The George E. Brown Memorial Lecture

Physiologic Considerations Concerned with the Pathogenesis and Treatment of Obstructive Vascular Disease

By Isaac Starr, M.D.

The therapy for thromboangiitis obliterans advised by George E. Brown and his collaborators in 1928 is taken as a starting point for a discussion of modern conservative measures now properly used in the treatment of peripheral vascular disease of the obstructive type.

The invitation to deliver the George E. Brown Memorial Lecture, with which your chairman has honored me, provides an opportunity to attempt something rather different from the ordinary scientific presentation, and I propose to make full use of this opportunity. I have no new research to report to you; although for a while the peripheral vascular field monopolized a great deal of my interest and time, this has not been the case in later years. I am, therefore, attempting the assessment of old knowledge rather than the announcement of new information (a state of mind not infrequently found in those who have no research to report), and you will also find that I have grown old enough to enjoy reminiscences of my younger days. I am, as it were, pausing and looking backward to evaluate the past before turning again to face the future, and, if the truth be known, I think we do far too little of this in American medical science, in which each of us is so likely to be concerned with the details of his own work that those either interested in, or, indeed, capable of taking a broader viewpoint are few indeed.

Of Brown's many contributions I have always been most interested in those summarized in the little book on thromboangiitis obliterans he published together with Dr. Allen and Dr. Mahorner in 1928. The book is an account of a physiologic study of peripheral vascular disease and the effects of treatment upon it, employing methods such as calorimetry and skin temperature, which are still standard today. It is concerned with vasomotor reactions, with securing maximal vasodilatation and with the development of a test based on the ability to secure maximal vasodilatation by which it is hoped to predict the success or failure of sympathectomy. How much that test has been used! In my opinion this book contains most of Brown's best work, although it was published seven years before he died. I suggest, therefore, that we return, as it were, to the year 1928 and study some of the ideas developed in this book and ask ourselves how they differed from those of Brown's predecessors in that field, and how the period of 25 years which has now elapsed has dealt with them, always remembering that it is our purpose, as it was his purpose, to learn so much about the diseases studied that new therapeutic steps will suggest themselves; then, by careful experiment and observation we can determine the value of each new therapeutic method which is suggested.

Conceptions Current Before 1928

Let us recall the background under which Brown was working in the years preceding 1928. At the time he and I were in medical school, clinical medicine in the U. S. was dominated by the great pathologic school of thought, whose primary interest was in the lesions found at necropsy. It was under the aegis of this school that the obstructive lesions of peripheral vascular disease had been discovered and described. As a result of such knowledge when a clinician detected diminution or lack of pulsation in a
peripheral vessel, he could confidently predict that at necropsy the vessel would be found obstructed by something solid and tangible, by a clot perhaps, by a sclerotic lesion of the vessel’s walls, either alone or accompanied by a clot, or possibly by pressure from without. This concentration of thought on the demonstrated arterial obstruction had led to a completely pessimistic therapeutic outlook. The vessel was obstructed and nothing could be done about it; the disease ran its malignant course, more vessels would become involved, the part supplied would suffer increasingly from lack of blood until eventually gangrene was inevitable. So there was only one thing to be done. High and early amputation was the treatment. I recall very well my early initiation into the methods of thought of this school when, as an interne, I ushered a surgical consultant on to the ward and showed him an area of superficial gangrene no bigger than a dime on the toe of an elderly patient who was having a certain amount of pain in his foot, but otherwise seemed in pretty fair condition. The surgeon’s reaction was immediate and certain: “This is as great an emergency as any case of appendicitis. The leg must come off. Send him to the operating room immediately and I will take off the leg above the knee as soon as he can be gotten ready.” The justification for such extreme measures lay in the experience with gangrene in diabetics before the insulin era, which had shown that, unless surgical treatment was both prompt and radical, the patient went into an acidosis which was quickly followed by death. From this experience the inference had been drawn that any gangrene was highly dangerous to life, a belief that died only slowly in the years which followed the discovery of insulin.

However, soon after that surgeon and I had talked in 1921—and he did take the leg off that afternoon—a new school of thought began to exert its influence on clinical medicine, a school which regarded disease not only from the anatomic but also from the physiologic point of view; and because the physiologic aspects of vascular disease are often amenable to treatment, whereas the anatomic ones are likely to be less so, it soon became possible to regard peripheral vascular disease from a different and more hopeful viewpoint. But old ideas sometimes die hard in medicine and this brings to mind my early struggles when I, a stripling with more laboratory than clinical experience, had the temerity to suggest that amputation might be postponed at least until some conservative measures had been tried and had failed, a position in which I received much encouragement from my chief, Dr. Stengel, who had always had in the back of his mind the feeling that the medical profession was somehow off the track in the peripheral vascular field. Despite his interest and support, things were teetering rather badly for conservative measures when a sudden streak of luck or good fortune turned the tide in my favor, for there came into my possession a consultation written by the then chief professor of surgery in my school, who, visiting a middle aged diabetic patient on my ward with both feet infected and an unhealed wound where a toe had been amputated at another hospital, wrote on the consultation blank, “I advise the amputation of both legs above the knees.” Despite the thundering of Jove, I, impudent young fellow that I was, demurred, and was loyally supported by my chief. The course of events fully justified us. The feet healed and although one of them eventually did come to amputation, this was performed over 10 years after the professor of surgery wrote that consultation, and during these years the patient had good use of both of them. Indeed he was still using the remaining leg when last seen in 1952, almost 20 years after the consultation mentioned. After that episode I had nothing but cooperation from the surgeons in my fumbling first attempts at conservative measures based on physiologic principles.

Influence of Sir Thomas Lewis

The person who had most influence on my way of thinking, and without doubt he influenced Brown also, was the Englishman, Sir Thomas Lewis, and I well remember the fascination that his books had for me. The book which summarizes his early work on the peripheral vessels was published in 1926 under the title of “Blood Vessels of the Human Skin and their Responses.” In preparation for this
lecture I looked over my old copy of this book, well worn with much reading and full of my marginal notes. Sir Thomas had been working on this subject for the preceding 11 years and knowledge of what was going on reached this country not only from his publications but also from the many American students whom he made welcome in his laboratory. These came in large numbers, many doubtless attracted by the vigor of his creative mind, and perhaps some attracted more by his earlier work with the electrocardiogram, and having in the back of their minds the practical plan of first mastering that instrument under his guidance and then establishing electrocardiographic stations in our country, being not unmindful of the financial rewards which might follow such a course. If this impertinent view of the situation is the correct one, some of my countrymen were rudely shocked by arriving at Sir Thomas's laboratory with the expectation of studying the heart and finding that, Sir Thomas having lost all interest in that organ, they were put to work studying the blood vessels of the skin. But in any event, that important information about the peripheral vessels in both health and disease was emerging from Lewis's laboratory soon became known to me and doubtless to Brown also, because his book, coming out about a year later than Lewis's, is imbued with the physiologic viewpoint and is certainly among the first publications in the clinical field which reflected it.

