Not the least important point is the individual operative technique. This, however, is beyond the scope of this paper, and those primarily concerned with the use of this prosthesis will be able to draw their own conclusions from the observations we have made.

Summary

The mechanics of the hip-joint have been examined, with special reference to the Judet prosthesis. The materials used in the manufacture of the prosthesis and its ultimate strength have been investigated under laboratory conditions. Thirty prostheses which were removed from patients either because of pain and/or mechanical failure were examined in conjunction with the clinical records of the patients concerned.

The disadvantages of the present design can be summarized as follows: (1) The stem is not strong enough. Flexural strength is diminished by fatigue; the acrylic is weakened by crazing and the metal by stress corrosion. Unless the prosthesis is placed in the most favourable position its load-carrying capacity will be exceeded. (2) The skirt is weak and vulnerable, and interferes with revascularization. (3) The head has not sufficient surface hardness. The distribution of the forces acting upon the prosthesis has been examined. It is clear that both the angle of insertion i and the distance AB (Fig. B) must be as small as possible. (4) The local blood supply should be interfered with as little as possible. The great trochanter should not be divided, for both mechanical and anatomical reasons.

The reasons for the large number of worn prostheses require further investigation. In the light of our present knowledge, the use of any prosthesis must be regarded as an experimental procedure. The need for a standardized method of radiological follow-up of cases has been apparent in this work, as well as for a method of recording the clinical results of treatment.

While there are many reasons for failure over which no one can have control, the development of standards governing the materials to be used in the manufacture of prostheses could by now have been devised.

Since writing this paper a further 20 prostheses that have had to be removed from patients have been examined. The information gained has further substantiated the conclusions drawn from our previous work.

We wish to express our thanks to Professor S. J. Davies, Faculty of Engineering, King's College, University of London, for his enthusiastic support in carrying out this work; Professor D. H. Hey and Mr. L. Singlehurst-Ward, King's College, University of London, for their help on metallurgical and chemical problems; and to Mr. G. D. Winter, technical assistant, Plastics Research Unit, for his unfailing willingness in working long hours while engaged with us on the Judet problem. We are indebted to Messrs. Down Bros. Ltd., Lusterlite Ltd., the London Splint Co. Ltd., and the Medical Supply Association Ltd. for supplying samples of material and Judet prostheses.

The following very kindly responded to our appeal for notes, x-ray films, and prostheses, and thus made the work possible: G. Arden, E. H. Bannister, J. Bastow, J. Briggs, H. J. Burrows, St. J. D. Buxton, P. Cromack, F. W. T. Davies, E. O. Davis, M. B. Devas, E. A. Devenish, G. R. Fisk, A. Fletcher, A. T. Fripp, J. Garden, W. Gissane, L. C. Gonet, C. Gray, W. Herschell, S. L. Higgs, K. F. Hulbert, J. P. Jackson, A. W. L. Kessel, T. King (Australia), W. B. Law, P. S. London, K. Lucas, D. V. Marshall, M. L. Mason, J. S. Maxwell, K. I. Nissen, G. Platt, E. Shephard, N. A. Stephens, D. Trevor, W. Waugh, W. A. Watt-Maney, K. G. Westcombe, V. H. Wheble, B. L. Whitaker, P. Wiles.

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HEPARIN AND ETHYL BISCOUMACETATE IN PREVENTION OF EXPERIMENTAL VENOUS THROMBOSIS

BY

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[WITH SPECIAL PLATE]

In recent years anticoagulant drugs have been increasingly used for the treatment of thrombo-embolic disease. There are two groups of these drugs—those which lengthen the clotting-time (heparin group), and those which lengthen the so-called prothrombin time (coumarin derivatives): of the latter group ethyl biscoumacetate (" tromexan ") is a typical example.

Many clinicians believe that heparin is more efficient in preventing thrombosis, and choose ethyl biscoumacetate only because it can be given by mouth. We have, however, found no clinical or experimental evidence for this belief; the only experiment reported in the literature which compares the ability of heparin with that of dicoumarol in preventing thrombosis following damage to the vein wall was one performed in rabbits, and led to the conclusion that neither drug was effective (Moses, 1945). This lack of support for clinical impressions prompted us to study the relative actions of heparin and ethyl biscoumacetate in preventing thrombosis following experimentally induced phlebitis in rabbits. The drugs were given in a manner as closely comparable as possible to the methods of administration used in clinical practice.

