The results of this investigation showed, as might be expected, that, whereas the uncomplicated bites of blood-sucking insects never cause any inflammation and are comparable to the injury which might result from the probing of a surgical needle beneath the skin, the stings of scorpions and of bees result in a very marked inflammation. In the case of the bee, the sections showed oedema, marked cellular infiltration, and some necrosis of the underlying muscle layer, which was followed within 24 hours by a walling-off of the damaged tissue by a palisade of inflammatory cells. In the case of the scorpion sting, the reaction was somewhat similar, though more severe, and was associated with an extensive coagulative necrosis of the underlying muscle.

"Immunity"

There remains one aspect of the association between the skin-piercing arthropod and its host to which, so far, no reference has been made. It is not unusual to encounter individuals who declare that a particular venomous arthropod, such as a bee, will not sting them, or that certain blood-sucking fleas or flies do not bite them. The first group of persons seem to depend for their immunity on their power to handle particular arthropods—in this case bees—without alarming them. The second group is more difficult to explain; unquestionably there are persons who are not so attractive to lice or mosquitoes as their less fortunate fellows, but in our experience such cases are rare, and we have not yet encountered a case of complete immunity.

Pepys—you may remember—declared that while at Portsmouth he shared a bed with a certain Dr. Clarke, and that the fleas bit the doctor but not the diarist, a happening which seems to have pleased the latter "mightily." Pepys's statement can never now be substantiated, but we have carried out a number of experiments in which persons who stated that they were seldom bitten by mosquitoes, together with controls claiming no such privilege, introduced their hands and forearms into a large cage containing many hungry mosquitoes. The cage was arranged in such a way that, though the observer could see what was going on inside, the persons volunteering for the experiment could not. Under these conditions the results of individual experiments were always similar; the persons claiming immunity continued to maintain that they were not being bitten, but the impartial observer recorded in his notebook that the mosquitoes were unimpressed by such an assertion and were biting the "immunes" as readily as the "non-immunes."

It would seem, therefore, that the majority of individuals who believe that they are relatively immune from the bites of a particular species of insect are mistaken, and that their apparent immunity is the result of their failure to notice the insect during the time that it is biting. This failure is due either to the individual's not having become sensitized to the species in question, or because, although previously sensitized, he has become desensitized as a result of regular and prolonged exposure.

Summary

The pathological effects produced by arthropods directly injurious to man—as distinct from those which as transmitters of diseases are regarded as indirectly injurious—can usually be classified in one of four categories.

1. Lesions due to mechanical trauma, in which the damage done is usually severe only when it is caused by certain of the larger species of myiasis-producing larvae or when an abnormal host is attacked.

2. Lesions due to secondary infections—these include the more serious effects of myiasis which follow the infection by bacteria of wounds previously made by invading arthropods.

3. Lesions due to the injection of substances which are normally harmless but to which the host has become sensitized as a result of previous exposure. Recent research suggests that any immediate and severe reaction associated with the bite of parasitic arthropods or with their invasion of the tissues is due to previous sensitization of the host. Such reactions are usually highly specific.

4. Lesions due to injection of directly injurious substances. Certain predatory arthropods, such as scorpions and spiders, secrete venom usually of high virulence which, when injected into mammals, causes both generalized symptoms and an extensive coagulative necrosis of the underlying muscle. In the case of non-predatory insects, such as bees, the reaction tends to be mild and to remain localized.

REFERENCES

- Crewe, W., and Gordon, R. M. (1949). *Ann. trop. med. Parasit.*, 43, 341.
Gordon, R. M., and Crewe, W. (1948). *Ibid.*, 42, 334.

DIVISION OF POPLITEAL VEIN IN THE TREATMENT OF SO-CALLED VARICOSE ULCERATION*

BY

GUNNAR BAUER, M.D.

Chief Surgeon to the General Hospital, Mariestad, Sweden

Non-specific ulcers of the lower leg have for a long time been termed varicose ulcers, evidently because varices of the subcutaneous veins were thought to be the cause of the ulcer formation. To-day, however, we know that this is only part of the truth and that the root of this evil goes much deeper. Knowledge of the normal and pathological physiology of the veins of the lower extremity has made very considerable progress during the past decade. Modern investigation tends to regard the entire vascular system of the leg as one system, similar to a U-shaped communicating glass vessel. The aorta and the large arteries form one branch of the vessel, the capillaries the bottom, and the large vein trunks and the vena cava the other branch. Being completely filled with fluid, this system is in perfect hydrostatic equilibrium. If a quantity of blood is introduced into one side of the system, as is the case each time the heart stroke pours blood into the aorta, an equal amount of blood flows out of the other end of the system, from the vena cava into the right side of the heart. This explains how the venous blood is made to return from the lower extremity irrespective of the body's position.