The Cutaneous Histamine Reaction

My own first investigation in the peripheral vascular field was directly suggested by one of Lewis's experiments. He had been interested in the reaction of the skin to histamine, then a new drug, which, when pricked into the normal skin, produced a reaction identical with the common mosquito bite; a reaction having most, but not all, of the attributes of the inflammatory reaction. Sir Thomas had found that if the circulation to an extremity was obstructed by an inflated blood pressure cuff, the reaction to histamine beyond the point of obstruction was markedly changed. In contrast to the normal, if the obstruction was slight the reaction developed more slowly; and if the obstruction was severe the reaction lacked both the central wheal and the wide area of erythema around it, the flare, the site of introduction of the drug being identified only by a small red spot of capillary dilatation.

These observations at once suggested to me that if the circulation was obstructed by disease the reaction would change similarly, an expectation easily proved to be the case. So this reaction is a rough test of the effectiveness of the circulation in any diseased extremity, and, perhaps, by virtue of its close relation to the inflammatory reaction, a measure of the resistance of the part to infection and of the integrity of the local reflex mechanisms. When I followed 89 diabetic patients for five years the histamine reaction proved to be of prognostic value, its abnormality indicating those more likely to get into trouble.

This histamine reaction, however, is only a rough measure of peripheral blood flow, for it is influenced by pressure as well as flow. Later work clearly demonstrated that, when compared with the vasodilation test, the reduction of blood flow must be considerable before the histamine reaction changes markedly, but when flow is much reduced the change in the reaction can provide much useful information. In addition, not only does this reaction tell about blood flow but it also makes it possible to detect abnormality of the peripheral nerves, for the integrity of these nerves is essential to the development of the flare. Certain precautions have to be observed in making the test, but it works well on the warm wards with the patient in bed. The position of the extremities made a difference; the reaction appearing more promptly when the feet are dependent than when they are horizontal, and it appears still more slowly when they are elevated. The external temperature is also a factor, a cold room delaying the reaction, a warm one accelerating it. A normal person coming indoors after exposure to cold gives a delayed reaction for some minutes until he has warmed up. Areas of unusually thick skin must be avoided. So care must be given to the circumstances under which the test is made.

Nevertheless the test has the great advantage of complete simplicity, and it could be readily
Fig. 1. Histamine reactions at various positions on the thigh, leg and foot of one normal person and three patients.

The drawings of the histamine reactions are semidiagrammatic, as no attempt has been made to follow the exact outlines of the flare and wheal, which are likely to be rather irregular. The drawings of the reactions are in scale, not with the diagram of the leg shown nearby, but with the centimeter scale shown in the left lower corner. The solid black spot indicates a wheal; the dotted circle of approximately the same size indicates the red spot of capillary dilatation in the normal reaction which precedes the development of the wheal, and is replaced by it. The difference between these two was always decided by my ability to find the wheal by palpation with my eyes closed, since the wheal protruding above the surface is easily felt and the red spot cannot be felt. The larger dotted circle represents the flare. These reactions are placed at the level of the diagrammatic leg at which they were elicited in the patient, the uppermost being always above the knee, the lowermost on the dorsum of the foot. The two intermediate reactions were placed on the upper and lower leg, but not directly over the shin. The subject was lying on his back at rest.

Each reaction is represented by four diagrams which show its development in time up to 15 minutes. The plus and minus signs placed near the leg diagram indicate the presence or absence of arterial pulsation at corresponding positions in the subject.

J. V. was a healthy person with a normal blood pressure and the reactions are all normal, that is, they are completely developed within five minutes. Even in healthy persons there is a tendency for the reactions to develop more slowly in the more peripheral positions, and this can be seen at the two and one-half minute observation, in which the reaction on the dorsum of the foot has not as yet whealed.

D. L. was a moderately severe diabetic with a blood pressure of 130/80. Despite the fact that no pulsations could be felt in his leg beyond the femoral artery, the histamine reactions indicate an entirely normal circulation. Obviously an increased collateral circulation has completely compensated for the blocked main vessels.

D. F. was a diabetic with a blood pressure of 170/88 who had developed an area of gangrene between the fourth and fifth toes. Note the abnormality of the reactions obtained below the knee in contrast to the normal reactions persisting above it. There is no whealing of any reaction below midleg, while the whealing below the knee is retarded. No flares appear below the knee which indicates, when whealing is present, an abnormality of the peripheral nerves which is very common in diabetics. Also notice how far up the leg one must go before the reactions become normal.

H. R. was a patient with thromboangiitis obliterans with rest pain in his foot. Notice the persistence of the flares indicating that the nerves are normal, but there is no whealing on the dorsum of the foot, with some delay in the whealing above the ankle. Typically in thromboangiitis obliterans the histamine reactions remain normal much closer to the lesion than is the case in diabetics.

* Most of the data given in figures 1 and 2 have not been published previously. But some of the illustrations used have been redrawn from figures previously published in the American Journal of Medical Science and permission to use these data has been kindly granted by the editor and publishers of that journal.
performed by any doctor. One need only put a drop of 1:1000 histamine on the skin, prick the skin with a needle which passed through the drop—I used to prick through each drop seven times—and observe the time and character of the reaction which appears in the next few minutes. A series of such tests placed along the leg and on the foot is very informing. In healthy persons lying horizontal in a warm room, the distal reactions develop a little more lack of normality, in this reaction does not disclose something well worth knowing about the condition, not only of the blood supply to the small vessels, but also of the small nerves which control them, surely factors of importance in any estimate of the ability of the part to respond effectively to stress, and I must admit some surprise that this simple physiologic test has not been more widely used by those interested in peripheral vascular disease. To try to

slowly than the proximal, but they all become fully developed within five minutes, looking like a row of mosquito bites. In contrast, in peripheral vascular disease, although the tests placed above the knee develop normally those placed distally lag far behind and may never reach complete development during the 15 minute period of observation, lacking the central wheal, or the surrounding flare, or both. It is hard for me to think that the normality, or revive your interest I have prepared some figures showing histamine reactions in patients with peripheral vascular disease (figs. 1 and 2).

