PAPERS AND ORIGINALS

Prevention of Deep Vein Thrombosis by Intermittent Pneumatic Compression of Calf

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Summary

A consecutive, randomly allocated, controlled clinical trial of the prophylactic effect of intermittent pneumatic compression of the calf on the incidence of postoperative deep vein thrombosis showed that in patients without malignant disease there was a highly significant reduction in the incidence of thrombosis. In patients with malignant disease the incidence of thrombosis was higher than in those without, and there was no reduction in incidence by the application of intermittent compression. In the absence of malignant disease, severity of operation and the age of the patient were the most significant aetiological factors. We found no relation between the incidence of deep venous thrombosis and obesity, length of preoperative stay, location of hospital, or duration of anaesthesia. We suggest that intermittent pneumatic compression as used in this trial is a safe, effective, and extremely practical method of preventing postoperative deep vein thrombosis in patients not suffering from malignant disease.

Introduction

Methods for the prevention of deep vein thrombosis have been slow to develop for two reasons. On the one hand the aetiology of the condition is still poorly understood, so that well-reasoned attempts at prophylaxis are difficult, and on the other hand there had previously not been a satisfactory objective method for assessing any reduction in the incidence achieved. In the past many erroneous claims have been made and later discredited.

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The advent of the radioactive fibrinogen test (Atkins and Hawkins, 1965, 1968; Flanc *et al.*, 1968) has to a large extent solved the second of these difficulties. In addition this test has disclosed an unsuspectedly high incidence of thrombosis of the leg veins after operation as well as showing that most thrombi occur during or shortly after the surgical procedure. The problem of aetiology remains, but the need for a preoperative prophylactic agent is urgent. On the assumption that stasis of blood is a major aetiological factor we designed a controlled clinical trial to investigate the use of intermittent pneumatic compression as a prophylatcic measure during and after surgery. The radioactive fibrinogen technique was used for assessing the incidence.

Materials and Methods

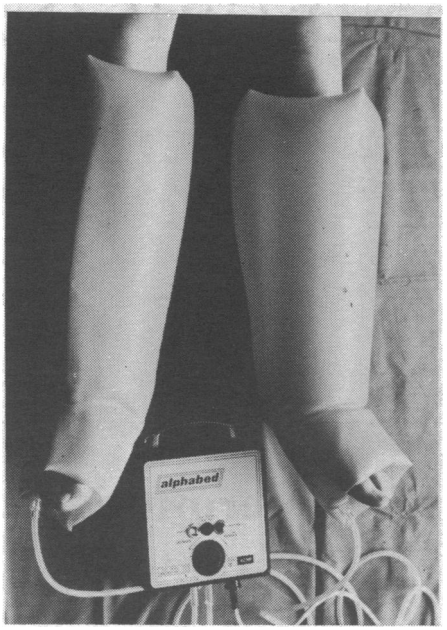
A pneumatic legging which produces intermittent calf compression was described by Calnan *et al.* (1970). The apparatus has since been modified and now consists of a single-piece P.V.C. legging incorporating the foot and calf in a unitary design (see Fig.). The electric pump inflates each legging alternately so that compression at 40-45 mm Hg for one minute is achieved followed by relaxation for one minute.

P.V.C. applied to the skin prevents evaporation of moisture and may become uncomfortable. An undersock consisting three layers of Tubegauze was therefore used beneath the legging, and this arrangement is comfortable for the patient and well tolerated for 24-28 hours without removal.

Selection of Patients

Patients were drawn from two hospitals—Hammersmith Hospital, a large postgraduate teaching hospital in London, and Barnet General Hospital, a busy district general hospital on the northern outskirts of London, serving an area which is partly urban and partly rural. In all cases the informed consent of the patient was obtained.