However, when the body is brought into the vertical position another factor is added. It is a well-known fact that in this position, because of the action of gravity, a large quantity of blood assembles in the lower parts of the leg. To explain this it is necessary to remember that the human U-shaped vessel, unlike those made of glass, does not have rigid and impermeable walls. Instead, the blood vessels, especially the veins, have elastic coats which are apt to give way under high pressure. The lumen widens and an ever-increasing amount of blood can accumulate. After some time a condition of pronounced venous stasis is created.

To get rid of this surplus of blood the healthy human being is in possession of a highly efficient auxiliary

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mechanism, consisting of the action of the muscle masses of the calf. When these muscles contract, as in walking, they act as a sort of peripheral heart, squeezing considerable amounts of blood from the lower leg up into the popliteal and femoral veins. From there the blood cannot return because of the action of the valves in these large veins.

It is not difficult to imagine what would happen if those important valves for one reason or another were no longer able to function properly. The blood that was squeezed out of the lower leg would return the moment the muscles relaxed, and no amount of walking or muscle movements would be able to rid the lower leg of stagnating blood. The venous stasis would steadily increase and oedema would soon begin to develop. If prolonged for weeks or years, graver tissue changes, such as induration and even ulceration, would set in, and, as a result of anoxaemia, there would be aching or pain.

It is impossible not to be struck by the fact that the pathological changes just described constitute the exact image of what is to be observed in cases of lower-leg ulcers. An ulcer is hardly ever found quite alone. It is nearly always accompanied by chronic pitting oedema and by large areas of brawny and indurated skin, and the patient generally complains of a dull aching or bursting pain whenever the leg is in the vertical position. In fact, these symptoms constitute the components of what may be called the "lower-leg-stasis syndrome."

The grave circulatory disturbances evidently underlying this syndrome caused me and my co-workers, about four years ago, to start an investigation into the conditions prevailing in the large deep veins of the entire leg. The results of this work have been described in detail elsewhere (Bauer, 1948, 1950a). Using a special phlebographic technique in which the contrast was introduced into the proximal end of the femoral vein, a large series of cases was studied. In practically all cases with a pronounced stasis syndrome the femoral and popliteal veins were found to be in a pathological condition, the main feature of which consisted in the complete, or nearly complete, absence of normally functioning valves.

The aetiological factor in many cases was found to be a previous deep venous thrombosis. When a vein trunk is recanalized after having been obliterated by thrombotic clots, the result is a thick-walled rigid tube without even traces of valves. In an even larger group, however, the valvular insufficiency was caused by phlebosclerotic or similar changes, and might be called idiopathic.

The conclusion was reached that the stasis was caused by this pathological condition of the valves. Later experience from several hundred cases entirely corroborated this view.

Treatment of Venous Overloading

The main problem when trying to devise a suitable therapy appeared to us to be this: in what way would it be possible to assist the action of the peripheral heart, or, in other words, by what action could we prevent the blood that is squeezed out from the lower leg by muscular contraction from flowing back again?

It seemed to us that if the large avalvular vein trunk was permanently blocked at its lower end, in the popliteal region, this would prevent the possibility of back-flow. Division of the popliteal vein was performed in a few cases, and the results were encouraging. The patients improved, and it could be demonstrated radiographically that after operation the calf-muscle contractions drove

the blood through numerous fine-calibred channels into the muscle veins of the thigh, and that no back-flow occurred.

It thus appeared as if a suitable form of treatment might be within reach, and ligation and division of the popliteal vein was taken up as a routine procedure and has remained so for more than three years.

Indications for Popliteal-vein Division

At the Mariestad Hospital, up to the time of writing, 245 popliteal-vein divisions have been performed in cases of proved valvular incompetence. The symptoms present at the time of operation are given in Table I. It will be

TABLE I.—*Leg Symptoms in 245 Patients Before Popliteal-vein Division*

Symptom	No. of Cases in which Present
Bursting pain	243
Oedema	244
Induration	236
Open ulceration	180
History of repeated ulceration but no ulcers open at the moment	33

seen that pain, oedema, and indurative skin changes were present in practically all the cases, and that open ulcers or a history of repeated ulceration were observed in seven-eighths of the patients.