Methods

Buck rabbits weighing from 1.8 to 3 kg. were used; they were fed on a mixture of bran and oats, with fresh greens and an unrestricted amount of water.

Administration of anticoagulants was controlled by frequent examinations of venous blood taken from a marginal ear vein reserved for this purpose. In the case of heparin, clotting-times were estimated by Wright's capillary

tube method, which is simpler than the Lee and White method, and was found by us to give equally satisfactory results. Normal clotting-times varied from 5 to 12 minutes Ethyl biscoumacetate administration was controlled by prothrombin times estimated by Quick's one-stage method, using human brain thromboplastin. Owing to the rapidity with which rabbit's blood will clot, consistent prothrombin times could not be obtained unless the following technique was adopted: all the glassware was treated with silicone and cooled before use, a solution of potassium oxalate was used as anticoagulant in the syringe, and the estimations were made within half an hour of taking the blood. With this method the normal prothrombin time varied between 11 and 16 seconds in rabbits, compared with 15–16 seconds in man.

A total of 95 rabbits was used: of these, 31 were treated with ethyl biscoumacetate and 34 with heparin, while 30 were used as controls. A satisfactory anticoagulant effect was first established and then the vein wall was damaged by chemical irritation. In both control and treated animals 0.1 ml. of monoethanolamine oleate ("ethamolin") was injected into one of the marginal ear veins in the direction of the blood flow and held in a 4-cm. length of vein for five minutes, by digital pressure above and below. The irritant effect of this procedure was confirmed by the fact that microscopical examination showed inflammation in and around the vein wall even when there was no thrombosis. Following the injection of monoethanolamine oleate the anticoagulant drugs were continued for a further five days. The rabbits were then lightly anaesthetized with sodium thiopentone, and phlebograms of the ear veins were made, using 1 ml. of 50% diodone. The animals were immediately killed and the ears were preserved for histological examination.

Experimental

Heparin

Throughout, the heparin was used in a concentration of 5,000 units per ml.; the doses per kilogram were two to three times those used in man. Monoethanolamine was injected 24 hours after treatment had started.

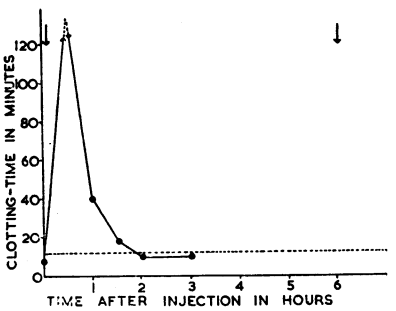

FIG. A.—Rabbit No. 95. Clotting-times following an intravenous injection of 800 units of heparin: six-hourly administration. The dotted line indicates the upper limit of the normal clotting-time, the arrows indicate times of injections.

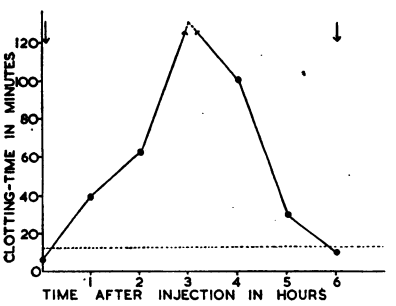

FIG. B.—Rabbit No. 81. Clotting-times following an intramuscular injection of 1,200 units of heparin: six-hourly administration.

Following Jorpes's (1950) recommendation for the most effective use of the drug in man, 11 rabbits were given intravenous injections of heparin every six hours: the doses were 500–1,000 units, according to weight. Clotting-times rose immediately after injection to over 120 minutes, but by two to two and a half hours they had returned to normal (Fig. A).

In 10 rabbits 1,000 to 1,500 units of heparin was given intramuscularly every six hours. The clotting-time was most prolonged at two and a half hours, and in the majority of animals did not return to normal until just before the next injection was due (Fig. B).

An attempt was then made in 13 rabbits to prevent the clotting-times from ever falling to normal. Intramuscular injections of 500 to 1,000 units were given every four hours. In most instances prolonged clotting times were well maintained (Fig. C), but of the 50 estimations made before injections were due 12 showed a fall to normal.