Hammersmith Patients.—All patients undergoing elective general surgical procedures under general anaesthesia over the age of 40 years were admitted to the trial with the following exceptions: (*a*) patients having operations on the legs, breasts,



Pneumatic leggings for production of intermittent calf compression.

or thyroid glands, because these interfered with the assessment method; (*b*) patients having vagotomy and drainage procedures, because such persons were the subjects of a separate study; (*c*) patients having had tracers likely to interfere with the radioactive fibrinogen test; (*d*) patients likely to be in hospital for less than five days postoperatively, who could not therefore be followed up long enough after surgery; and (*e*) patients on prophylactic anticoagulants before operation. All patients were then stratified into three groups according to age. Thus group 1 comprised patients aged 40-49 years, group 2 patients aged 50-59 years, and group 3 patients aged 60 years and over.

Barnet General Patients.—At Barnet Hospital selection was confined to patients aged 60 years and over, and those undergoing vagotomy and drainage were included. The patients were divided into two groups—those not suffering from malignant disease, and those known to have some form of malignant disease.

In both series patients were entered into the trial consecutively and were allocated to treatment or control groups by a series of random numbers predetermined for each stratum and contained in sealed envelopes. The patients in the treated group had the leggings applied at the time of premedication and received intermittent calf compression throughout the preoperative, peroperative, and postoperative periods. The leggings were removed when the patient was ready to get out of bed, usually on the day after operation.

Diagnosis

The diagnosis of deep vein thrombosis was made with the radioactive fibrinogen test by using the modification described by Negus *et al.* (1968). All patients received approximately 100 μCi of ^{125}I-fibrinogen intravenously one to six hours after operation, and scintillation counts (with a J. & P. counter) were performed daily for seven days. If the presence of a thrombus was diagnosed counting was continued for at least 10 days.

A thrombus was deemed to be present if there was a difference in percentage uptake of 15% or more between adjacent points on the same leg, or corresponding points on the opposite leg, and if this difference was maintained for at least 48 hours.

Results

HAMMERSMITH HOSPITAL

A total of 104 patients from Hammersmith Hospital were studied. Four of these were later withdrawn from the trial—one had the operation performed under local anaesthesia, two had their operations cancelled after being allocated to the trial, and one patient in the treatment group did not have the leggings applied until after the induction of anaesthesia and then had them removed almost immediately after operation. The remaining 100 patients were divided equally into treated and control groups. The male/female ratio was almost identical in both groups (Table I). The mean values for height, weight, and age, with standard deviations for each group, are shown in Table II. The closeness of the figures in the two groups provides some indication that an effective random allocation was achieved.

The incidence of deep vein thrombosis (D.V.T.) in the control group was 30% (Table III), whereas in the treated group it was only 12%, which is a statistically significant reduction in thrombosis at the 5% level of confidence. Nevertheless, five of the six patients in the treated group who in fact developed a thrombosis were suffering from histologically proved malignant disease. Since the overall proportion of patients with malignant disease in the trial was only 25% five out of six of the treated group seemed to be a very high figure.

The incidence of thrombosis in the 25 patients with proved malignant disease is shown in Table IV. It is seen that there was an incidence of 50% in the control group and a slightly higher figure in the treated group, but clearly there was no significant difference between the two; hence intermittent compression was not effective in reducing the occurrence of thrombosis.

The remaining 75 patients were not suffering from malignant disease, and the incidence of thrombosis for this group was very different (Table IV). Thrombosis occurred in 21% of

TABLE I—*Sex Distribution in the First 100 Patients (Hammersmith)*

	Males (n = 57)	Females (n = 43)	Total
Controls ..	28	22	50
Treated.. ..	29	21	50

TABLE II—*Mean Age, Weight, and Height (with Standard Deviations in Parentheses) in the First 100 Patients (Hammersmith)*

	Age (years)	Weight (kg)	Height (cm)
Controls ..	59 (16·4)	63 (13·7)	163 (12·8)
Treated.. ..	59 (10·0)	65 (12·7)	164 (10·6)

TABLE III—*Incidence of Thrombosis in the First 100 Patients (Hammersmith)*

	No D.V.T.	D.V.T.	Total	Incidence
Controls	35	15	50	30%
Treated	44	6	50	12%

$\chi^2 = 4{\cdot}94$; $0{\cdot}05 > P > 0{\cdot}02$.