Physiologic Methods of Treatment
Looking at peripheral vascular disease from the physiologic point of view, one sees the possibility of saving the limb threatened by arterial obstruction by paying attention to two matters: (1) by reducing as much as possible

Fig. 2. Changes in histamine reactions with time. The symbols are the same as in figure 1.
L. B. had gangrene at the tips of the right first and third toes, which was treated conservatively and eventually healed. Note the improvements in the histamine reactions which indicate an improving collateral circulation. His blood pressure on May 8 was 140/70, on June 7 it was 148/70.
A. F. had a gangrenous area between the fourth and fifth toe. The clinical condition of the foot deteriorated rapidly and there must have been a marked obstruction of the circulation between the two tests as the degree of deterioration of the histamine reactions is most alarming. The blood pressure on April 1 was 142/70 mm. Hg; on April 8 it was 130/65. The patient came to amputation.
S. G. was followed for over two years. At first there was some improvement on conservative measures, but later there was marked progression and eventually the entire left great toe became gangrenous, and amputation was performed at midleg. The blood pressures for the four tests were 125/72, 132/68, 140/80, and 120/70.
the need for blood in the area supplied by the obstructed vessel, and (2) by increasing the supply of blood as much as possible by dilating the vessels still remaining open. And by such means one hopes to tide the patient over a period of acute ischemia until thrombi have been canalized and the development of collateral circulation has time to take place.

Needless to say, some of the methods advocated in 1928 are no longer in use today, but let us look over the list of therapeutic items advocated in Brown's book (table 1) and select certain of them for further discussion of their physiologic implications.

**Pumping Devices**

An important therapeutic item on Brown's list is postural exercises. The rhythmic elevation and depression which constitute these exercises is presumed to increase the blood supply of the limb. Physiologically it is not only possible but probable that such exercises will increase the flow to any limb because of the changes in hydrostatic pressure on elevation and depression and the valves in the veins. But one wonders whether this pumping action is powerful enough to make the exercises worth while and whether the increase might not go to the working muscles where it is not needed rather than to the ischemic area which is so in need of it. Indeed studying the circulation of diseased legs by skin temperature measurements, I found it difficult or impossible to show that any increase in circulation to the skin resulted from such exercises. Certainly most of us nowadays believe that they are of minor importance. However, persons with peripheral vascular disease threatened with gangrene are likely to be in bed for a long time, and when I was treating such cases I used to think that exercises were psychologically useful in giving the patient something to do at regular intervals. Certainly the Saunders rocking bed would produce the same effect on the circulation and would have the great advantage of doing it constantly, even when the patient was asleep; and it pump without muscular exercise and so without diversion of blood to the muscles. Again one wonders whether the increased circulation and the gain to the patient are great enough to warrant the expense of the apparatus and its maintenance, but I can think of no other objection to the treatment, which probably has a small but real place in our armamentarium against obstructive vascular disease.

On the other hand the elaborate suction and pressure devices, reaching their highest degree of perfection in Landis' apparatus, while they can be demonstrated to increase the circulation to a diseased limb somewhat, seem to have resulted in a gain hardly worth the effort and expense involved. In addition there was always the real danger that not only blood but also infection might be pumped through the tissues. But occasionally, especially after an acute embolus in an otherwise normal limb, the method seems to be of real help, color returning and pain diminishing. It takes skill to use such apparatus properly, and, turned over to unskilled technicians, the leg may be so constricted by the sealing cuff that more harm is done than good.

**Heat and Cold**

Two items on Brown's program, contrast baths and radiant heat, I wish to consider together, because increased knowledge of the physiologic mechanisms involved has resulted in the abandonment of these methods. I well recall my own initiation into the field. As a young visiting man at the University of Pennsylvania Hospital I found myself second in command of a ward full of diabetics who had come in large numbers to the hospital to receive insulin, which had just been discovered and so was available to us though it was not available
to doctors practicing outside large university centers. One of these diabetics came in with severe peripheral vascular disease, suffering from rest pain in one foot. I started to treat him as I had been taught to do, that is, I secured a foot cradle inside of which were a battery of electric lamps designed to play their radiant heat on the diseased foot. When I made rounds next day the patient said to me, "Doctor, my foot hurts more when it is in your cradle than if I keep it outside." In the height of my ignorance at the time, an ignorance that I believe was shared by the rest of the profession, I answered the patient this way: "The trouble is that the main blood vessels are plugged up and your foot is not getting enough blood. Heat is a very powerful dilator of vessels, the most powerful we know. Keep your foot inside the cradle and the heat will dilate the vessels and cause the foot to get more blood." The patient took my advice and kept his foot inside the cradle despite the increased discomfort; the foot soon went gangrenous and high amputation had to be performed.

One does not cause pain in patients lightly, and this most unfortunate episode started me wondering whether the patient had not known more about the situation than I did, and whether the gangrene would have ensued if he had not taken my advice and kept his foot in the cradle. I was so bothered about this that I started a series of experiments to answer the questions raised. I knew that the velocity of chemical reactions in vitro was increased as temperature rose. In one of my three summers at the Marine Biological Laboratory at Woods Hole I had attended the physiology course conducted chiefly on marine organisms, and there I had learned that in poikilothermic animals the rate of many vital processes is a function of temperature. Also the basal metabolic rate of man increases roughly 7 per cent for every degree Fahrenheit rise in temperature. Gessler had found that raising the temperature of excised skin from 34 to 48 degrees increased its respiration by 30 to 100 per cent, heating above 48 degrees decreased oxygen utilization, above 52 degrees respiration ceased, probably due to death of tissue. And recently Horwitz and co-workers showed that warming intact skin increases its oxygen tension until skin surface temperature reaches 40 to 45 C., then oxygen tension decreases. Normally the blood flow to a heated part is much increased, placed in hot water our hands become red and the pulse increases. In the sympathectomized paw of the dog Freeman and Zeller found that blood flow varied directly with the temperature of the bath in which the paw was immersed. Perhaps therefore by heating the diseased part I had caused gangrene by increasing the demand for oxygen and other necessary materials brought by the blood, a demand met in the normal limb by a vasodilatation and an increased blood flow, which not only supplies more oxygen but also prevents undue rise of the temperature of the part by carrying heat away. But when my patient's diseased limb had been heated the demand for more oxygen that I had created could not be met because of the vascular obstruction which prevented the needed increase of blood flow.

