal clearance technique does not allow, of course, shorter clearance periods than 10 minutes. However, we have found renal vasoconstriction to outlast this period in only 2 of 9 subjects with a normal pressure.

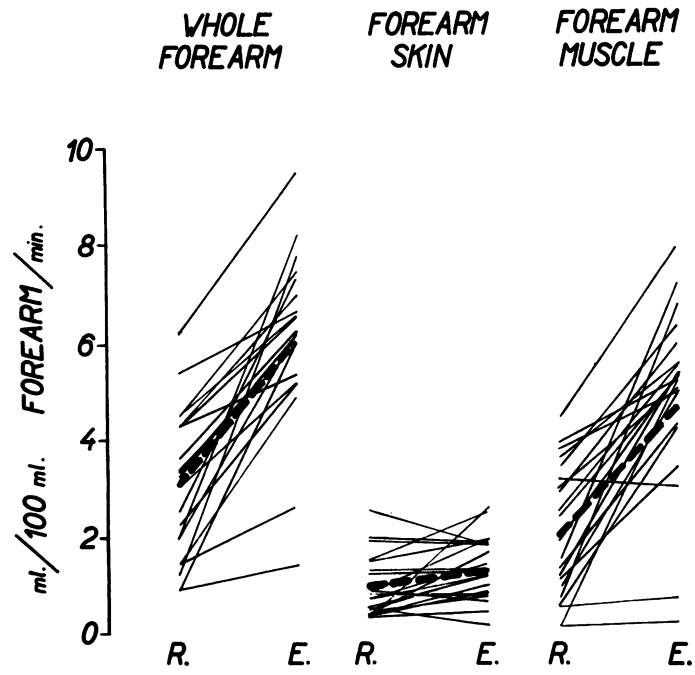

FIG. 6.—Changes of the blood flow through the whole forearm, the forearm skin, and forearm muscle, during the blood pressure rise caused by mental stress (mental arithmetic) (Fencl *et al.*, 1959).

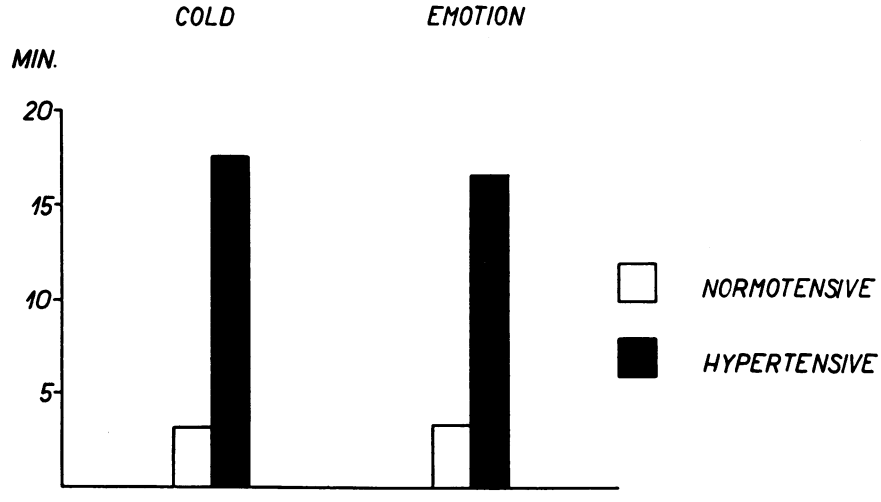

FIG. 7.—Duration of the pressor response to mental stress (mental arithmetic) and immersion of leg into 4°C. cold water in normal, and in hypertensive subjects.

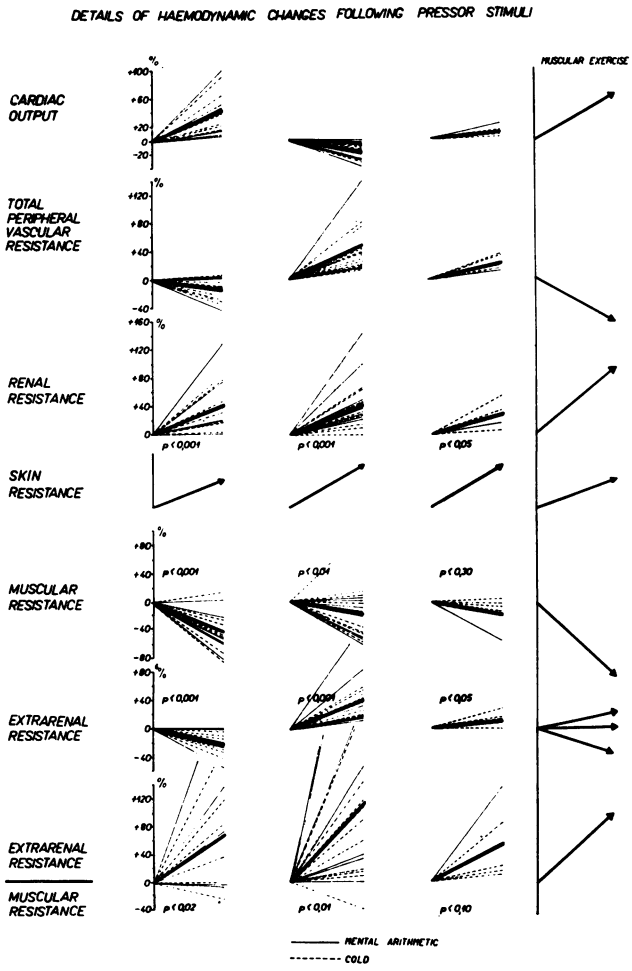

FIG. 8.—General and regional hæmodynamic changes in subjects with a normal, and others with a raised, blood pressure during pressor reactions due to mental stress (mental arithmetic) and immersion of a leg into 4°C. cold water. The division into three columns corresponds with that of Fig. 1: blood pressure rise due to increase in cardiac output (column 1), to increase in total peripheral vascular resistance (column 2), and to increase in both parameters (column 3). The responses in normal subjects and hypertensive patients are qualitatively similar.