TABLE IV—*Incidence of Thrombosis in Patients with and Patients without Malignant Disease (Hammersmith)*

	No D.V.T.	D.V.T.	Total	Incidence
Patients with Malignant Disease (n = 25)				
Controls	8	8	16	50%
Treated	4	5	9	55·5%
Patients without Malignant Disease (n = 75)				
Controls	27	7	34	21%
Treated	40	1	41	2·4%

For patients without malignant disease P = 0·015 (Fisher's test).

the controls but in only 2·4% of the treated group—a highly significant reduction as shown by Fisher's test, giving the exact value of P=0·015.

Whereas age did not appear to be a significant factor in the incidence of thrombosis in those with malignant disease there was a pronounced difference in the non-malignant group. The incidence of thrombosis in those aged 40-59 was low (less than 6%) in both the treatment and the control groups (Table V). In those aged 60 and over the incidence was 38%

TABLE V—*Distribution of Thrombosis according to Age in the 75 Patients without Malignant Disease (Hammersmith)*

Age (Years)	Controls			Treated		
	No D.V.T.	D.V.T.	Total	No D.V.T.	D.V.T.	Total
40-59 ..	17	1 (5·6%)	18	23	1 (4·2%)	24
≥60 ..	10	6 (38%)	16	17	0 (—)	17

For age group 60 years and over P = 0·01 (Fisher's test).

in the control group; no patient in this age group who was treated with intermittent compression developed a thrombus, and even on such small total numbers a significant reduction was achieved (P=0·01).

BARNET GENERAL PATIENTS

At Barnet General Hospital a further 51 patients were studied, 11 of whom had malignant disease. There were more males than females in this section but the distribution between control and treatment groups was not statistically significantly different (Table VI). The mean age, height, and weight and standard deviations are shown in Table VII; the values in both groups were similar. The incidence of thrombosis in patients not suffering from malignant disease is shown in Table VIII. The incidence of thrombosis in the controls was 40% (similar to that for the comparable group at Hammersmith Hospital), whereas the incidence in the treated group was 5%. This is a highly significant reduction statistically (P=0·01) and confirms the results obtained at Hammersmith. The combined totals of patients aged 60 and over without malignant disease are shown in Table IX.

The number of patients suffering from malignant disease in this part of the trial was very small, but it is of interest that thrombosis occurred in 50% in both the treated and the control groups. This again confirms that the incidence of

TABLE VI—*Sex Distribution in the 40 Patients without Malignant Disease aged 60 Years and over (Barnet)*

	Male	Female	Total
Controls ..	13	7	20
Treated.. ..	16	4	20

TABLE VII—*Mean Age, Weight, and Height (with Standard Deviations in Parentheses) in 40 Patients without Malignant Disease aged 60 Years and over (Barnet)*

	Age (years)	Weight (kg)	Height (cm)
Controls ..	69·2 (7·0)	63·4 (10·3)	165 (9·8)
Treated.. ..	70·1 (8·0)	62·7 (8·8)	167 (11·3)

TABLE VIII—*Incidence of Thrombosis in 40 Patients without Malignant Disease aged 60 Years and over (Barnet)*

	No D.V.T.	D.V.T.	Total	Incidence
Controls	12	8	20	40%
Treated	19	1	20	5%

P = 0·01 (Fisher's test).

TABLE IX—*Incidence of Thrombosis in All Patients aged 60 Years and over without Malignant Disease*

	No D.V.T.	D.V.T.	Total	Incidence
Controls	22	14	36	39%
Treated	36	1	37	3%
Total	58	15	73	

thrombosis was higher than in the non-malignant group and, further, that there was no reduction in incidence from the use of intermittent compression.