The only form of bleeding which occurred in any rabbit receiving heparin was into the site of the injection, which in the last group was occasionally sufficient to produce a temporary but obvious anaemia.

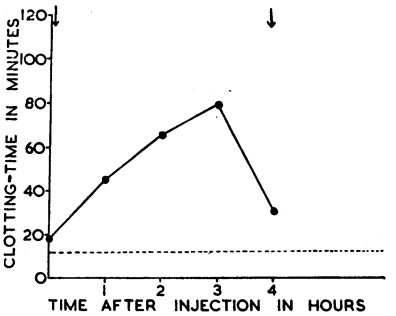

FIG. C.—Rabbit No. 103. Clotting-times following an intramuscular injection of 800 units of heparin: four-hourly administration.

Ethyl Biscoumacetate

The drug was given in capsules twice a day: the initial loading dose was estimated according to body weight, and the maintenance dose was controlled by daily estimations of prothrombin time. This dose varied from 20 to 80 mg. a day, and was two to three times the dose used in man. In most cases the prothrombin time reached a steady level in three to four days and the injection of the sclerosing agent was then given.

Rigid control of the effect of ethyl biscoumacetate was difficult, resulting in a wide range of prothrombin times, and according to these it was found that the animals could conveniently be divided into three groups. The prothrombin times for one rabbit in each group are shown in Fig. D.

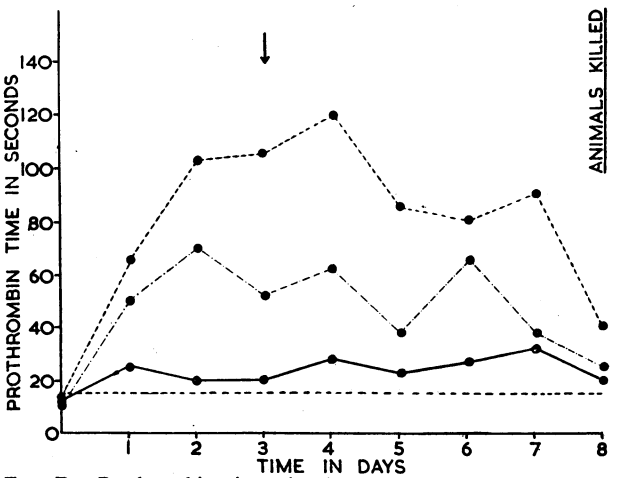

FIG. D.—Prothrombin times in three rabbits during an eight-day period on ethyl biscoumacetate. The arrow indicates injection of sclerosing agent.

Seven animals had prothrombin times which rose above 75 seconds, in 12 they rose to between 35 and 75 seconds, and in 12 to between 19 and 35 seconds. The last two groups had times comparable to those maintained with safety in man. With ethyl biscoumacetate there was no example of spontaneous external or internal bleeding, although in the presence of the more prolonged prothrombin times it was sometimes difficult to arrest the bleeding at the site of venepuncture.

Results

The phlebograms showed one of three findings: (*a*) complete patency, (*b*) a filling defect representing a partial

block, or (*c*) complete occlusion (Figs. E, F, and G). Similarly the microscopical examination of the vein made on 5–8 transverse sections of the traumatized area showed (*a*) absence of thrombus, (*b*) small mural thrombus, (*c*) large mural thrombus, and (*d*) blockage by thrombus (Plate, Figs. 1 and 2).

Control Group.—In 28 of the 30 control animals extensive thrombosis occurred, and there was radiological evidence of this in 26 of the 27 veins examined.

Heparin-treated Group.—The effects of heparin are summarized in Table I. As many as 25 of 34 veins of heparin-treated animals showed extensive thrombosis, six showed mural thrombosis, and only three veins were quite normal: in fact, there was no significant difference between these results and those of the control group. When the results with the three different modes of heparin administration were examined it was found that they were all equally unsuccessful (Table II). Even when the prolonged clotting-times were almost continuously maintained the results were not significantly better.

