THE PHYSIOPATHOLOGY OF PHLEGMASIA CAERULEA DOLENS

JOSEPH PATRICK SAVAGE M.B., B.S..

Submitted for the degree of Master of Surgery at the University of Adelaide, January 1961.

DEPARTMENT OF SURGERY,
UNIVERSITY OF ADELAIDE.

TABLE OF CONTENTS.

TABLE OF CONTENTS CONTD.

TABLE OF CONTENTS CONTD.

TABLE OF CONTENTS CONTD.

SUMMARY.

This thesis contains the report of a laboratory investigation into the cause of the ischaemia occurring in Phlegmasia caerulea dolens. The rabbit was chosen as the experimental animal.

1. A historical review of the growth of knowledge relating to phlegmasia caerulea dolens is presented.

2. The clinical and pathological features, the results of treatment, and the outcome of one hundred reported cases are analysed.

3. The results of the investigation are reported :

   (a) Chemical stimulation of major vessels in the groin does not give rise to reflex vasomotor effects.

   (b) Chemical stimulation of the perivascular tissues does give rise to such reflexes, which are vasodilator in nature.

   (c) A technique of producing massive venous occlusion is reported. In a high percentage of cases, the features of phlegmasia caerulea dolens can be reproduced.

   (d) These experimental "blue" limbs suffer a serious degree of ischaemia.

   (e) In such limbs, reflex vascular spasm plays no part in determining the ischaemia.

4. An analysis of these results suggests that :

   (a) Mechanical venous occlusion, if of sufficient extent, can cause ischaemia and gangrene.

   (b) If vasomotor effects follow the inflammatory

stimulation of "thrombophebitis", they are probably vasodilator in nature.

5. It is concluded that, on the available evidence, the ischaemia of phlegmasia caerulea dolens should be attributed solely to a massive degree of mechanical venous occlusion.

6. The treatment of the condition is discussed in the light of these findings.

STATEMENT.

This thesis is a report of work done by the author whilst holding the position of Research Fellow in the Department of Surgery, University of Adelaide.

It contains no material which has previously been accepted for the award of any other degree or diploma in any University; and to the best of my knowledge and belief, the thesis contains no material previously published or written by another person, except when due reference is made in the text of the thesis.

J. P. SAVAGE.
DEPARTMENT OF SURGERY.
UNIVERSITY OF ADELAIDE.

INTRODUCTION.

The term "Phlegmasia Caerulea Dolens" was introduced into clinical medicine by Gregoire (1938) to designate a syndrome in which serious ischaemic effects and even gangrene follow a purely venous occlusion in the extremities. Perusal of the literature would lead one to believe that the condition is extremely rare. DeBakey (1946) collected fifty six cases from the literature, while Haimovici (1950), restricting his interest to venous gangrene, in an excellent review allowed only twenty-seven proven cases. Undoubtedly, the condition is not a common one, but neither is it as uncommon as is generally believed; and all writers on the subject agree that the apparent rarity is a rarity of diagnosis rather than of occurrence. Personal series of up to eleven cases have been reported (Veal, Duggan, Jamison and Bauersfeld, 1950), and two cases are known to the author to have occurred in Adelaide in the last year.

The syndrome is characterized by the sudden onset of severe pain, massive oedema and blue discolouration of an extremity, often proceeding to gangrene. Numerous post-mortem and post-amputation dissections have demonstrated the absolute organic integrity of the arterial supply to the affected limb, together with almost total occlusion of the venous tree by thrombus.

Despite the absolute consistency of the clinical features and of the morbid anatomy, there is no general agreement on

the physio-pathological basis of the condition, and in particular on the factors responsible for the ischaemia. That this division of opinion is not of purely theoretical interest, is seen in the prevailing confusion as to the best line of treatment. It is clear that no unanimity of opinion can be expected on this subject until more definite answers have emerged to the basic physiological questions involved, and it is in the hope of answering some of these questions that the following experimental investigation has been undertaken.

CHAPTER 1.

HISTORICAL SURVEY.

GANGRENE.

Although gangrene was known to and described by Hippocrates (c.460 B.C.) it is not surprising that an elucidation of its relation to vascular pathology made no headway until the work of William Harvey (1630) and Marcello Malpighi (1628-1694) demonstrated the circulation of the blood. A century before this work, there had been isolated reports of thickening of arterial walls (Leonardo da Vinci, 1452-1515) and arterial calcification (Gabriel Fallopius, 1523-1562), and in the latter years of the 17th Century William Cowper (1666-1709) suggested a connection between this vessel pathology and ischaemia. Thereafter an understanding of arterial pathology and its relation to gangrene progressed steadily. Albrecht von Haller (1708-1779) described atheroma and Giovanni Morgagni (1682-1814) described in some detail the lesions of arteriosclerosis. Cruveilhier (1791-1814) noted arterial thrombosis in association with arteriosclerotic plaques, and the subsequent work of Maurice Raynaud (1834-1881) and Leo Buerger (1908) is too well known to need comment.

VENOUS THROMBOSIS.