OTHER FINDINGS

In analysing other factors which may have contributed to the occurrence of thrombosis it is necessary to consider those patients without malignant disease who acted as controls. This is because all other factors seem to be overwhelmed in the presence of malignancy, and in the non-malignant treated group we effectively interfered with the "natural" occurrence of thrombosis. Several interesting trends, however, appear in the total of 54 patients in this category.

Height and Weight.—We compared the weights and heights of patients who developed a thrombus with those who did not and no significant correlation was found. By using the formula described by Hume (1966) the lean body mass was calculated, and from this, by deduction, the total adipose tissue; again there was no direct correlation with the incidence of thrombosis. The ratio of adipose tissue to height was also not significant statistically.

Duration of Anaesthesia.—There was a significant difference in duration of anaesthesia between those with and those without thrombosis. The mean length of anaesthesia in the no-thrombus group was 1·40 (±0·83) hours, compared with 2·62 (±2·05) hours in the group with thrombosis. The f ratio (6·107) for these two standard deviations shows that there was no normal distribution, and therefore the standard *t* test is not applicable. When a modified *t* test is used, however, this difference is significant at the 2·5% level of confidence; but this does not take account of the severity of the operation.

Type of Operation.—The types of operation have been classified into three groups, as shown in Table X. The first

TABLE X—*Types of Operation in 54 Controls without Malignant Disease (Both Hospitals)*

	No D.V.T.	D.V.T.	Total
Hernia repairs	11	1	12
Major gastrointestinal..	19	12	31
Miscellaneous	8	3	11

group included all inguinal herniorrhaphies, the second all major gastrointestinal surgery (such as cholecystectomies, partial gastrectomies, and bowel resections), and the third included a miscellaneous collection ranging from one Heller's operation to several haemorrhoidectomies. The incidence of thrombosis was low in herniorrhaphy operations—only 1 case in 12. In the major gastrointestinal group of 31 patients, however, the incidence was 39%. The mean length of anaesthesia for the herniorrhaphy group was 1·30 (±0·81) hours. Several of these operations were bilateral, which accounts for the rather long mean duration. In the gastrointestinal group the mean duration of anaesthesia was 2·73 hours (±2·28) in those who developed a thrombus; in those who did not it was 1·81 (±0·77) hours. These figures suggested that operations in the no-thrombus group were significantly shorter than those in the thrombus group. Analysis, made with a modified *t* test because of the skew distribution, showed, however, that this was not so (even at the 5% level of confidence). It is stressed that the total number of patients considered here was small.

Length of Preoperative Hospital Stay.—The duration of stay in hospital before operation was 4·97 (±7·78) days for the no-thrombus group and 7·00 (±9·81) days for the thrombus group. Again with use of the modified *t* test there was no significant difference between the two.

Detection and Distribution of Thrombi.—Forty-seven per cent. of the thrombi were present on the first postoperative day—that is, at the first time of counting—and 94% were detectable by the third day after operation. Of the total of 53 thrombotic episodes 18 were bilateral, 11 occurred in the right leg, and six occurred in the left leg.

Physical Signs.—Physical signs were present in only nine of the 53 legs with thrombosis. In all nine cases the signs were found two days or more after the scan was positive. The signs were often transient while the scan remained positive. Furthermore, of those with a negative scan six patients developed signs suggestive of thrombosis (a 10% incidence of false positives).

Natural History of Thrombus.—Fifty-two thrombi occurred in the calf and only one in the lower thigh region. Extension from the calf to the thigh occurred in four patients, and of these two developed pulmonary emboli in spite of anticoagulant therapy with heparin for 48 hours and later warfarin. In one case the infarct was small but in the other it was massive, though the patient survived. In seven legs the raised counts returned to normal within 10 days but in the remaining 41 the raised counts persisted for at least 10 days.

Discussion

It is now becoming accepted that clinical diagnosis of deep vein thrombosis is inaccurate, not only because it fails to detect a high percentage of thrombi but also because of the high incidence of false-positive signs (Kakkar *et al.*, 1969; Lambie *et al.*, 1970; Rosengarten, *et al.*, 1970). The present study lends further confirmation.