I soon discovered many other cases in which gangrene had followed the application of heat. So it seemed of vital importance to study the effect of heat on limbs in which the main vessels were obstructed and to determine whether such treatment was beneficial or harmful. To answer this question I used a method which Sir Thomas Lewis had devised, based on the estimation of the color of the skin by means of a color scale. My old friend, Dr. E. M. Landis, now professor of physiology at Harvard, had been working in Sir Thomas's laboratory and he had brought back a color scale made there; so I had an artist make several copies for me.

As you all know, in advanced peripheral vascular disease the skin changes color markedly but the abnormal color is by no means uniform throughout the involved area. To study the skin color of diseased limbs, and so determine the degree of cyanosis, one must therefore choose several areas each of which, marked with a spot of ink, can be matched with the colors on the scale in successive tests. The graduated colors on the scale—at one end the yellowish red of normal skin when the vessels are fully dilated and blood flow very rapid, at the other end the deep blue of full cyanosis—seldom
exactly matched the colors found on the skin of patients, but the method could be used none the less. One began the comparison by comparing the patient's skin color with that at the yellow-red end of the scale. If this scale color was plainly a yellower red than the skin of the patient, one then compared the succession of colors down the scale until it became doubtful whether a certain color was too yellow a red or not. One then moved to the bluer end of the scale, and finding this much too blue, one moved up the scale until one was doubtful whether the scale color was a bluer red than the skin. Thus it was usually found that a single color of the diseased limbs is very great, as this color, so largely due to that of blood in the subpapillary venous plexus, reflects the oxygen content of the venous blood. Provided extreme cold is avoided, for cold makes the oxygen in blood less available to tissues, the degree of cyanosis of the skin is what one wants to know about peripheral vascular disease, because the oxygen remaining in venous blood measures the relation between the metabolic demands of that part and the oxygen supplied by the flowing blood, and so skin color is a physiologic measure of the patient's abnormality. To my mind the use of such a scale provides information bearing more directly on the point at issue than would the analysis of blood samples, taken from veins draining the diseased part. The difficulty with such samples, besides the practical point that the veins are usually constricted and it is hard to secure blood from them, is that the bulk of the blood drawn will come, not from the diseased areas where circulation is minimal, but from the most normal areas where circulation is relatively much better, so the result of chemical analysis may be misleading.

Provided with a color scale I was ready to perform a very simple experiment designed to answer my question of the effects of heating on a limb where vessels were obstructed. The discolored foot of a patient threatened with gangrene from peripheral vascular disease was placed in a tank of water and the temperature of the water was varied, while skin color was estimated by the scale at frequent intervals. I also inquired from the patient concerning the presence or absence of pain, being particularly concerned with finding the temperature at which he was most comfortable. The results, an example is shown in table 2, were definite and clearcut. Most patients preferred a temperature of approximately 92 F. and at temperatures at or near this the skin color was best. In water hotter than this not only did pain begin but the foot often became bluer. The temperatures colder than the optimum 92 F. also caused bluing of the foot, so that I thought of the temperature of 92 F. as the optimum for most persons, the point at which the blood supply most nearly met the metabolic requirements.

<table>
<thead>
<tr>
<th>Temp. (C.)</th>
<th>Color*</th>
<th>Sensation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>XII</td>
<td>Severe Pain</td>
</tr>
<tr>
<td>27</td>
<td>XI</td>
<td>Still aching</td>
</tr>
<tr>
<td>29</td>
<td>VIII</td>
<td>Pain now intermittent</td>
</tr>
<tr>
<td>30</td>
<td>VIII</td>
<td>Pain gone</td>
</tr>
<tr>
<td>32</td>
<td>VIII</td>
<td>Occasional twinge</td>
</tr>
<tr>
<td>33.5</td>
<td>VIII</td>
<td>Patient has gone to sleep</td>
</tr>
<tr>
<td>35</td>
<td>VIII</td>
<td>Awake—no pain</td>
</tr>
<tr>
<td>36</td>
<td>X</td>
<td>Comfortable</td>
</tr>
<tr>
<td>37</td>
<td>X</td>
<td>Comfortable</td>
</tr>
<tr>
<td>37.8</td>
<td>X</td>
<td>Continuous pain</td>
</tr>
<tr>
<td>38.6</td>
<td>X</td>
<td>Continuous pain</td>
</tr>
</tbody>
</table>

* Colors recorded were observed (1) on the dorsum of the foot 2 cm. above the line of demarcation, and (2) 2 cm. above the second toe. On the Lewis scale the Roman numerals increase in size as the color becomes more cyanotic.

scale color could be selected as a red neither too blue nor too yellow, and so the degree of cyanosis could be recorded, even though the color in the scale did not exactly match the color of the skin.

Such a color scale is extremely easy to use and in my opinion gives most valuable information. It has always seemed to me an excellent clinical instrument and I have never been able to understand why it seems to have dropped entirely out of use. Perhaps this is because there is no place where one can purchase these scales that I know of. But the advantage of having a rough quantitative measurement of the skin
After these experiments the radiant heat cradle was discarded at the University Hospital and I believe that it is no longer used anywhere today. I built myself several types of thermo-regulated cradles by which I could maintain any temperature I desired around the foot. In treating a diseased foot the cradle was started at a temperature of 92 F., but I always allowed the patients to change this to any temperature they found more comfortable. Most patients chose a temperature close to 90 F. which was in good accord with the results of my experiments. These thermoregulated cradles had a vogue for a time but I believe they are used rather less today, probably because their maintenance and repair required more knowledge of electrical equipment than most doctors and nurses possess; and, in summertime, or indeed often in our usually overheated wards at other times of the year, the gain over an unheated cradle was perhaps not great enough to warrant the trouble of operation. But we have all learned a vitally important point, that one dare not apply anything but the mildest degrees of heat to an extremity to which the circulation is obstructed, for fear of producing an increased demand for blood which cannot be supplied, and for which destruction of the tissue may be the penalty. The proper therapeutic aim is to maintain the temperature of the foot at the level at which the relation of demand to blood supply is most favorable.