Our knowledge of the pathology and effects of venous thrombosis is of more recent origin. Francois Mauriceau (1637-1709), a Parisian, and the leading obstetrician of his time, is usually credited with the first description of the white leg of

the puerperium, in 1698. A little later John Hunter (1728-1793) described venous thrombosis and attributed it to a primary lesion of the vein wall. Matthew Baillie (1761-1823), a nephew of Hunter's, discussed the role of slowing of the circulation and primary changes in the blood as a cause of thrombosis, and finally in 1823 Davis described the causal connection between venous thrombosis and the white leg. The great Rudolph Virchow (1821-1902) supported and elaborated the opinion of Baillie, and it was left to Carl Rokitansky in 1852, to see that both factors could contribute to the genesis of a thrombus.

PHLEGMASIA CAERULEA DOLENS.

1. The period of speculation.

To see these two streams of thought finally and firmly brought together in a conscious realization that venous thrombosis can lead to gangrene we need look back into history only a century, but long before this the possibility had been raised.

Fabry, of Hilden (near Dusseldorf) also known as Fabricius Hildanus (1560-1624), the father of German Surgery, is usually credited with the first clinical description of what was probably venous gangrene.

In the early years of the eighteenth century, Francois Quesnay (1694-1774), a neurosurgeon, and ahead of his time in many ways, opined that while dry gangrene was due to arterial obstruction, wet gangrene was caused by obstruction to the veins.

The first half of the nineteenth century was a time of considerable interest in the effects of vein ligation; and a

controversy amongst the French Surgeons of the period, has ensured that their views are preserved for us.

Baron Guillaume Dupuytren (1777-1835) the famous Surgeon-in-Chief of the Hotel Dieu, was the first to advocate the theory that traumatic division of the femoral vein inevitably led to gangrene, and he advised that in such cases, the artery also should be ligated to prevent this unfortunate sequel. Considering his eminence, it is not surprising that his views gained very great acceptance, and we find them upheld by the Englishman, George Guthrie (1785-1856), the Germans, Georg Stromeyer (1804-1876) and Bernard von Langenbeck (1810-1887) and the Russian, Ivanovich Pirogoff (1810-1881), as well as by many French Surgeons over half a century - Joseph Roux (1780-1854), Gensoul (1826), Pierre Chassaignac (1804-1879), Louis Ollier (1825-1900) and Auguste Nelaton (1807-1873).

Over the same fifty year period, a number of reports appeared of gangrene in association with thrombophlebitis - Jean Alibert (1827), Francois Ribes, Jr., (1825), Victor Francois (1831), Charles Sedillot (1832), Adolph Pierry (1833), Gaudin (1836). None of these cases, however, can be accepted as due to pure venous occlusion, and the authors make little attempt to disentangle the possible aetiological factors.

2. <u>Early case reports.</u>

In 1855 Virchow founded the now famous Archives of Pathological Anatomy, universally known as Virchow's Archives.

It was in the September issue of this journal in the year 1859 that there appeared a report of a "case of gangrene in association with venous obliteration", which as a clinical and pathological description of the disease has not been bettered. Its author was a Dr. Hueter, a general practitioner of Waldcappel.

Huerter's case was a previously healthy middle-aged man, who was suddenly seized with severe pain in his right calf. He was confined to bed because of the severity of the pain and was closely observed over the next eight days. Dr. Huerter records that there were no physical signs whatever in the leg and he was unable to make a diagnosis until on the ninth day, when the patient was very much better, a tender cord was palpable deep in the right calf. The next morning, following the administration of an enema, there was a sudden onset of pain of very great severity, and within thirty minutes the entire right lower limb had taken on a bluish red discolouration. By the evening of the same day, the entire extremity was enormously swollen, discoloured and exquisitely painful. Purpuric spots and echymotic patches were apparent in the skin and blisters were appearing on the dorsum of the foot. The pulsations of the anterior tibial artery were still distinctly palpable. The unfortunate man survived a further two days, becoming progressively more shocked and eventually succumbed from the effects of oligaemia.

At postmortem the entire arterial system was normal but every vein in the limb was occluded by clot which extended up into the

external iliac vein. The clot in the mid-calf was organizing, while that above and below was clearly of more recent origin.

In discussing the case Hueter says that he hesitated to ascribe the catastrophy to pure venous occlusion despite the suggestive clinical signs, because ischaemia of venous origin had never previously been described; and his great contemporary, Virchow, had stated that it did not occur. The postmortem, however, was convincing, and he put forward the simple explanation that venous occlusion, preventing flow through and diffusion from the capillaries, could well give rise to ischaemia and gangrene.

Nearly forty years passed before the next significant report from the Frenchman, Gaillard (1894) - unmistakable proven venous gangrene occurring in a young woman with a gastric carcinoma. Soon after Reyt (1897) reported another case in a young man with pulmonary tuberculosis, and Pons (1905) recorded venous gangrene complicating a fractured femur.

The position, then, at the turn of the century was that the condition, although not widely known, was thoroughly understood from a clinical and pathological viewpoint. The obvious simple explanation had been offered, that massive venous occlusion must halt capillary circulation and so give rise to ischaemia.

3. <u>The French Period</u> - the "spasm" theories.