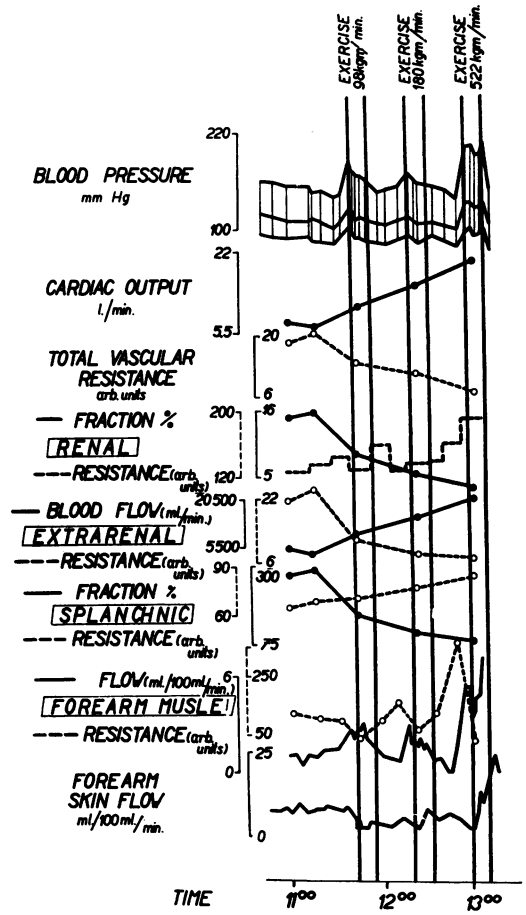

FIG. 9.—General and regional hæmodynamic changes during graded muscular exercise on a bicycle ergograph in a healthy subject (Fencl *et al.*, 1960).

producing this circulatory readjustment. This was carried out in 10 healthy volunteers in a fair state of physical training. The exercise was carried out in a recumbent position with a bicycle ergograph at approximately 100, 200, and 500 kg. per minute, and Fig. 9 is a typical example of such an investigation. It may be seen that while the cardiac output progressively increased in response to increasing metabolic demands and total peripheral vascular resistance progressively decreased, obviously as a result of the opening up of the vascular bed in the muscles, a measurable increase in the renal vascular resistance occurred only with the heaviest exercise. Splanchnic vascular resistance, though steadily rising in the investigation shown, showed in the whole group a statistically significant increase only at the 500 kg./min. load. In the skin, however, a vasoconstriction was noted with a

work load at 100 kg./min.; and with heavier exercise loads this was followed during the course of exercise by vasodilatation, obviously in response to a need for increased heat elimination. The analysis of all the data in healthy subjects revealed that a fully-developed circulatory readjustment of the type we are discussing is produced only with a relatively severe exercise load, obviously when in an attempt to maintain an adequate venous return, when the capacity of the total vascular bed increases, other measures fail (e.g. decreased capacity of the venous vascular bed).

An interesting feature of the hæmodynamic response to muscular exercise is the opening of the vascular bed not only in the working muscles, but also in the forearms which were, at least visibly, relaxed. This seems to be due to an accompanying emotion or increase in tone, since it is possible to eliminate this vasodilatation in the forearm muscles by training, as demonstrated by Blair *et al.* (1959) and confirmed by ourselves (Brod, Hejl, and Ulrych, so far unpublished).

The Mechanisms Involved in these Responses

This hæmodynamic response can be produced, however, not only by actual strenuous exercise, but also by its verbal suggestion, as demonstrated in the right half of Fig. 3. Moreover Madlafousek (1957) in our laboratory has demonstrated in dogs that during the so-called "orientation reflex" of Pavlov (1949), which is always accompanied by a rise of the blood pressure lasting some 15 to 20 seconds, there is a vasoconstriction in the paw, but not in the muscular part of the extremity, and this suggests that a reaction analogous to that under study has been brought into play.

It was demonstrated by Uvnäs and his collaborators (Eliasson *et al.*, 1951; Eliasson, Lindgren, and Uvnäs, 1952) that an increase in blood pressure along with vasoconstriction in the splanchnic area and skin and vasodilatation in muscle can be produced in anæsthetized cats by electrically stimulating an extensive area in the hypothalamus. Abrahams and Hilton (1958) obtained the same reaction in unanæsthetized cats with electrodes permanently implanted into the same hypothalamic area. They found, moreover, that with a mild intensity of the stimulating electric current the animal manifested—in addition to the above-mentioned hæmodynamic alterations—changes in behaviour reminiscent of the "orientation reflex": with a higher current intensity a typical rage reaction was produced.

The question naturally arises whether all this similarity actually means an identity of the hæmodynamic response. Looking for a common denominator we might assume that the basic situation under which this reaction is produced is severe muscular exercise with its need for the maintenance of an adequate venous return. We may further assume that in the long phylogenesis, and also during ontogenesis, this hæmodynamic response became so firmly established that it was now produced not only by actual physical work, but also by its preparation or by any situation that might have been phylogenetically or ontogenetically connected with severe muscular exercise. This conditioning of the reaction would explain its production not only by a verbal suggestion of strenuous exercise, but also by any situation of danger or threat to the organism, that might necessitate for the sake of self-preservation fight or flight, survival depending on the ease and efficiency with which maximum muscular effort is mobilized. Conditions producing the orientation reaction might be potentially dangerous and the readiness of the circulation for maximum effort is, therefore, understandable. A rage reaction arises, of course, under situations of actual danger and the reason for the circulatory readjustment to maximum effort seems clear.

This gives a clue also for the understanding of the origin of this hæmodynamic reaction during unpleasant emotions. This is a subjective state, accompanying such situations that at lower stages of phylogenesis might be likened to danger or threat to life. Obviously, the hæmodynamic response to such a situation persists in adult men, even if the muscular component is suppressed by social inhibitions.