During the first year of this work all cases were examined by retrograde phlebography before being subjected to popliteal-vein division, because a need for further study was felt. To-day we feel convinced that in practically all cases with a clear-cut stasis syndrome there is also deep valvular insufficiency, and we do not hesitate to operate on the strength of an ordinary careful clinical examination alone, without recourse to phlebography.

In a fair number of cases there will be found, in addition to the typical syndrome, the well-known signs of incompetence of the great saphenous vein or of incompetence of one or two of the large communicating veins arising out of the depths in the lower third of the thigh. In these cases there is every indication to divide and inject or strip these veins as well. It is our belief that no good can possibly come from any vein with a retrograde blood-flow, and it has been our practice for a long time to deal with these veins at the same time as we are doing the popliteal-vein division. We have seen no harm arise from this.

Now and then there come under observation borderline cases in which some of the components of the syndrome are not very well marked and in which, at the same time, a large, tortuous, and incompetent great saphenous vein is demonstrated. In such cases the question may arise whether the lower-leg changes are caused by the saphenous alone or whether there may not, in addition, be a deep insufficiency. In these circumstances phlebography is indicated. The examination should, however, not be done by puncture of the femoral vein. It is much easier to introduce the contrast medium *via* the saphenous vein. This vein must in any case be exposed at its upper end and tied. After tying the lower ligature, but before applying the upper one, the needle of a syringe containing 20 ml. of diodone ("diodrast") (35%) is introduced into the saphenous vein. Before injecting, it is absolutely necessary to make sure that the valves in the superficial femoral vein, if any, are closed at the moment when the dye runs into the vein. According to our experience this can best be done, and the most uniform results obtained, if the foot

end of the operating table upon which the patient lies is suddenly lowered to 45 degrees or more. Then, but not until then, should the injection be made, occupying about thirty seconds. At the end of that period the x-ray exposure is made.

If with this technique the contrast medium is seen to have run down into the femoral vein and to have passed the knee level, indications for popliteal vein division are present. If, on the other hand, this technique is not strictly followed, the contrast medium, which is heavier than the blood, may sometimes be observed to trickle downwards for some distance, even in persons in whom there exists no valvular incompetence. Instances are known in which this phenomenon has caused some observers to doubt the value of the method.

At this point it should be mentioned that we have devised a method to make absolutely sure, on the operating table and before actually dividing the popliteal vein, that the femoral vein is incompetent. After exposing the popliteal vein a loosely tied ligature or a clamp is applied on the distal end of the exposed vein. After that, we insert in the vein, proximal to the ligature, the needle of a manometer similar to that used in lumbar puncture but with a much longer glass tube. The foot end of the table is then slowly lowered to 45 degrees. If blood enters the glass tube and rises to a level of 40 to 60 cm., which, incidentally, corresponds to the level of the patient's heart, this is a sure sign that the femoral valves are incompetent.

Results

There were no post-operative deaths among the 245 cases operated upon. No complications were observed, with the exception of slight wound haematomas in five cases. In no case was there any demonstrable harm to the circulation in the lower leg as the result of the operation.

A marked improvement was observed in all the patients. The aching or bursting pain was relieved almost at once. The ulcers generally healed in a shorter time than might have been expected with conservative treatment.

Follow-up Examination

It is a well-known fact that patients with leg ulcers nearly always show a considerable improvement after an interval of hospital care, whatever treatment is given. The utmost care must therefore be exercised when the effect of an additional new form of therapy is to be evaluated. A considerable period of time, preferably several years, must be allowed to pass before final judgment can be pronounced.

In the Mariestad Hospital material only one patient has been observed for more than three years and only 55 have passed the two-year mark. Nevertheless, in order to obtain a preliminary idea of what may be expected after popliteal-vein division, follow-up studies were made of all those cases, 196 in number, in which the time of observation was at least six months. It was found very informative not merely to examine all the patients at a given date but also to follow the course of their illness in detail from the time of operation up to the present (Table II).