From this experience you will also see why I have been unsympathetic to the idea that diseased limbs should be artificially cooled. Certainly we hardly needed the modern experimental studies in frostbite, such a problem in warfare, to tell us that cold would harm tissues. If there is any proper place for such measures at all, it would be when one had a gangrenous limb far beyond all aid except amputation, in a patient so ill that immediate amputation was contraindicated. In such cases packing the diseased limb in ice might relieve pain and diminish the absorption of noxious products into the general circulation and so perhaps gain a little time in which the patient could be built up to undergo amputation with a better prospect of survival.

The Use of Vasodilating Drugs

The next proposal on Brown's therapeutic list is to dilate the vessels of the diseased limb by means of typhoid vaccine, and indeed by means of skin temperature measurements he proved that this could be accomplished. From our present vantage point of 25 years it is hard to realize the impact of this proposal, for the current medical view of the period was that the main vessels were altogether blocked and this view was supported by knowledge that the best vasodilators of the period, the nitrites, had been tried in peripheral vascular disease and found wanting, a fact which contributed to the pessimistic outlook of the time. The reason for this failure was borne in on me from some experience undergone several years after the publication of Brown's book.

The drug Mecholyl, having been synthesized by Major, was being tested in Dr. Richard's laboratory of pharmacology, where I was working at the time, by the Belgian pharmacologist Simonart, and was proving to be the most powerful vasodilator known up to that time; it would break through the action of adrenaline in animal experiments while the nitrites would not. I immediately seized upon the new drug in hopes that it would be of major assistance in peripheral vascular disease. I tried it both on healthy persons and patients in the clinic, seeking to record its vasodilating action by measuring the skin temperature of the feet. Figure 3 shows such a record. The results not only disappointed me but they also greatly surprised me. After a subcutaneous injection of the drug violent effects appeared within a minute or two, the face flushed and became warmer as vasodilatation manifested itself there, but the feet became much colder. Obviously I was getting not a pure vasodilating action but a mixture of actions, vasodilatation in some places such as the face, but vasoconstriction in other places as in the feet where I so desired to secure the reverse. It was some time before the physiologic implications of this were clear to me, and before discussing this aspect of the situation in detail let us see what general principles can be learned from more recent experiments in the field.
Studies with the plethysmograph have thrown light on many aspects of this problem. The physiologic phenomenon involved in getting an increased flow of blood to one part of the peripheral circulation has been intensively studied by Burch and his associates by means of plethysmographic technics over many years, and the experience has been summarized more recently. With their views of the matter I am in entire accord; what one needs to remember may be briefly summarized as follows:

Blood flow to a foot may be enhanced by increasing the cardiac output but this also increases the blood flow to places where such increase serves no useful purpose. This is what happens when increased flow to a foot is secured by fever, as after typhoid vaccine, and by certain drugs. The injection of large amounts of salt solution intravenously increases blood volume and must cause a vasodilatation somewhere in the body to accommodate it; thus the periphery may be included in a general vasodilatation, and if the injection is large enough some increase of cardiac output may be expected as well. But these methods should be thought of as a very inefficient way of increasing the blood supply to a foot. It would seem far preferable to increase the flow in the diseased foot by borrowing the blood from another part of the body which does not need it. Indeed as Burch and his collaborators have shown by measurements made with several peripheral plethysmographs recording simultaneously, there is normally a continuous shifting of blood flow from one part of the body to another, a process which they dignify by the term hemometakinesia, and which they regard as serving the useful purpose of supplying the organs with blood according to their varying needs, with the greatest economy of effort. We still lack knowledge about shifts of blood flow between the peripheral organs in which it can be measured easily, and the abdominal organs in which, with the possible exception of the kidney, blood flow can be measured only with difficulty or not at all in man, but we have every reason to expect that an exchange of blood flow, a borrowing-lending process, similar to that demonstrated in man for two parts of the periphery, will also take place between the periphery and the deep organs, as many animal experiments indicate.

It is impossible to think of a generalized vasodilatation without a concomitant increase in blood volume and there is good reason to believe that rapid increments of blood volume are not possible to the body, as blood volume is restored so slowly after hemorrhage. Therefore the blood needed to fill vessels whose diameter has rapidly increased must be withdrawn from other vessels whose diameter must diminish correspondingly. A fall of blood pressure, as from a hemorrhage, causes reflex vasoconstriction. Therefore the train of events when one gives a powerful vasodilator like Mecholy1 may be thought of as follows: vasodilatation of certain areas, fall in blood pressure, reflex vasoconstruction. So, far from having a pure vasodilator action we have a competition between dilatation and constriction. I do not know with certainty why dilatation always wins out in the face and constriction in the feet; perhaps the vessels of the "blush" area, more exposed to the elements than other parts of the body, might be thought of as more susceptible
to vasodilator influences than those vessels elsewhere in the body which are usually covered by clothing. Perhaps the constriction should be thought of as for the purpose of conserving body heat which is being lost from the dilated areas. But whatever the reason, the fact remains that large doses of vasodilators by mouth or by injection are followed by constriction in the extremities, an effect the reverse of that sought in peripheral vascular disease. However, this line of thought gives us a hint; perhaps the way to get vasodilatation in the feet by means of drugs is to give them so that a fall in blood pressure is avoided as far as possible. This idea seems to be borne out by experience. The slower acting choline derivatives such as Doryl and Uricholine have little effect on blood pressure; considerable increases of skin temperature of the feet may at times follow their administration, and I have occasionally seen very striking relief of rest pain, exceeding that secured by morphine, after the subcutaneous administration of these drugs, even though I was unable to detect a concomitant rise in skin temperature. I presume such relief of pain was due to a vasodilatation too slight or too deep to be recorded by a skin temperature change.

Other factors than the state of cutaneous vessels enter into the problem of increasing the circulation to the feet, and one of these is the cardiac output, for you might well increase the flow to the feet by increasing flow to all parts of the body. The febrile reaction to the typhoid vaccine used by Brown would have just such an effect as is demonstrated in figure 4, in addition to effects on the peripheral vessels. But the peripheral effects of typhoid vaccine are mixed, an undesired vasoconstriction in the stage of the chill while body temperature is rising, then the desired vasodilatation as the chilly sensations pass off and are succeeded by the feeling of warmth. So this method of securing vasodilatation in peripheral vascular disease is far from ideal, for vasoconstriction has an element of danger in this disease; thrombosis sometimes follows it. In addition treatment with typhoid vaccine could not be indefinitely repeated because the development of immunity soon abolished the febrile response, and it is little used today.