To make all this more than attractive hypothesis, it would be necessary to prove that the physiological mechanisms underlying these responses are the same as in the reaction studied by Uvnäs and his colleagues and by Abrahams and Hilton. Electrophysiological research on the hypothalamic

area of the brain in man, though feasible, is, of course, difficult. However, we thought that if we could demonstrate an identity of the efferent pathways of the reaction in man and in the cat, our argument would gain in strength. The vasoconstrictor stimuli in the animal reaction are, of course, mediated by adrenergic sympathetic fibres, and my colleague Dr. Jirka (1958) demonstrated that the renal vasoconstriction during muscular exercise in man also is mediated by sympathetic fibres, disappearing after renal periarterial sympathectomy (Fig. 10).

We have also succeeded in eliminating the increased renal vascular resistance, produced by fear in three subjects, by adrenergic blockade with dibenamine (Fig. 11) (Brod, Fejfar and Fejfarova, 1954). However, it seemed much more important to obtain information about the more specific vasodilator component of the reaction which Eliasson *et al.* (1951) have shown to be carried by the cholinergic sympathetic fibres.

This part of our study has been carried out in close collaboration with the Dept. of Physiology of St. Thomas' Hospital Medical School in London (Barcroft *et al.*, 1960). It was found that the delay time of the vasodilatation in the muscles varied from 0 up to 35 seconds. While the long

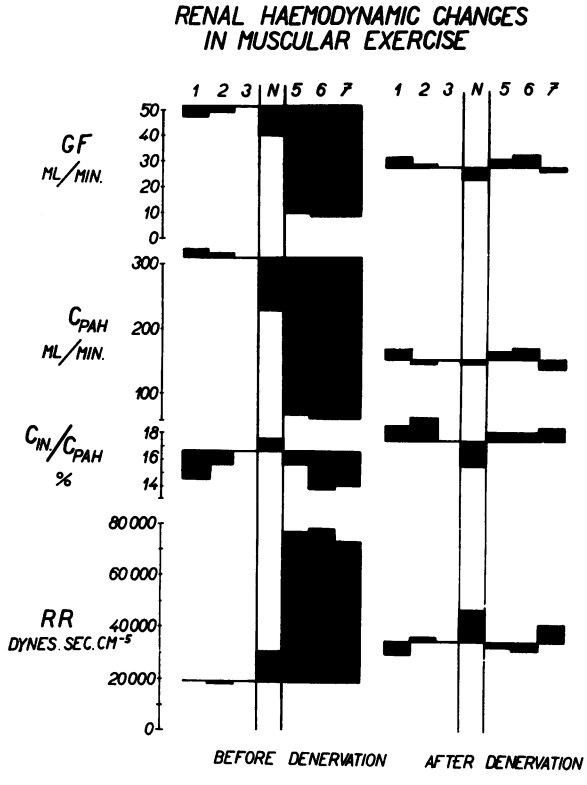

FIG. 10.—Influence of denervation and decapsulation of the kidneys on the renal hæmodynamic changes due to muscular exercise in two subjects with chronic glomerulonephritis. Following operation renal vasoconstriction during exercise (drop in C_{PAH}, increase in renal resistance) disappeared. The operation was carried out in an attempt to stop the downhill course of the disease. C_{PAH}=PAH clearance; C_{IN}/C_{PAH}= filtration fraction; RR=renal resistance (Jirka, 1958).

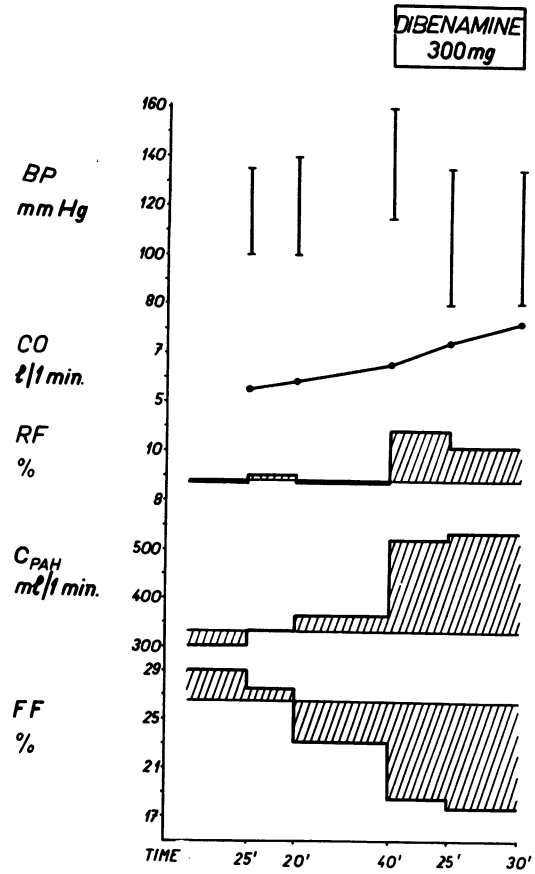

FIG. 11.—Influence of the infusion of dibenamine (5 mg./1 kg. b.w.) on renal vasoconstriction produced by anxiety, visible from the low renal fraction and C_{PAH} and an increased filtration fraction. The blood pressure was also slightly raised and was brought to normal by dibenamine. BP=blood pressure; CO=cardiac output; RF= renal fraction of the CO; C_{PAH}=PAH clearance; FF=filtration fraction.

delay period suggested possible participation of a humoral agent, the immediate response was explicable only by a reflex mechanism. The response was preserved in subjects whose arms were surgically sympathectomized, but this could have been due to an increased sensitivity of the vessels to circulating adrenaline or to incomplete sympathectomy. On the other hand pharmacological sympathectomy (stellate ganglion anæsthesia) diminished the vasodilator response to emotional stress in the experimental forearm in four of five subjects examined (Fig. 12).