TABLE II.—*Post-operative Course After Popliteal-vein Division in 196 Cases. Time of Observation: Six Months to Three Years*

	No. of Cases
Uneventful post-operative course. Steady progress towards complete recovery	165 (84%)
Intervals of recurrence	31 (16%)

In 165 patients the post-operative course was entirely uneventful. These patients were relieved from their previous bursting pain and enjoyed instead an unaccustomed feeling of lightness and comfort in their legs. They had, as a rule, no demonstrable oedema; in a few cases there were at times traces of it in the evening. In all cases the ulcers had completely healed, and remained healed, often leaving no traces. The indurative changes showed considerable regression and in many cases had entirely disappeared. In short, there existed in this group a steady progress towards what looked like complete recovery.

In 31 cases the post-operative course was disturbed by shorter or longer periods of recurrence. These cases were made the object of careful analysis in order to ascertain why recurrence had occurred and how it might be avoided (Table III).

TABLE III.—*Recurrence of Leg Symptoms After Popliteal-vein Division in 31 Cases*

Reason for Recurrence	No. of Cases
Persisting insufficient venous channels	18
Superimposed arterial disease	11
Other reasons	2

It was observed that in not a single case had the major stasis phenomena returned. All of the 31 cases were free from the bursting pain they had had before operation, and with very few exceptions the oedema of the whole lower leg also failed to return. Ulcers, on the other hand, had reappeared at the old site or in a new place.

Upon careful examination the reason for recurrence in 18 cases was found to be the existence of *untreated venous channels showing signs of evident insufficiency*. In some cases these had been overlooked at the time of the operation on the popliteal vein. In another group, with incompetence of the great saphenous vein, this had been noted from the beginning, but no treatment had been instituted because, during the first period of popliteal treatment, some doubt was felt about the wisdom of dividing both the popliteal and the great saphenous veins at the same time. Out of the 18 patients in this group, seven were healed after division of the great saphenous vein and six after leaking communicating veins in the lower third of the thigh had been dealt with. In four patients improved bandaging was sufficient to secure a good result, while one patient remains unhealed.

In another group of 11 patients a very interesting reason for the recurrence of the ulceration was found—namely, *superimposed arterial disease*. In these cases examination showed that the popliteal division had eliminated the previous symptoms of venous stasis and that the recurrence of ulceration was instead caused by obliterative changes in the major arteries of the lower leg, generally at about mid-calf level or higher. A characteristic feature of these cases was the extreme painfulness of the ulcers. While there was none of the old aching all over the lower part of the leg, which had been most pronounced in the daytime, there was a sharp pain, especially marked at night. These ulcers were also found to be extraordinarily slow in healing. The blood pressure in general showed a considerable increase and the pulse in the dorsalis pedis artery was absent. A more detailed report of this condition, which hitherto does not seem to have been sufficiently taken into consideration, has been given elsewhere (Bauer, 1950b).

Treatment with antispasmodic drugs had a favourable effect in two cases only. One patient was healed after

repeated sympathetic blocking. In six cases lumbar sympathectomy resulted in very rapid healing. This operation is probably the treatment of choice.

Post-operative Treatment

This report must not be concluded without a few words on the importance of careful after-treatment. It must be remembered that after popliteal-vein division the blood that is being squeezed out of the lower leg by muscular contractions has to find its way to the thigh through a number of rather fine-calibred veins passing the knee level. Until these veins have enlarged and become fully capable of taking over the entire blood flow there is the risk that some blood may be forced from the depth, through incompetent communicating veins, into the surface veins of the lower leg. To counteract this it is necessary to keep the subcutaneous veins in a state of compression for some time. It is our custom to make all patients wear some kind of supporting bandage for at least two months after the operation. After that time a large proportion of them have been allowed to discard these bandages. Others are instructed to wear them whenever the day's work involves much standing or walking. A small proportion do not seem able to carry on without continuous support.

Summary

So-called varicose ulceration is nearly always found to be connected with chronic oedema, indurative skin changes, and bursting pain. Together, these components form what may be termed the lower-leg-stasis syndrome.

The erect position in man causes a certain amount of venous overloading in the lower parts of the leg. In healthy individuals this superfluous blood is easily removed by contractions of the calf muscles, which act as a peripheral heart. This mechanism postulates normal functioning of the valves in the femoral and popliteal veins.