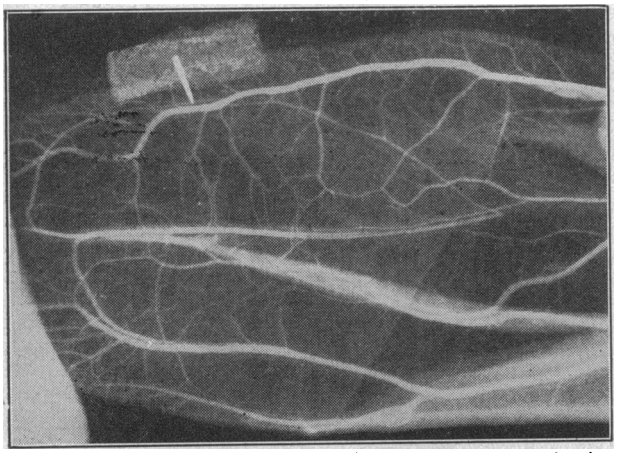

FIG. E.—Phlebogram of an ear showing apparently normal veins in a rabbit which received ethyl biscoumacetate. The marker indicates the point of injection of the sclerosing agent.

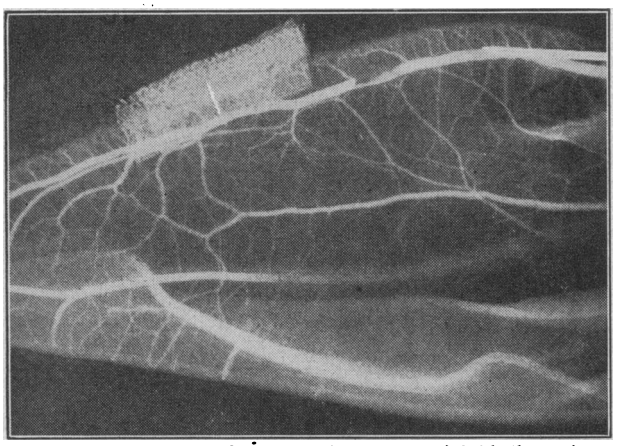

FIG. F.—Phlebogram of an ear showing partial blockage in a rabbit which had received heparin.

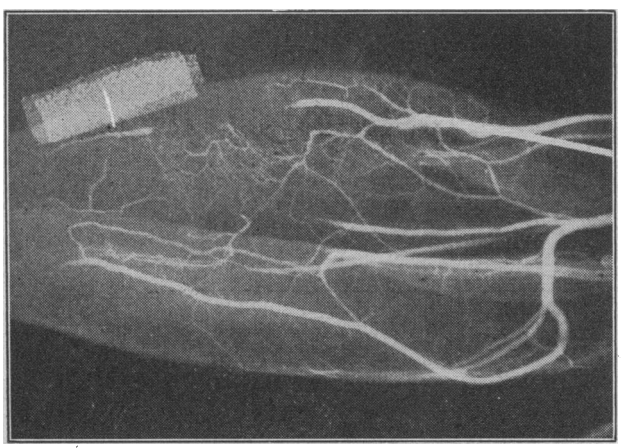

FIG. G.—Phlebogram of an ear vein showing complete blockage in a rabbit which had received heparin.

TABLE I.—*Effects of Heparin on the Occurrence of Venous Thrombosis*

A. Phlebography

	Total	Patent	Partial Block	Complete Block
Heparin ..	32	5	8	19
Control ..	27	1	3	23

0·2>P>0·1

B. Histology

	Total	Normal	Small Mural Thrombus	Large Mural Thrombus	Complete Occlusion
Heparin ..	34	3	6	10	15
Control ..	30	1	1	8	20

0·2>P>0·1

TABLE II.—*Effect of Different Methods of Administration of Heparin on the Occurrence of Venous Thrombosis*

A. Phlebography

Method	Total	Patent	Partial Block	Complete Block
Intravenous ..	10	1	1	8
Intramuscular 6-hourly ..	9	1	4	4
Intramuscular 4-hourly ..	12	3	3	6

B. Histology

Method	Total	Normal	Small Mural Thrombus	Large Mural Thrombus	Complete Block
Intravenous ..	11	0	2	3	6
Intramuscular 6-hourly ..	10	1	2	4	3
Intramuscular 4-hourly ..	13	2	2	4	5

Group Treated with Ethyl Biscoumacetate.—The results with this drug are summarized in Table III. Of the 31 animals which had received ethyl biscoumacetate, only four showed extensive thrombosis. It is interesting to note, although not statistically significant, that the four animals in which ethyl biscoumacetate failed came into the group with the least-prolonged prothrombin times. Even in this group, however, there was significantly less thrombosis than in the control animals ($P<0.01$).