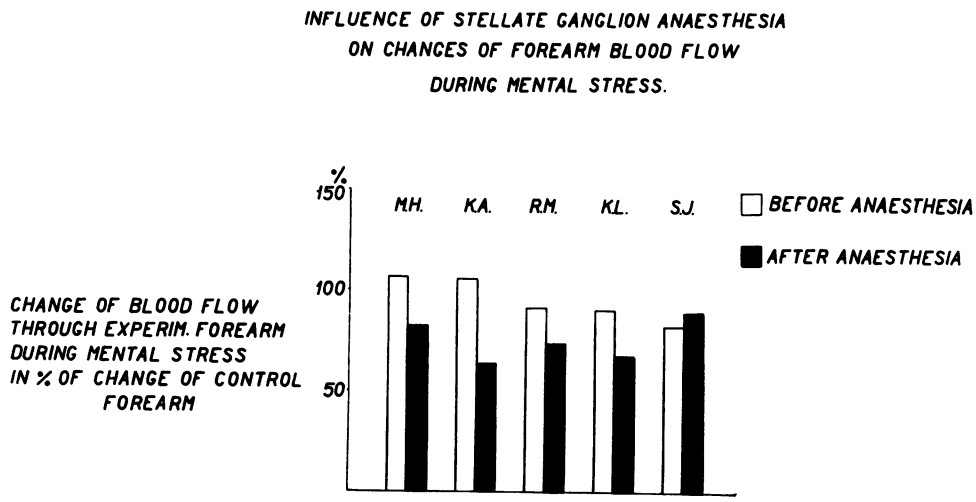

FIG. 12.—Influence of stellate ganglion anæsthesia on the emotional muscular hyperæmia as percentage of the hyperæmia in the control forearm (Barcroft *et al.*, 1960).

There was one difficulty, however, in the interpretation of the results: stellate ganglion anæsthesia itself produced, of course, an increase in blood flow in the experimental forearm, and the possibility could not be ruled out that the vasodilator stimulus could not increase the capacity of the vascular bed beyond a certain point. Although the investigation in one patient speaks against such a possibility, the forearm blood flow during emotion following stellate anæsthesia being actually less than that produced by the anæsthesia *per se*, it was difficult to duplicate such an experiment. We have attempted, therefore, to block instead the peripheral transmitter with atropine. The emotional vasodilatation was less after atropinization in all four investigations in which atropine was administered intravenously (Fig. 13).

It was, of course, possible that the general effects of intravenous atropine altered the responsiveness of the vessels to emotion. Therefore we carried out a further series of investigations in which atropine was injected through an indwelling polyethylene cannula into the brachial artery. We have ascertained in each experiment that the dose of atropine was sufficient to block a dose of acetylcholine that before atropinization produced a vasodilator response of magnitude similar to the emotional stress. It was found that in 9 out of 12 investigations the emotional vasodilatation after atropine was less than before, although it was fully abolished only once (Fig. 14). Whether this means that in addition to a reflex mechanism there is also a humoral component untouched by atropine, such as circulating adrenaline, or that a mediator liberated at the nerve endings is blocked with greater difficulty than acetylcholine injected into the blood (Bacq, 1962), is so far impossible to decide. In favour of the second possibility would be the fact that there is no correlation between the length of the delay period and the efficiency of the atropine-blocking effect. On the other hand the shape of the emotional vasodilatation recalls that produced by intra-arterial injection of adrenaline. The results of these investigations are, however, strongly suggestive of a cholinergic reflex

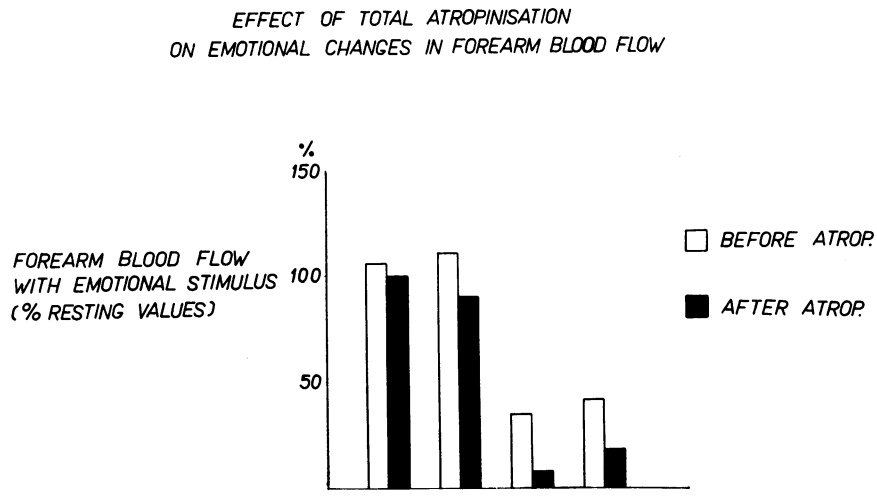

FIG. 13.—Influence of intravenous atropine on the emotional muscular hyperæmia expressed as percentage increase over the base line (Barcroft *et al.*, 1960).