We are searching even now for the perfect means of increasing the flow of blood through the feet, and looking for the perfect drug which will cause vasodilatation without stimulating cardiac output, and so will increase the flow to the diseased extremity by diversion of blood flow from other sources. The direct introduction of drugs into the skin of the diseased extremity by iontophoresis obviously meets this need, but the special skill and apparatus required have limited the usefulness of the method. Injections of vasodilators directly into

![Fig. 4. Ballistocardiograms showing the effect of typhoid vaccine given to a case of peripheral vascular disease. The points of interest are the increase in ballistic amplitude which occurs before the rise in temperature, the tachycardia and diminution of amplitude at the time of the chill, the continuing tachycardia and increased amplitude when the fever rose, and the final return to an amplitude somewhat smaller than the control. The reproduced tracings are one-third actual size. The time record at the top applies to all the ballistocardiograms; its longest interval is one second.](http://circ.ahajournals.org/)

Typhoid vaccine was given at 10:45 a.m. The calculated cardiac output at 11:30 a.m. does not differ from the control. By 11:55 a.m. the patient had a sensation of fullness in the head though his temperature had not yet risen. At this time the cardiac output had increased by 61 per cent of the control value. At 1 p.m., at the time of the chill, it was 32 per cent above the control value, and at 3:30 p.m., the temperature having risen, it was 65 per cent above the control value. By 10:00 a.m. next day the febrile reaction had passed off and the calculated cardiac output was 9 per cent below the control value of the day before.
the artery supplying the part has been tried recently.28 Such drugs might be injected through one of the small plastic catheters29 which can be inserted into an artery through a needle and left in situ without discomfort after the needle is withdrawn. This seems well worth trying as an emergency procedure, though how long this could be properly continued has not been determined, and such procedures are still in the experimental stage.

Our chairman, Dr. Montgomery, with Dr. Horwitz and their collaborators30 have been among the most active in the attempt to identify a satisfactory peripheral vasodilator which can be taken by mouth or injection. It was first found that our old friend alcohol met the need for a gentle vasodilator, which would increase the circulation to the feet without stimulating the cardiac output or reducing the blood pressure, better than the other drugs available at that time.29 Recently Priscoline has looked more promising.31-38 Whether the newer drugs on the list, especially the adrenolytic group and the sympathetic blocking agents,36, 37 will be found superior to these older drugs I do not know, but I do know that our methods of testing for effects of these drugs have greatly improved, and that by taking skin temperatures in a thermoregulated cool room, with a ballistocardiogram to detect effects on cardiac function, an evaluation of the steady stream of new drugs is possible with an accuracy not available a few years ago. And that there is a place for drug therapy in peripheral vascular disease is obvious.

**Harmful Vasocostriction**

The same tests used to identify beneficial drugs may also be applied to learn about agents harmful to the patient and certainly the discovery of the constrictor effect of the nicotine in smoking tobacco and subsequent realization of its harmful effects in peripheral vascular disease have permitted a great advance in therapy. There seems no doubt that, as originally pointed out by Silbert,28 these patients should avoid the use of tobacco; Brown realized this in 1928, and Grace Roth has contributed much to our knowledge of the subject more recently.29 There is no longer room for doubt that the improvement following abstinence from tobacco may be long continued.40

**Reflex and Postprandial Vasodilatation**

I must not pass the subject of vasomotor responses in peripheral vascular disease without emphasizing another most effective means of securing vasodilatation in the extremities. We dare not heat the diseased limb itself, but we can readily secure a powerful vasodilator effect on the vessels of the diseased limb by heating some other part of the body like the hands or abdomen, as was shown by Lewis in work summarized in his later book, "Vascular Disorders of the Limbs,"41 and by Gibbon and Landis.42 Here is a maximal vasodilatation secured without any of the untoward side effects so often found after drugs, and it seems the ideal method of securing vasodilatation for short periods of time in bed patients. But prolonged heating is not well tolerated even by bed patients, and heat to the body cannot be readily applied to ambulatory patients. We can, however, keep all our patients warm, and I do not doubt that this is an important factor in keeping their peripheral vessels dilated, as Brown well knew.

Vasodilatation of fingers and toes also follows the ingestion of a substantial meal by normal subjects and the duration of the vasodilatation can be prolonged by feeding at frequent intervals.43 I am not aware of data indicating that similar effects can be secured in peripheral vascular disease but one expects that they could.

**Surgical Vasodilatation**

It is the difficulty of securing long-enduring vasodilator action in a diseased limb by means of drugs or physical agents which makes the surgical means of securing it so attractive, and Brown's series, operated upon by Adson,44 was one of the first, if not the first, in which advantage was taken of the new knowledge concerning the effects of sympathectomy on peripheral vessels. This operation brings about a long continuing increase in blood flow to the denervated part as Brown showed,1 and this has been amply confirmed everywhere.45 This operation has since been used all over the world, with marked benefit in many cases.
That it is no final answer all would agree today, I believe. Perhaps the fault lies in the increased sensitivity to adrenaline which occurs in vessels deprived of their sympathetic innervation though this effect is easier to demonstrate in animal experiments than in man. Perhaps, as Freeman has emphasized, the ability to dilate the vessels preferentially may be lost within the denervated area, so that despite the increase of blood flow to the limb as a whole, the ability to concentrate a greatly increased blood flow around an area of local infection may be impaired by the denervation. Perhaps the disease progresses or the nerves regenerate, or both, but in any event the beneficial effect of sympathectomy is usually limited to a period of years. You are as familiar with the evidence as I, and I do not see the need of reviewing it here.

In addition, rapid deterioration of a diseased extremity after sympathectomy is seen occasionally, and this aspect has been recently emphasized with the thought that somehow the denervation was allowing the extra blood to flow through A-V anastomoses without increasing the flow at the point of need, or was adversely affecting the collateral circulation. Certainly our lack of knowledge of the physiology controlling the distribution of blood within a single part, and of the factors which aid or hinder the development of collateral circulation is greatly to be deplored—it is a point on which the histamine reaction would throw light—for while our therapeutic methods may tide the limb over acute episodes, we count on the development of collateral circulation to restore the limb to health; and increased knowledge of the factors which assist, and of those which hinder this development is greatly needed.

Certainly the other operative procedures have not fared as well as sympathectomy. Caudal block with procain, producing the same vasodilator effect, but for a period of hours only, has a place; but the operation of sectioning the peripheral nerves, though it temporarily relieved pain by rendering the part anesthetic, has proved to have so many untoward after-effects that it has been abandoned in most clinics.