TABLE III.—*Effects of Ethyl Biscoumacetate on the Occurrence of Thrombosis*

A. Phlebography

	Total	Patent	Partial Block	Complete Block
Ethyl biscoumacetate ..	26	24	0	2
Control ..	27	1	3	23

P<0·01

B. Histology

	Total	Normal	Small Mural Thrombus	Large Mural Thrombus	Complete Occlusion
Ethyl biscoumacetate ..	31	22	5	3	1
Control ..	30	1	1	8	20

P<0·01

Discussion

Our experiments indicate that heparin fails to prevent the occurrence of thrombosis in veins damaged by chemical irritation. Even when achieving almost continuous prolongation of clotting-time, with heparin given intramuscularly every four hours, no significant inhibition of thrombosis was obtained. This failure might be explained in part by the fact that we used discontinuous administration, either intravenously or intramuscularly, as suggested by Swedish workers (Crafoord, 1939; Jorpes, 1950), and in no rabbit could we be sure that the clotting-time was always above normal. Our results would seem to support those obtained in the original experiments with heparin, in which good effects were achieved only when the drug was given by continuous transfusion (Murray *et al.*, 1937).

On the other hand, ethyl biscoumacetate was found to be highly successful in preventing thrombosis. Similarly successful results were obtained with ethyl biscoumacetate using the arteries of dogs (Reinis, 1950), and also with dicoumarol (Dale and Jaques, 1942; Richards and Cortell, 1942; Thill *et al.*, 1943). The doses of ethyl biscoumacetate used by us were only slightly (two to three times) greater than those used in man, and they produced a comparable prolongation of prothrombin time, which differs from the findings of Wright *et al.* (1953), who found it necessary to give much larger doses of ethyl biscoumacetate (more than 20 times the human dose) to achieve comparable effects.

While experimental results in rabbits cannot be applied directly to man, we feel that the unexpected differences found between the two drugs makes it desirable that their comparative value in the prevention of thrombosis in man should be critically assessed.

Summary

A comparison was made between the actions of heparin and ethyl biscoumacetate in preventing thrombosis in chemically induced thrombophlebitis in rabbits. Ethyl biscoumacetate was strikingly successful when given in doses comparable to those used in man, whereas under the same conditions heparin did not significantly reduce the incidence of thrombosis.

We are extremely grateful to Professor T. Crawford for his guidance and for performing all the histological examinations, to Dr. S. D. Elek and Dr. J. N. M. Chalmers for their help and encouragement, and to Dr. Fraser Roberts for the statistical analysis. We are indebted to Evans Medical Supplies Ltd. for the supplies of heparin, and to Geigy Ltd. for supplies of tromexan. We wish to thank the Board of Governors of St. George's Hospital for a grant from their Endowment Fund towards the expenses of the investigation.

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An Ehrlich–von Behring Centenary postage stamp was issued in March by the West German Government. It is a 10-pfennig stamp with the heads of Ehrlich and von Behring facing right on a mid-green background, the names of the two scientists and the dates "14 und 15 Maerz 1854." The stamp has now been included in the Ehrlich exhibition arranged by the Wellcome Historical Medical Museum at 183, Euston Road, London, N.W.1.

THE NUMBER OF MELANOCYTES IN HUMAN EPIDERMIS

BY

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[WITH SPECIAL PLATE]

Melanomas of skin (cf. Raven, 1950; Pack *et al.*, 1953; Clark and MacDonald, 1953; Wright *et al.*, 1953) have a characteristic regional frequency distribution. Melanomas are more frequent per unit area on the face, neck, feet, and external genitalia than on other regions of the body. It is now almost universally believed that, in cellular origin, melanomas of skin arise from pigmentary dendritic cells, "myelanocytes."