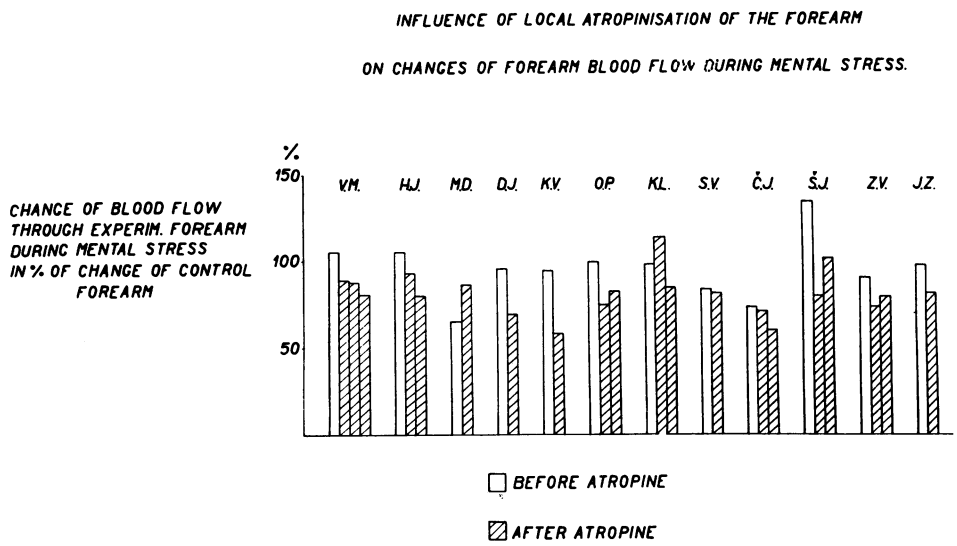

FIG. 14.—Influence of atropine injected into the brachial artery on the emotional muscular hyperæmia. Blood flow through the experimental forearm is expressed as the percentage of the emotional change of blood flow through the control forearm (Barcroft *et al.*, 1960).

mechanism, transmitted probably in sympathetic fibres, as responsible for the emotional vasodilatation in muscle, which strengthens our suspicion that we are dealing with the same response that can be produced in cats by hypothalamic stimulation.

It seemed of interest to study the reason for emotional vasodilatation in muscle. Was the primary step an increase in metabolic demand in muscle during emotion, or was the hæmodynamic reaction primary, mediated by the central nervous system? This we (Brod, Hejl, and Ulrych, 1962b) have studied in 10 subjects in whom we have cannulated separately veins draining forearm muscles

and forearm skin (the position of the cannulas was controlled by X-ray) and in whom we have measured total forearm blood flow by Whitney's (1953) "mercury-in-rubber" strain gauge plethysmograph and skin blood flow by the Hensel-Bender (1956) thermocapsule on the same forearm. Oxygen and glucose consumption were calculated as products of flow and a-v difference of these substances in the appropriate tissue. Metabolic changes during emotional muscle hyperæmia were compared with those during actual exercise of the forearm muscles of such magnitude to produce a comparable hyperæmia as the emotional stress.

The result of a typical experiment is shown in Fig. 15. Muscle blood flow increased to the same extent both during emotion (mental arithmetic) and exercise. However, oxygen consumption increased only very slightly during emotional stress and oxygen a-v difference consequently decreased, which was just the opposite of what happened during actual muscle work. Glucose consumption

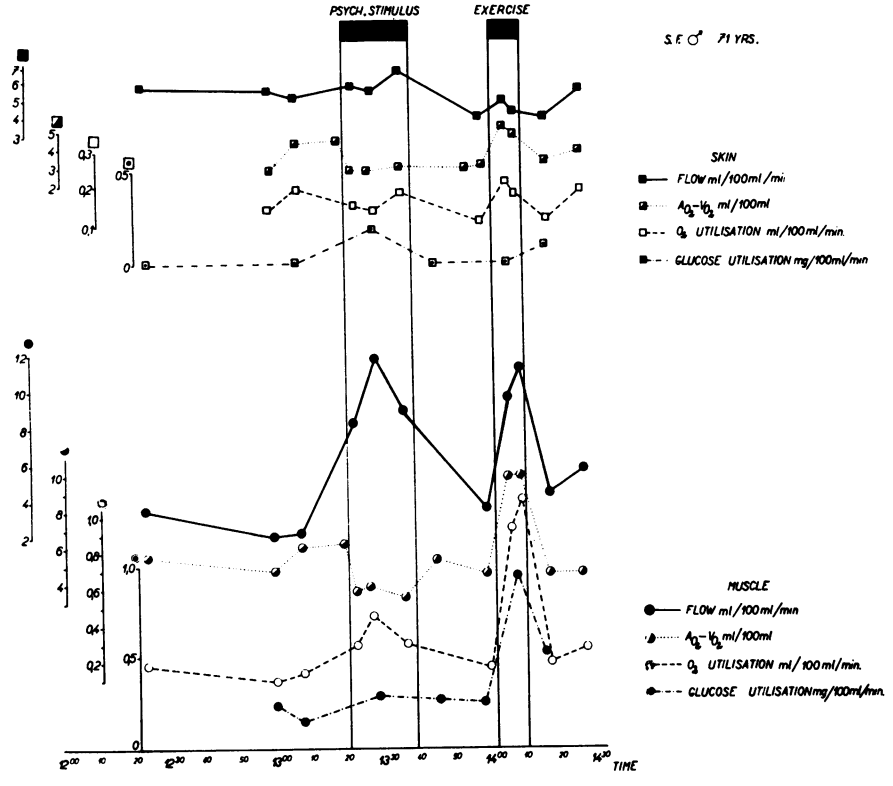

FIG. 15.—Oxygen and glucose consumption in the forearm muscle and skin during emotional stress (mental arithmetic) and during opening and closing of the hand (Brod *et al.*, 1962b).

did not change significantly during emotion and rose during exercise. Changes in skin metabolism were irregular and not significant in the whole group and will, therefore, not be discussed further. Fig. 16 summarizes the results of all the investigations showing that while the increase in muscle blood flow was comparable during emotion and exercise, oxygen consumption during emotion rose slightly only in 6 experiments and did not change in 4; while, of course, it always increased considerably during exercise. That this increase exceeded the increase in blood flow found its expression in the increased a-v-oxygen difference in all the subjects during exercise, while this parameter did not change significantly or fell during emotion. Glucose consumption behaved in these instances in the same way as oxygen consumption.

These investigations suggest that while the increase in muscle blood flow during muscle exercise subserves the actual increased metabolic demands, the increased muscle blood flow during emotional stress occurs independently of any metabolic change in muscle. The circulatory system is obviously ready to deliver more oxygen to muscle immediately, should the environmental situation result in strenuous exercise. The slight increase in oxygen consumption, noted in part of the experiments, might be explained probably by a slight increase in tone, found electromyographically under exactly the same conditions by von Eiff (1960).