Methods of prophylaxis, the fibrinogen technique being used for assessment, are beginning to appear in the literature. Raising the legs (Rosengarten and Laird, 1971) and elastic compression bandaging of the legs (Rosengarten *et al.*, 1970) and a combination of the two (Flanc *et al.*, 1969) seem to be ineffective, and a more active method is clearly required.

Browse and Negus (1970) showed that electrical stimulation of the calf muscles during operation caused a reduction in the incidence of thrombosis, and Sabri *et al.* (1971) have shown passive flexion of the ankles to have a similar effect. The use of external compression in venous disorders of the lower limbs is not new. It was suggested by Pierre Dionis in the seventeenth century (Foote, 1960), and there has been a renewal of interest, concurrent with the development of pneumatic splints for the immobilization of fractures and elastic bandages. A considerable amount of work has been reported on the effects of compression on venous flow measured by plethysmography (Ashton, 1966), by isotopes (Makin *et al.*, 1969), and by electromagnetic flow probes (Roberts *et al.*, 1971). The inference has been that if pressure is maintained above 20 mm Hg the total limb flow and the flow in the femoral vein are reduced. It is worth emphasizing that these conclusions were all obtained when sustained compression was used. Applying intermittent pressure, as used in this trial, Calnan *et al.* (1970) showed that there is a phasic response in venous flow and that arterial inflow into the limb is not affected. It is possible that this phasic flow is important in the prevention of the accumulation of thromboplastic substances by "flushing" them away and that its absence may account for the failure of compression bandaging in preventing venous thrombosis

The first part of the trial reported here suggests that there is a significant reduction in the incidence of thrombosis with the use of intermittent pneumatic compression in patients aged 60 and over who do not have malignant disease. This inference is open to the criticism that though the patients had been stratified for age they had not initially been stratified for the presence or absence of malignant disease. What we had, in fact, done was to omit a group of patients in order that the results in the remainder appeared more impressive.

It could be argued that we had in effect carried out a retrospective analysis of the results and from this that we could produce only a hypothesis, not a conclusion. In order to confirm or refute this hypothesis the second trial at Barnet General Hospital was done, restricting entry to the high-risk age group and stratifying for malignancy. The results confirm the original hypothesis, and it seems to us that intermittent compression is an effective prophylaxis against deep vein thrombosis in patients who do not have malignant disease.

In both hospital trials there was one patient in the non-malignant group who developed a thrombus in spite of intermittent compression. At Hammersmith this was the first patient of the whole series. We have no explanation of why thrombosis occurred and it must be designated as a failure of the method. At Barnet, however, the patient who developed a thrombus had had an operation seven days previously; it may well be that she developed a thrombus during the first operation and not during the second one, when intermittent compression to the legs was applied.

Patients found the apparatus to be comfortable for long periods, even when wide awake, and, in fact, many seemed to enjoy its rather relaxing effect. In most instances surgeons were not aware of movement of the leggings throughout the operation, and the motor is practically silent. The nursing staff found no difficulty with their application and there has not been any resistance to their use (Doran *et al.*, 1970). Even with several machines working in one ward they are virtually inaudible. In short, we believe that this system is safe, reliable, and an extremely practical method for the prevention of deep vein thrombosis in patients not suffering from malignant disease.

In considering the patients who were suffering from some form of malignant disease two points of importance emerge. Firstly, the incidence of thrombosis was higher than in the non-malignant group and, secondly, intermittent compression of the calves had no effect in reducing this. That venous thrombosis commonly occurs in this group of patients has long been recognized; it was first reported by Trousseau in 1877, and Sproul (1938) recorded an incidence of thrombosis of 56·2% in patients who died from carcinoma of the body of the pancreas (an interesting figure in the light of those reported here). Many reports followed, but Miller and his co-workers (1967) were among the first to present the results of a systematic study of coagulation mechanisms in such patients, and produced a hypothesis to explain the hypercoagulable state they had found. They postulated that when circulating tumour cells died a thromboplastin was released into the circulation which caused a secondary rise in fibrinolysins. The haemostatic mechanism was thus still in equilibrium but set at a higher level, the balance being more precarious and more easily disturbed. Hence when a relatively minor stimulus, such as tissue trauma, occurred this might be enough to precipitate thrombotic manifestations in such patients.