There are alternative (but not mutually) exclusive reasons why the frequency of melanomas should vary from one part of the body to another: (*a*) the individual melanocytes have different degrees of susceptibility to malignant change, or are more exposed in certain areas to stimuli predisposing them towards this transformation; or (*b*) the likelihood of a melanocyte's undergoing malignant transformation is fairly constant throughout the body, and the observed differences of frequency are mainly due to differences of population density. Wright *et al.* (1953) have already suggested that there may be a greater concentration of "melanoblasts or precursors" in the skin of lower limbs, head, and neck than of upper limbs. Their opinion was based on observations of the duration of sun-tanning and not on statistical cellular counts.

The present investigation therefore represents a first attempt to estimate the frequency distribution of melanocytes in different regions of the human body. It was founded upon the use of Bloch's "dopa reaction" in conjunction with the "skin-splitting" technique of Billingham and Medawar (1951), which causes the epidermis to separate cleanly from the corium by enzymatic fission. By using these methods, counts of melanocytes were carried out by the methods described in full by Billingham and Medawar (1953). These authors have already shown that there are about twice as many melanocytes per mm.^{2} in guinea-pig's ear skin than in trunk skin, but both showed great variation between individuals. There was no correlation between melanocyte concentration and differences of colour.

This report contains only a first series of estimations, relating chiefly to the melanocytes of the skin of the thigh and arms.

Material and Methods

Human skin was obtained in the course of plastic surgical operations through the kindness of Mr. Rainsford Mowlem, at the Middlesex Hospital. The skin samples, removed as Thiersch (thin "split thickness") grafts, were incubated in buffered commercial trypsin solution to bring about the disengagement of the epidermis. The epidermis was thereupon stuck to a cover-glass, inner (dermal) side uppermost, with paraffin and rubber stopcock lubricant, fixed in 1–2% formol-saline overnight or sometimes longer (two to four days), and then incubated at 38° C., until the melanocytes turned dark, in a 1:1,000 solution of 3:4-dihydroxyphenylalanine adjusted by phosphate buffer to *p*H 7.4. After a second fixation in 4% formol-saline, followed by dehydration and cleaning, the pure epidermal sheets were permanently mounted in Canada balsam for inspection from the inner

A. B. SEMPLE, J. B. M. DAVIES, W. E. KERSHAW, AND C. A. ST. HILL: OUTBREAK OF TRICHINOSIS IN LIVERPOOL IN 1953

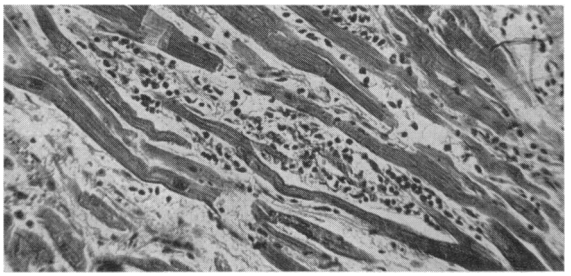

FIG. 1.—An area of early polymorphonuclear and eosinophilic infiltration between heart muscle fibres. (×120.)

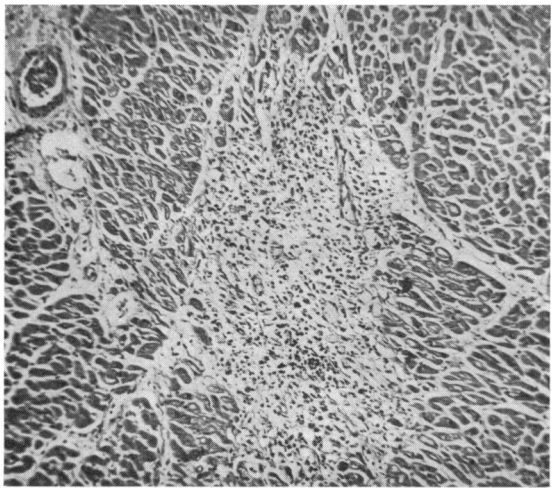

FIG. 2.—A small area of necrosis of heart muscle fibres. (×40.)

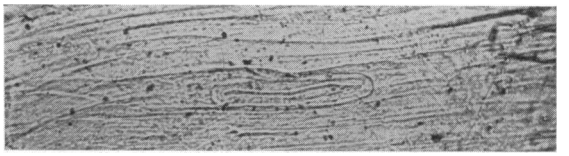

FIG. 3.—Showing a partially developed larva bent upon itself and lying longitudinally in the axis of the muscle fibres in an unstained fresh preparation. Seen with some difficulty. (×54.)