The question through which channels the extra blood flows during emotion was studied in 10 subjects. A small amount of KI^{131} was injected into the forearm muscles and its disappearance was followed by continuous counting during both the emotional and exertional increases in muscle blood flow. Fig. 17, reproducing a typical experiment, shows that although the degree of hyperæmia was the same during emotion and exercise, there is no increase in the slope of the disappearance curve during mental stress, while exercise of the forearm muscles increased the slope greatly. This result suggests that the surplus blood during emotion by-passed the muscle capillaries and could not pick up more of the KI^{131}, as happens during exercise, when, of course, more muscle capillaries open up.

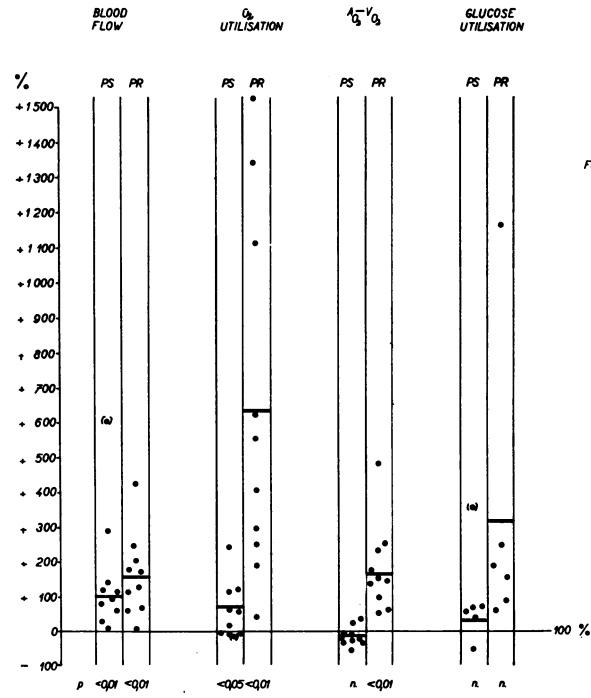

FIG. 16.—Individual data on forearm muscle blood flow, oxygen a-v-difference and consumption, and glucose consumption in the forearm muscles during mental stress (mental arithmetic) (PS) and during muscular exercise (opening and closing of the hand) (PR). The base line indicates the control level (Brod *et al.*, 1962a).

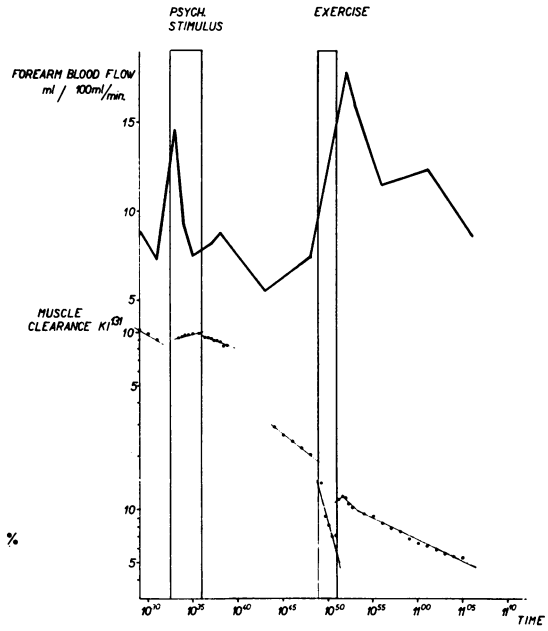

FIG. 17.—Disappearance curve of KI^{131} injected into the forearm muscles during emotional hyperæmia and hyperæmia due to opening and closing the hand (Brod *et al.*, 1962a).

APPLICATIONS TO ESSENTIAL HYPERTENSION

Let us now revert to the problem of the relation of these acute pressor responses to the permanent rise of blood pressure in essential hypertension. It is clear from the foregoing section that the normal cardiac output and high total peripheral vascular resistance in the hypertensive subject no

longer form an insurmountable obstacle for comparison with the hæmodynamic picture of the acute blood pressure rises that, at least in part of the subjects and in response to certain stimuli, are produced by a similar general hæmodynamic change. However, one difficulty remains: it is believed that in essential hypertension the rises in all the regional vascular resistances are more or less parallel and of a similar degree, while during the acute pressor responses we have found divergent changes of the regional vascular resistances in the muscles and in the viscera.

The conclusion about the regional flows in subjects with essential hypertension is based on the sound assumption that should the vascular resistance be increased only in some regions, e.g. splanchnic area, the blood flow through the regions with normal vascular resistance, e.g. forearm, should be increased. Pickering (1936) by Stewart's calorimetry and Prinzmetal and Wilson (1936), using occlusion plethysmography of the total forearm and hand, found the blood flow in the extremity unchanged. However, Stewart's calorimetry is capable of registering blood flow only through the skin to the depth of 3 to 5 mm. at the most, and a forearm and hand plethysmograph