It had also been suggested that this hypercoagulable state in combination with venous stasis could account for the presence of thrombosis in the legs. This now seems unlikely, since we have shown that even if stasis is prevented by the use of the leggings thrombosis may still occur. It seems to us that a more likely explanation is that thrombosis occurs in the legs because the intrinsic fibrinolytic activity in the leg veins is lower than elsewhere (Nilsson, 1967) and is insufficient to overcome the thrombotic tendency induced by a combination of operative trauma and the hypercoagulable state. It is likely, however, that in patients without malignant disease stasis alone plays a major part in the development of thrombosis, because we have shown that the application of intermittent compression reduces the incidence dramatically. It may be simply that the prevention of an accumulation of thromboplastins by inter-

mittent compression in a patient who has a normal coagulation mechanism before operation allows the relatively low fibrinolytic activity of the leg veins to cope with the thrombotic tendency induced by operation.

The trials conducted by Browse and Negus (1970) and by Sabri *et al.* (1971) were in the form of a sequential analysis, stimulating one leg only and using the other as a control. We chose to use an interpatient control because we believe that it has several advantages. For instance, we were not convinced that by altering the flow in one femoral vein the opposite side was not affected. Furthermore, legs are rarely symmetrical. Perhaps most important, information regarding aetiological factors operating in different patients is gathered more readily from this form of clinical trial.

There were only 54 patients in the control group who did not have malignant disease and from these it is possible to discern some interesting trends.

AGE

There was a pronounced disparity in the incidence of thrombosis in the age groups 40-59 and 60 and over in the Hammersmith trial. This may to some extent reflect the method of selection of patients, for most of those who were excluded fell into the younger age group. For instance, patients undergoing vagotomies (who were excluded because they were already the subject of an intensive metabolic survey) were mostly aged 40-59. The same was true for most of those who had thyroid operations. Thus the series of patients below 60 years was heavily weighted with relatively minor operations, such as herniorrhaphies, in which the incidence is low anyway (Table X). In spite of this, age appears to be a most significant factor (Kakkar *et al.*, 1970).

OBESITY

It has long been assumed that obesity is one of the major aetiological factors in deep vein thrombosis. Henderson (1927), on the basis of postmortem examinations, and Snell (1927), on the basis of clinical causes of death, suggested that obesity was an important factor in deaths from pulmonary embolism.

The reports in the literature linking obesity with thrombosis in the leg veins on clinical grounds are now known to be subject to serious errors, but Kakkar *et al.* (1970) found a significant correlation in a study using the radioactive fibrinogen technique for diagnosis. In the present study, however, we have been unable to confirm this by considering height and weight direct or by calculating lean body mass and hence amount of adipose tissue. It seems that further study is necessary to elucidate this point.

ANAESTHESIA

The mean duration of anaesthesia was shown to be greater in those patients who developed a thrombus than in those who did not. It is difficult to separate the effects of anaesthesia alone from the degree of surgical trauma. This is reflected in the separation into groups of operations where patients undergoing herniorrhaphy are at low risk (8%) of developing a thrombus, whereas those undergoing gastrointestinal surgery have a much higher risk (38%). Both the severity of the operation and the length of anaesthesia are correspondingly increased in the latter group. We have shown, however, that in this high-risk group there is no statistically significant difference in length of anaesthesia between those patients who developed a thrombus and those who did not when account is taken of the abnormal distribution. This suggests, therefore, that it is the degree of operative trauma which puts these patients at risk, rather than just the length of anaesthesia.