In patients with the lower-leg-stasis syndrome it has been demonstrated that the above-mentioned large veins are incompetent, their valves having been destroyed by previous thrombosis or by phlebosclerotic processes. In such cases superfluous blood cannot be effectively removed by contraction of calf muscles, every relaxation of these muscles being immediately followed by a back-flow of blood down the valveless main trunk. This results in permanent venous stasis, and in due time is followed by pain and tissue changes.

A remedy for this condition has been devised at the Mariestad Hospital in the form of blocking of the main deep trunk in the popliteal region. After this operation the calf-muscle contractions drive the blood through numerous fine-calibred channels into the muscle veins of the thigh, and no back-flow can occur.

Popliteal-vein division has been performed 245 times. The operation seems to be entirely free from risk. There were no deaths and no complications. The immediate results were favourable. The post-operative observation time is too short to allow a final evaluation of the late results to be made. However, a follow-up examination of 196 cases after six months to three years showed that 165 patients (84%) remained healed and without stasis symptoms. In 31 patients (16%) intervals with recurring symptoms were observed.

REFERENCES

- Bauer, G. (1948). *J. int. Chir.*, **8**, 937.
 — (1950a). *Angiology*, **1**, 1.
 — (1950b). *Acta chir. scand.* In press.

The Association of British Insecticide Manufacturers has published (price 1s., from 166, Piccadilly, London, W.1) a chart summarizing the laws relating to the sale of poisons used to kill weeds, rats, moulds, etc. It is issued in a folder and is suitable for pinning on a door or wall.

TOXIC EFFECTS IN ANIMALS AND MAN AFTER TETRAETHYLAMMONIUM BROMIDE

BY

ALEXANDER J. P. GRAHAM, M.B., B.S., F.R.C.S.

(From the Wilkie Surgical Research Laboratory, Department of Surgery, University of Edinburgh, and the Royal Infirmary of Edinburgh)

Tetraethylammonium bromide (T.E.A.B.) is a quaternary ammonium compound introduced into medical investigation as a vasodilator. It acts by blocking the transmission of vasoconstrictor impulses in autonomic ganglia, and has been used in cases of peripheral vascular disease to assess the capacity for vasodilatation.

Dangerous reactions following its administration have been reported, but do not appear to be sufficiently appreciated. During the course of recent experimental investigations on the action of this drug in animals and man certain toxic effects were observed.

In Animals

During an investigation of changes in peripheral blood pressure following arterial ligation in dogs a 10% solution of T.E.A.B. in doses of 2.5 mg./kg. was given intramuscularly and repeated half-hourly for two and a half to five hours. Preliminary trials had shown that with the animal supine this dosage was just insufficient to cause a fall of blood pressure of more than 10 mm. Hg. Total doses administered before toxic effects developed ranged from 100 to 240 mg., depending on the weight of the animal. For a man weighing 70 kg., doses over similar periods would be 475–1,200 mg. The usual single intravenous dose in man is 400–500 mg. (Boyd *et al.*, 1948). Other doses recommended in the literature are 4–7 mg./kg. (Birchall *et al.*, 1947) and 4–6 mg./kg. (Hayward, 1948), whereas Berry *et al.* (1946) have used 20 mg./kg. intravenously to a total of 1–1.2 g. Therefore although the individual dose per kilogram used in this experiment was well on the safe side, the sum of the half-hourly doses was two or three times that usually given.

In 7 out of 20 dogs toxic effects were noted. The first signs of these appeared after T.E.A.B. had been given for a period of two to three and a half hours: paralysis of intercostal breathing developed, and respiration continued with irregular diaphragmatic movements of diminished strength and frequency. Prominent features were bradycardia and hypertensive change with increased pulse rate—characteristics of the effect of anoxia in dogs. Cyanosis was also apparent. In two animals, when T.E.A.B. was stopped a gradual return to the previous state occurred over a period of one to one and a half hours. The remaining five died. In three of them normal respirations almost ceased, an anoxic hypertensive state followed, and death occurred 15, 20, and 60 minutes later respectively; during this time the few respiratory efforts were feeble and jerky in nature and entirely diaphragmatic, but as a result of movements of the heart some diffusion of air in and out of the lungs occurred. In the other two a slow rise in systemic blood pressure and in pulse pressure was followed by sudden respiratory failure and death. At post-mortem examination the only positive finding was gross dilatation of the heart and large veins.