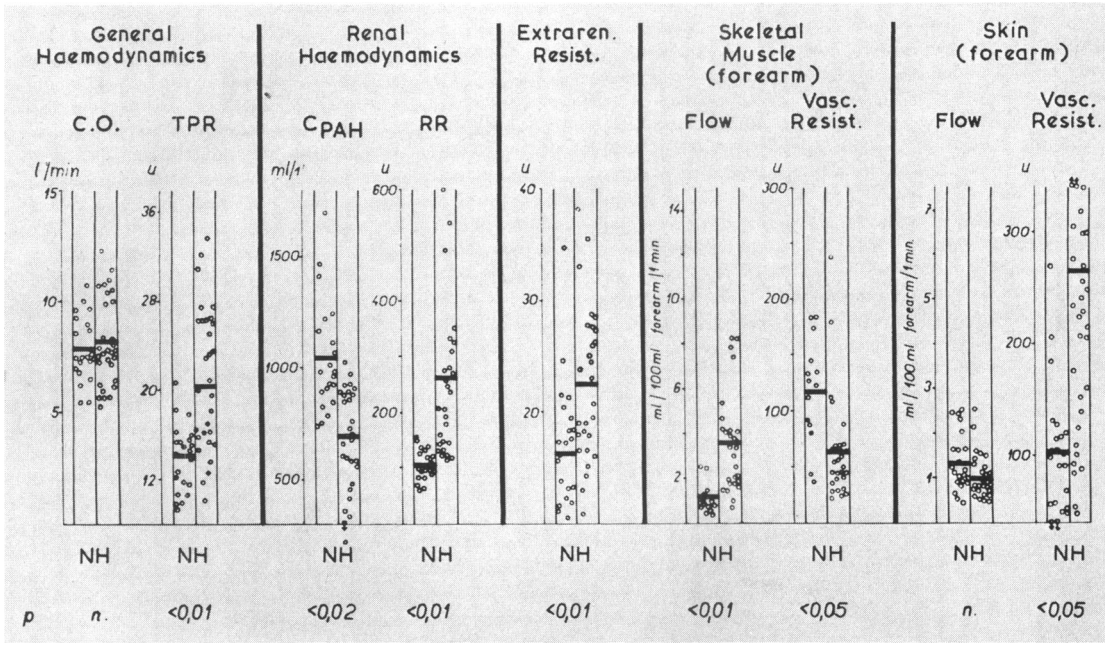

FIG. 18.—Individual data on general and regional hæmodynamics in normal controls (N) and in patients with essential hypertension (H). In 5 out of the 34 measurements in hypertensive subjects cardiac output exceeds 10 litres. (Brod *et al.*, 1962a.)

includes muscle and skin in which the flows might alter, as we have seen, in opposite directions and the changes might, therefore, cancel out each other. Moreover, Abramson and Fierst (1942) noted by occlusion plethysmography of the forearm an increase in blood flow in the hypertensive subjects.

Because of these difficulties we have re-investigated the problem of overall and regional blood flow changes under resting conditions in a group of patients with essential hypertension, whose diagnosis was established by excluding any other known pathology (thorough renal functional investigation was carried out in all of them), with the possible exception of renal artery stenosis, since aortography was not yet a routine procedure at the time of this investigation. However, later work of my colleagues Hejl, Prát, and Dejdar (1962) has shown this condition to be a rarity in

adults with hypertension in whom no organic sequelæ of the raised blood pressure are found*, and the majority of our subjects were in this early developmental stage of the disease.

Fig. 18 is a summary of our experiments. As could be expected, the cardiac outputs of the hypertensive subjects do not differ significantly from those of the normal controls, although their scatter is greater and some of the hypertensive values are above the normal resting range. Total peripheral vascular resistance is, of course, higher in essential hypertension, but again there is considerable scatter with at least some values well within the normal range. There is nothing new in the data of the vascular resistance in the kidneys, skin, and total extrarenal area: they are all increased in accordance with current views. However, muscle blood flow in the hypertensive subjects is greatly above that in the normal controls and the vascular resistances in this region are on the lower side of the normal range or below it, and the difference is statistically significant.

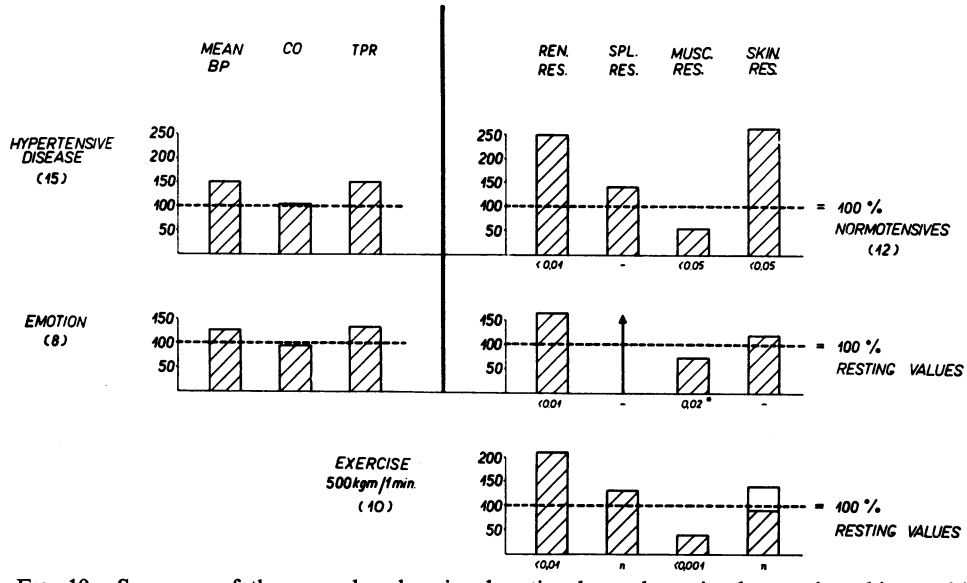

FIG. 19.—Summary of the general and regional resting hæmodynamic changes in subjects with essential hypertension with the resting hæmodynamic data of normal controls (indicated as 100% by the dotted line). For comparison, summary of emotional pressor responses of the second overall hæmodynamic type (see Fig. 1) in normal subjects: resting level indicated by the dotted line (=100%). The arrow indicates the direction of the change of splanchnic resistance for the quantitative evaluation of which we had not enough data. In the third line regional hæmodynamic changes during heavy muscular exercise (500 kg./min.): dotted line indicates the resting level. Because of the vasodilatation in the working muscles total peripheral vascular resistance decreases in this instance and cardiac output increases, whereas in essential hypertension and in the type of the emotional pressor response, represented in line 2, visceral vasoconstriction predominates over muscular vasodilatation: total peripheral resistance therefore increases and cardiac output has a decreasing tendency (Brod, 1960).