Sripad *et al.* (1971) have suggested that in operations lasting less than one hour there is a low incidence of thrombosis, and we must agree with this. We suspect, however, that this is because these are less severe operations and consequently shorter. They also implied that length of preoperative stay in hospital was related to the occurrence of thrombosis, but we failed to find a significant correlation in this study. It seems reasonable to conclude, however, that patients undergoing simple operations, such as repair of a hernia, are unlikely to be admitted several days previously for investigation. Measuring length of anaesthesia and preoperative stay in hospital, therefore, may just be an oblique way of assessing the severity of operation.

LOCATION OF HOSPITAL

Sripad *et al.* (1971) have shown a noticeably lower incidence of venous thrombosis at two country hospitals when compared with teaching centres. In our series, however, we found that at the two hospitals concerned the incidence of thrombosis was almost identical. The reasons for the discrepancy are not clear but the explanation may be due to the difference in the number of patients with malignant disease and the types of operation performed in the two hospitals.

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References

Ashton, H. (1966). *British Medical Journal*, **2**, 1427.
Atkins, P., and Hawkins, L. A. (1965). *Lancet*, **2**, 1217.
Atkins, P., and Hawkins, L. A. (1968). *British Journal of Surgery*, **55**, 825.
Browse, N. L., and Negus, D. (1970). *British Medical Journal*, **3**, 615.
Calnan, J. S., Pflug, J. J., and Mills, C. J. (1970). *Lancet*, **2**, 502.
Doran, F. S. A., White, Mary, and Drury, M. (1970). *British Journal of Surgery*, **57**, 20.
Flanc, C., Kakkar, V. V., and Clarke, M. B. (1968). *British Journal of Surgery*, **55**, 742.
Flanc, C., Kakkar, V. V., and Clarke, M. B. (1969). *Lancet*, **1**, 477.
Foote, R. R. (1960). *Varicose Veins*, 3rd edn. London, Butterworths.
Henderson, E. F. (1927). *Archives of Surgery*, **2**, 231.
Hume, R. (1966). *Journal of Clinical Pathology*, **19**, 389.
Kakkar, V. V., Flanc, C., Howe, C. T., O'Shea, M. J., and Flute, P. T. (1969). *British Medical Journal*, **1**, 806.
Kakkar, V. V., Howe, C. T., Nicolaides, A. N., Renney, J. T. G., and Clarke, M. B. (1970). *American Journal of Surgery*, **120**, 527.
Lambie, J. M., Barber, D. C., Dhall, D. T., and Matheson, N. A. (1970). *British Medical Journal*, **2**, 144.
Makin, G. S., Hayes, F. B., and Holroyd, A. M. (1969). *British Journal of Surgery*, **56**, 369.
Miller, S. P., Sanchez-Avalos, J., Stefanski, T., and Zuckerman, Linda (1967). *Cancer (Philadelphia)*, **20**, 1452.
Negus, D., Pinto, D. J., Le Quesne, L. P., Brown, N., and Chapman, M. (1968). *British Journal of Surgery*, **55**, 835.
Nilsson, I. M. (1967). *Acta Chirurgica Scandinavica*, Suppl. No. 387, p. 15.
Roberts, V. C., Sabri, S., Piltroni, M. C., Gurewich, V., and Cotton, L. T. (1971) *British Medical Journal*, **3**, 78.
Rosengarten, D. S., and Laird, J. (1971). *British Journal of Surgery*, **58**, 182.
Rosengarten, D. S., Laird, J., Jeyasingh, K., and Martin, P. (1970). *British Journal of Surgery*, **57**, 296.
Sabri, S., Roberts, V. C., and Cotton, L. T. (1971). *British Medical Journal*, **3**, 82.
Snell, A. M. (1927). *Archives of Surgery*, **2**, 237.
Sproul, E. E. (1938) *American Journal of Cancer*, **34**, 566.
Sripad, Sushila, Antcliff, A. C., and Martin, Peter (1971). *British Journal of Surgery*, **58**, 563.
Trousseau, A. (1877). *Clinique Médicale de l'Hôtel-Dieu de Paris*, vol. 3, pp. 80, 739. Paris, Baillière.