Early Adventures with Oxygen and Desiccation

Before going on I shall yield to the temptation of reminiscing about some of my early adventures with a type of therapy which taught me a great deal though the method itself has long since been properly discarded. That oxygen could penetrate the skin had long been known to physiologists, and, with oxygen tents for pneumonia all about my ward I began to wonder what would happen if a cyanotic foot was placed in such a tent. I tried and the answer was that nothing happened that I could see. But in such a tent the concentration of oxygen could not be raised above 50 per cent so I

TABLE 3.—Effect of Increasing Concentration of Oxygen around the Foot of a Patient with Gangrene of the Great Toe

<table>
<thead>
<tr>
<th>Time</th>
<th>Oxygen (%)</th>
<th>Color* (1)</th>
<th>Color* (2)</th>
<th>Sensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:25</td>
<td>21</td>
<td>XV</td>
<td>XIII</td>
<td>Severe pain</td>
</tr>
<tr>
<td>12:30</td>
<td>50</td>
<td>XV</td>
<td>XIII</td>
<td>Severe pain</td>
</tr>
<tr>
<td>12:35</td>
<td>68</td>
<td>XIII</td>
<td>XII</td>
<td>Pain better</td>
</tr>
<tr>
<td>12:50</td>
<td>77</td>
<td>XII</td>
<td>XI</td>
<td>Pain gone</td>
</tr>
<tr>
<td>1:10</td>
<td>82</td>
<td>VIII</td>
<td>XI</td>
<td>Comfortable</td>
</tr>
<tr>
<td>1:40</td>
<td>84</td>
<td>VII</td>
<td>X</td>
<td>Patient asleep</td>
</tr>
<tr>
<td>3:45</td>
<td>74</td>
<td>VI</td>
<td>X</td>
<td>Comfortable</td>
</tr>
<tr>
<td>3:53</td>
<td>21</td>
<td>VI</td>
<td>XII</td>
<td>Pain begins</td>
</tr>
<tr>
<td>4:00</td>
<td>21</td>
<td>IX</td>
<td>XII</td>
<td>Pain persists</td>
</tr>
</tbody>
</table>

* The colors were read at (1) 2 cm. above the line of demarcation at the base of the great toe, and (2) on the dorsum of the proximal phalanx of the second toe. On the Lewis scale, the Roman numerals increase in size as the color becomes more cyanotic.
ease, wide open aortic regurgitation and auricular fibrillation, six weeks after cesarian section suffered from embolism first in one leg and three days later in the other. On admission both feet were cold and edematous, with mottled cyanosis below midleg. Because of the severe cardiac complications the surgical consultant, a man extremely sensitive about his operative mortality, believed the patient would not survive two amputations and firmly declined to interfere. Now this was the same surgeon who had advised bilateral amputation in my case which recovered without it, so perhaps he winked the other eye when he left me with the responsibility. I had no choice but to go ahead and do the best I could. At that time my apparatus would permit the treatment of only one leg at a time with oxygen, so the right, the worse leg, was inserted in a thermo-regulated cradle with a gas tight cover and kept exposed to a concentration of 60 per cent to 80 per cent oxygen as determined by frequent analyses. This had a most striking effect on the color of the skin of this leg; cyanosis disappeared, many areas turned bright red and pain in it diminished, in contrast to the other leg which, exposed to room air, remained both painful and cyanotic. The accumulation of moisture within the cradle covered with air-tight material caused trouble, but I soon learned to prevent this by desiccation of the contained air by pans of calcium chloride placed within the cover. However, despite the encouraging change of color of the right, gangrene started in the toes of both legs.

Within a few days my apparatus had been altered to permit both legs to be exposed to the high concentration of oxygen and the improvement in color of the left leg then equalled that of the right. Nevertheless, gangrene slowly ascended both legs at an equal rate, apparently uninfluenced by the treatment employed. Doubtless the oxygen did not penetrate deeply into the tissues, but I prefer another explanation for my failure, for I slowly came to realize how much needed material the blood carries to the tissues besides oxygen. By putting oxygen through the skin we could restore its oxygen tension to normal, but the tissue died nonetheless. So while it is now possible to measure oxygen tension in the skin by polarographic methods with rough accuracy as Dr. Montgomery and Dr. Horwitz have done, and to raise the oxygen tension both deeply and superficially in the extremities by having the subject breathe pure oxygen, as they have shown, I have little hope that much of great practical therapeutic value can be secured by such methods.

But another part of that experience may still be of some interest to those who are interested in the therapy of peripheral vascular disease. The desiccation I used to keep down the moisture content of my closed gas chamber around the legs had a most interesting effect. My desiccators collected about 50 cc. of water a day and the gangrenous areas became mummified, shrunk to about half the natural size of the part and with a surface as hard as wood. The desiccation kept down all infection until, a line of demarcation forming just below both knees, spontaneous amputation began. This cleavage finally went down to the bones which were eventually cut through by the surgeon without anesthesia and without pain, leaving the ends of the bones protruding from the stumps, which were cleaned up by maggots, a treatment then in vogue. The patient stood this well, the stumps became clean and were granulating nicely, and I was envisioning the ease of attaching artificial limbs to the projecting bones. But she died of heart failure three months and six days after her admission and about three weeks after the surgical completion of the spontaneous amputation.

Modern surgical technics and the antibiotics have made this experience sound medieval, and it was indeed a dreadful ordeal for the most unfortunate patient, something to be avoided at all cost, but I have often wondered whether desiccation might not have a small place somewhere. The old conceptions were of the most dangerous "wet" gangrene, and the far less dangerous "dry" gangrene, and it is certainly in our power to convert the former to the latter by means of desiccation. This experience occurred long before the discovery of the antibiotics and had we been provided with these modern therapeutic agents we might have done much better for the unfortunate patient, as it
was infection in the line of demarcation which was our chief difficulty. I am glad to see that interest in conservative measures for the treatment of gangrene has not entirely died, there is a brief article on this field in a recent number of the Journal of the American Medical Association. Let us not forget the healthy tissue sacrificed because the surgeon must amputate so far above the level of the lesion. Perhaps with thought, skill and inspiration we could do better for these unfortunate patients than we do now.

Newer Methods of Treatment and Prevention

For the sake of completeness let us now consider some of the newer methods which have been of no little service, although, before discussing them, I will have to admit that my own experience with them has been slight; for by the time they appeared on the horizon I was turning my attention to other matters.