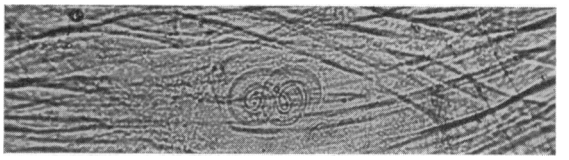

FIG. 4.—Showing a more developed larva arranged spirally in the muscle in an unstained fresh preparation. A cyst wall has not yet been formed. (×54.)

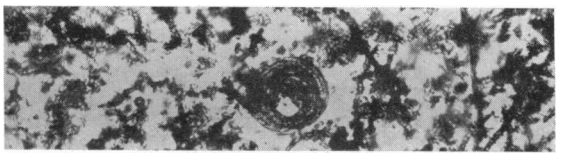

FIG. 5.—Showing a nearly mature larva in the muscle digest. (×54.)

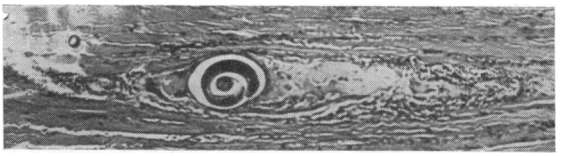

FIG. 6.—Showing a larva lying in the muscle in a fusiform focus of necrosis with cellular reaction at each end. The cavity in which the coiled-up larva lies is probably an artifact and probably does not represent the early stages of formation of the cyst. (×54.)

P. JEWELL, T. PILKINGTON, AND B. ROBINSON: HEPARIN AND ETHYL BISCOUMACETATE IN PREVENTION OF VENOUS THROMBOSIS

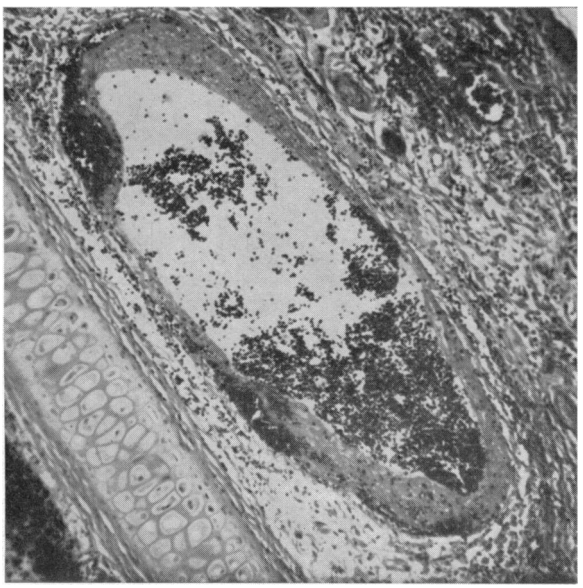

FIG. 1.—Section of an ear vein showing a small mural thrombus. Rabbit had received ethyl biscoumacetate. (H. and E. ×60.)

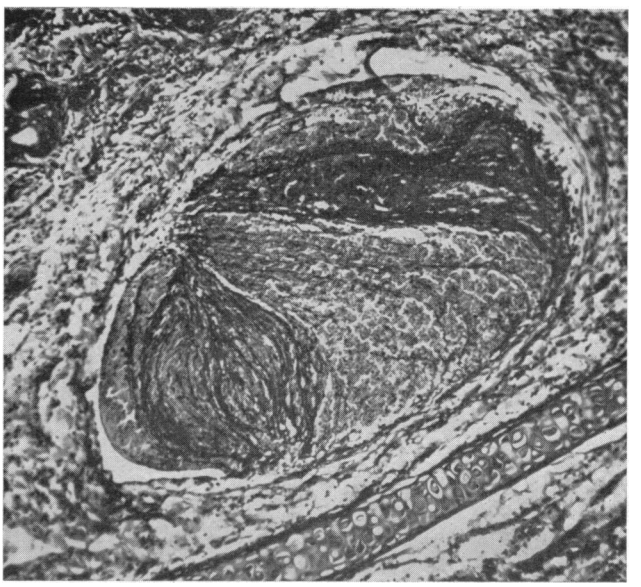

FIG. 2.—Section of an ear vein showing complete occlusion. Rabbit had received heparin. (Picro-Mallory. ×50.)