Thus, our results, far from speaking in favour of a parallel increase in vascular resistance all over the body, suggest that the circulation in essential hypertensive subjects is reconstituted in a similar way to that in the acute blood pressure responses to emotional stress (Fig. 19), even to the extent that in some patients the overall pattern might be an increase in cardiac output with a normal or low normal total peripheral vascular resistance. This general pattern seems especially frequent in the juvenile or early hypertensive subjects, as suggested by the studies of my colleagues Widimský, Fejfarová, and Fejfar (1957) and Hejl (1957).

Similarity of hæmodynamic pattern is, of course, not yet proof of an identity of the physiological

* Stage 1 of the new classification of hypertension suggested by an expert committee of the W.H.O. in 1961.

mechanisms involved. However, the afore-mentioned exaggeration and protracted nature of the acute pressor responses in some of the candidates of later essential hypertension support the idea that the rise of blood pressure in essential hypertension is due to a disturbed regulation of this basic hæmodynamic reaction which is mobilized probably many times a day in the course of an ordinary life. Further studies are required to get some information about the reasons why this reaction becomes protracted and distorted with prevalence of the vasoconstrictor component. However, Fig. 20, showing that a similar divergency in the regional vascular resistance changes is encountered also in heart failure (Brod *et al.*, so far unpublished), demonstrates the possible importance of this hæmodynamic reaction in the genesis of this condition and the usefulness of its more detailed study in a number of physiological and patho-physiological states.

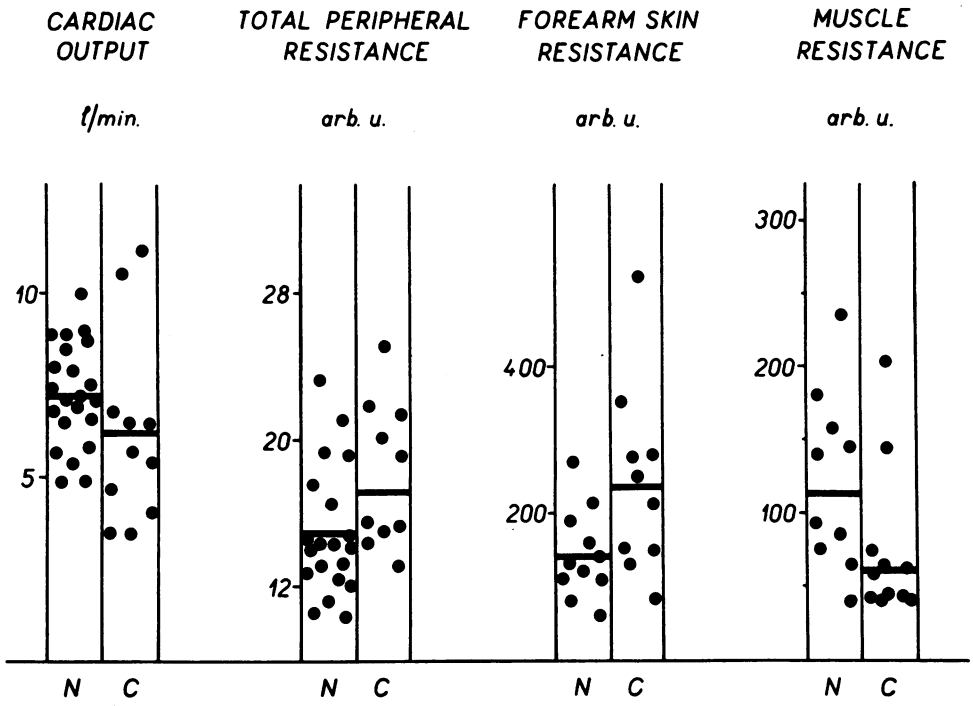

FIG. 20.—Individual data on general hæmodynamic change and skin and muscle blood flow and vascular resistance in heart failure. N = Normal. C = Cardiac failure

SUMMARY

During acute blood pressure rises in response to unpleasant emotions or a cold stimulus, blood is shifted from the viscera and skin to muscle. Total peripheral vascular resistance may drop or increase according to the prevalence of the vasodilator (muscular) or vasoconstrictor (visceral) component of this reaction. An increase in cardiac output is an integral part of this reaction and is superseded by a decrease only in those instances where total peripheral vascular resistance increases greatly.

This hæmodynamic reaction is analogous to that produced by strenuous muscular exercise or by its verbal suggestion. Similar reactions were observed in animals during an orientation reflex, rage reaction, or on stimulation of a hypothalamic area. It is suggested that preparation of the circulation for strenuous muscular exercise is the common denominator and that in adult men preparation to severe muscular action (fight or flight) takes place during unpleasant emotions, though any visible muscular action is suppressed by social inhibition. Similarly, as with hypothalamic stimulation, the efferent vasoconstrictor pathway of the emotional hæmodynamic reaction

in man lies in the adrenergic sympathetic fibre and can be blocked by dibenamine, the vasodilator pathway to muscle in the cholinergic sympathetic, and can be partly blocked by atropine or by stellate ganglion anæsthesia. Metabolic studies of muscle during emotion and muscular exercise show that muscular hyperæmia during emotion is not called forth by increased metabolic demands and is obviously a component of a centrally co-ordinated preparation of the circulatory system to strenuous exercise. This is further documented by the fact that the extra blood during the emotional muscle hyperæmia by-passes the capillary bed as suggested by studies of the slope of the disappearance curve of KI^{131} from muscle.

Under resting conditions general and regional hæmodynamic changes in subjects with essential hypertension are analogous to those observed in normal subjects during emotion. It is suggested that this might be due to the protracted nature of the acute pressor responses and that the starting point of essential hypertension might be a faulty regulation of one of the basic hæmodynamic reactions that is mobilized many times during the day under ordinary conditions of life.

We are grateful to the editors and publishers of *Clinical Science* for permission to reproduce Fig. 2–6 and 12–14, and of the *Lancet* for permission to reproduce Fig. 19.

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