The idea that thrombosis was the final event in the train which closed the vessel is an old one and the attack by anticoagulants a logical one as soon as drugs of this nature became available. Here I must pause, however, to mention an experience which has had considerable effect on my view of the matter.

A most emaciated young woman with rheumatic heart disease and wide open aortic regurgitation was admitted to my ward many years ago. Because of the combination of emaciation and aortic regurgitation the pulsation in her peripheral arteries was visible, and of course palpable also, to a most unusual degree; it could be seen all the way from the axillae to the wrists. While under my care the patient had a sudden pain in the right arm and it was found that the pulsation had disappeared below mid arm. Indeed the point of obstruction, surely embolic, could be located exactly, for pulsation in the brachial artery was seen down to a definite point, and there it stopped. We had no anticoagulants in those early days so we simply watched the arm closely, and I was greatly surprised to see how rapidly the circulation was restored. The lower limit of visible pulsation moved slowly down the arm and within 48 hours no sign of obstruction remained. Certainly I had been underestimating the ability of the body to dispose of an intravascular obstruction which, in this case, was probably an embolus of clotted blood, with thrombosis below it. Certainly we have the right to attempt to assist the natural process of restoration by using anticoagulants, even though strong positive evidence of their effectiveness is hard to secure in any given case, and the published studies deal chiefly with their effect in heart disease, rather than peripheral vascular disease.

I have no need to emphasize the tremendous contribution of the antibiotics to the therapy of peripheral vascular disease. In the old days it was so often infection which led to the change from the chronic disease to the acute emergency, and with these new agents at hand the outlook for the infected case has changed greatly for the better. In the old days the patient's attempts at local antisepsis sometimes led to trouble, and the use of tincture of iodine as a routine antiseptic was one of the most frequent causes of disaster to cases of peripheral vascular disease in my early experience. That highly irritating and painful agent, originally designed as a stock solution for dilution before use—it is the only official iodine solution that can be diluted with water in all proportions without precipitation—by some trick of fate became the household antiseptic of choice of thousands of American homes, and I fear was prescribed by a host of doctors and even more nurses, perhaps with the thought that the severe pain caused by its application to a wound was somehow a testimony to the power of its beneficial action. We now think of this same pain as providing strong evidence of its destructive action on living tissue. Tincture of iodine is gone for good, I think, rated as causing so much tissue destruction that liability to infection was increased by the presence of devitalized tissue, a factor which might overbalance the drug's undoubted killing action on bacteria. But so popular was it that I well recall my struggles to get it out of the medicine chest in my own home. Indeed it took a second world war to get tincture of iodine out of the first-aid kit and directions of no less an organization than the American Red Cross. But it has gone for good now, and there will be fewer cases of
gangrene among those with peripheral vascular disease in consequence.

I must also say a word about more positive preventive measures which are now taught to those with diminished circulation to the feet, and so living under the constant threat of trouble. Patients are nowadays educated on such hygienic measures as extreme cleanliness in the care of the skin, keeping the feet warm and dry, wearing thick stockings and well-fitting shoes, avoiding all trauma, especially when cutting the nails, avoiding the application of chemical irritants, and especially to seek medical advice immediately for the smallest trauma or infection. It is hard to get positive data on the effectiveness of any preventive program, but I have little doubt that such educational measures are a major factor in the improvement of the general outlook for peripheral vascular disease, which has been so noteworthy in my medical lifetime. In the school year before Brown’s book was published, 1926 to 1927, the total number of major amputations of the leg done on the general surgical service of the University of Pennsylvania Hospital was 24, 25 years later the number of major amputations of the leg in the same period of time had diminished to 13, although in this interval the clinic, judged by the total number of major operations done, had increased over two-fold. So I conclude that preventive measures and conservative treatment are saving about three-fourths of the cases who formerly came to major amputation.

I must end by saying that I do not take a hopeless view of the possibility of a direct attack on arteriosclerosis itself. Starting my medical career before the first big break, insulin, I have seen the medical wards change completely during my medical lifetime, and certainly the advance of medical knowledge at this moment is as rapid as at any time in history. Animal experiments have demonstrated that lesions much like, or as some claim, altogether similar to human atherosclerosis can be produced, and after establishment will regress under appropriate conditions. Also I have been extremely interested in some experiments being conducted by Dr. Urbach of my medical school and my former associate, Dr. Hildreth, on a group well known to be subject to early atherosclerosis, the idiopathic hypercholesterolemies. Placed on an extremely low fat diet for a long period of time the visible skin lesions of several of these patients have regressed and disappeared. Whether the invisible arterial lesions do likewise I do not know, but Dr. Montgomery tells me he has seen peripheral pulses in the limb of one of these cases absent at the beginning of the diet return after the patient was so treated for about six months, which Dr. Urbach tells me is not a unique experience. This is far from conclusive evidence, but it is ample reason for continuing attempts in this direction.

So I come to the end of my lecture. An old teacher from whom I learned a great deal, Professor E. G. Conklin of Princeton used to say, “Things are not discovered, they grow.” This is particularly true of the peripheral vascular field which has seen, not epoch making discoveries, but steady growth, until the outlook for those with the misfortune to suffer from obstruction of the peripheral circulation is far different from what it was 25 years ago. And in this growth George Brown played a worthy part.

REFERENCES*


* No attempt has been made to give a complete bibliography of the wide range of subjects covered in this lecture. The references given are to older work which seems to the author unusually important and to very recent work which contains references to other papers in the field. By looking up the bibliographies of these recent papers the author believes that a complete coverage of the field could be secured by anyone who was interested.


16 Editorial on Frostbite, J. A. M. A. 148: 940, March 15, 1952. (References to recent work.)


24 Roth, Grace M.: personal communication.


BSTRUCTIVE VASCULAR DISEASE


38 Silbert: Cited in reference 1.


49 —, Zinsser, H. F., and Horwitz, O.: Oxygen tension of tissues by the polarographic method. II. Detection of right to left shunts by changes in skin oxygen tension resulting from inhalation of oxygen. Circulation 2: 845, 1950.


The George E. Brown Memorial Lecture: Physiologic Considerations Concerned with the Pathogenesis and Treatment of Obstructive Vascular Disease
ISAAC STARR

Circulation. 1952;6:643-660
doi: 10.1161/01.CIR.6.5.643

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1952 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/6/5/643

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/