Following the communication of Pons, there was a hiatus of twenty-five years before the next case was reported by Pallin (1929). At the same time, there was another report by Tremoliere

and Verran (1929). These two authors were the first to suggest an element of reflex arterial spasm in the production of the ischaemia. Pallin explored the femoral vessels and was struck by the small calibre of the artery, which he interpreted as reflex spasm. Tremoliere and Verran were led to the same conclusion because they considered that they had produced clinical improvement by administering acetylcholine.

These two reports were shortly followed by two others - Bergendal (1931) and Bergeret, Guillaume and Delarue (1932). The latter authors wrote only a factual description of the disease. Bergendal however discussed the origin of the ischaemia, and suggested a combination of venous occlusion, massive oedema, and arterial spasm. The last suggestion he made on the authority of Pallin and Tremoliere, and not as a result of his own observation.

Before any further reports of Phlegmasia Caerulea Dolens had appeared, some papers, concerned mainly with ordinary thrombophlebitis - in particular the white leg - were published. Leriche and Jung (1931) investigating the pathogenesis of post-phlebitic oedema found that they were quite unable to produce a lasting oedema by vein ligation. They reasoned that if the oedema were not due to venous obstruction, it must be caused by a reflex vasoconstriction.

The idea gained support from further work by Leriche and Kunlin (1934) who claimed excellent results in the treatment of

the white leg, by repeated lumbar sympathetic block. Finally, in 1937, Fontaine and Souza-Pereira (1937), working in Leriche's department confirmed that even extensive resections or chemical obliterations of major venous trunks, combined with lymphatic ligation, never resulted in a lasting oedema. Fontaine and Souza-Pereira are also notable as the first workers to produce venous gangrene experimentally, which they did by ligating all the veins at the root of the limb.

This conception of arteriospasm as the dominant factor in the causation of the symptoms and signs of thrombophlebitis gained very wide acceptance, particularly in France and America over the next two decades, and it was immediately accepted as the cause of the ischaemia in Phlegmasia Caerulea Dolens.

The first case reports in which this idea is explicit came from Wertheimer (1935) who discusses three cases. The third of these cases he treated with a lumbar sympathetic block and claimed a good result, although the case terminated in a major amputation for gangrene. From this time onwards, cases have been reported at fairly regular intervals. The last half of the thirties saw reports from Gutzeit (1936) in a child, the Americans, Tilley (1937) and Edwards (1937), the Frenchmen, Fontaine, Israel and Souza-Pereira (1936), Salmon, Audier, Jouve, and Haimovici (1938), Gregoire (1938), Decoulx and Bastien (1939), and the Scot, J. Hogarth Pringle (1938).

Pringle, who was the first to report the disease in a British Journal, confined himself to a factual description

of his findings, but the other authors without exception offer their cases in support of the theory of arteriospasm.

A critical evaluation of these theories will be deferred to a later discussion. Meanwhile, the next decade saw a new phase in the history of thought on these matters, and the centre of interest shifted from France to America.

4. The American Period.

There have been two main series of experimental observations, prior to the one reported here, directed particularly at the elucidation of the pathogenesis of Phlegmasia Caerulea Dolens. The first, that of Leriche, Fontaine, and others, we have already considered. The second, done by DeBakey, Oschner and their co-workers, like the first, had a profound influence on thought on this subject over the ensuing decade. DeBakey, Burch and Oschner (1939) reported that ligation of the common femoral vein in the dog regularly reduced pulse volume by fifty per cent. This effect persisted despite sympathectomy. They found also that irritation of a venous segment with 40% Sodium salicylate reduced pulse volume by an extra 30%. This effect they reported could be abolished by sympathetic interruption or by local procaine infiltration of the perivascular sheath. By inference, they suggested that pulse volume in these circumstances was an adequate measure of blood flow, and they concluded, therefore, that simple venous interruption could seriously prejudice

blood flow, and that irritation of a vein wall had a similar though smaller effect mediated by a vascular reflex. Carrying their dissection further, Burch, DeBakey and Sodeman (1939) offered evidence that the effect produced by the vein tie was due solely to a reduction in the elastic properties of the vessel due to distension.

One year later Oschner and DeBakey (1940), on the basis of the previous work, constructed a complex theory to account for the clinical features of thrombophlebitis (Fig.1.) and reported seventeen cases in which they claimed dramatic improvement following treatment by lumbar sympathetic blocks.

As the work of Leriche had determined the view of the thirties to accept reflex arterial spasm as the dominant factor in pathogenesis, so the work of DeBakey moulded the opinions of writers during the nineteen-forties to consider pure venous occlusion as the dominant factor, with reflex spasm playing an important subsidiary role.

This decade saw a continuation of sporadic interest in the condition. Cases were reported by Leriche and Giessendorf (1939), Audier and Haimovici (1939), Faure, Rochet, Freith and Godinot (1940), Sachenreiter (1940), Swartley, Weeden and McLaughlin (1940), Guttermuth (1942), Morales Aparicio (1944), Fontaine and Forster (1946), DeBakey (1946), Haimovici and Suffness (1948) and Oaks and Hawthorne (1948). The period ended with an excellent review

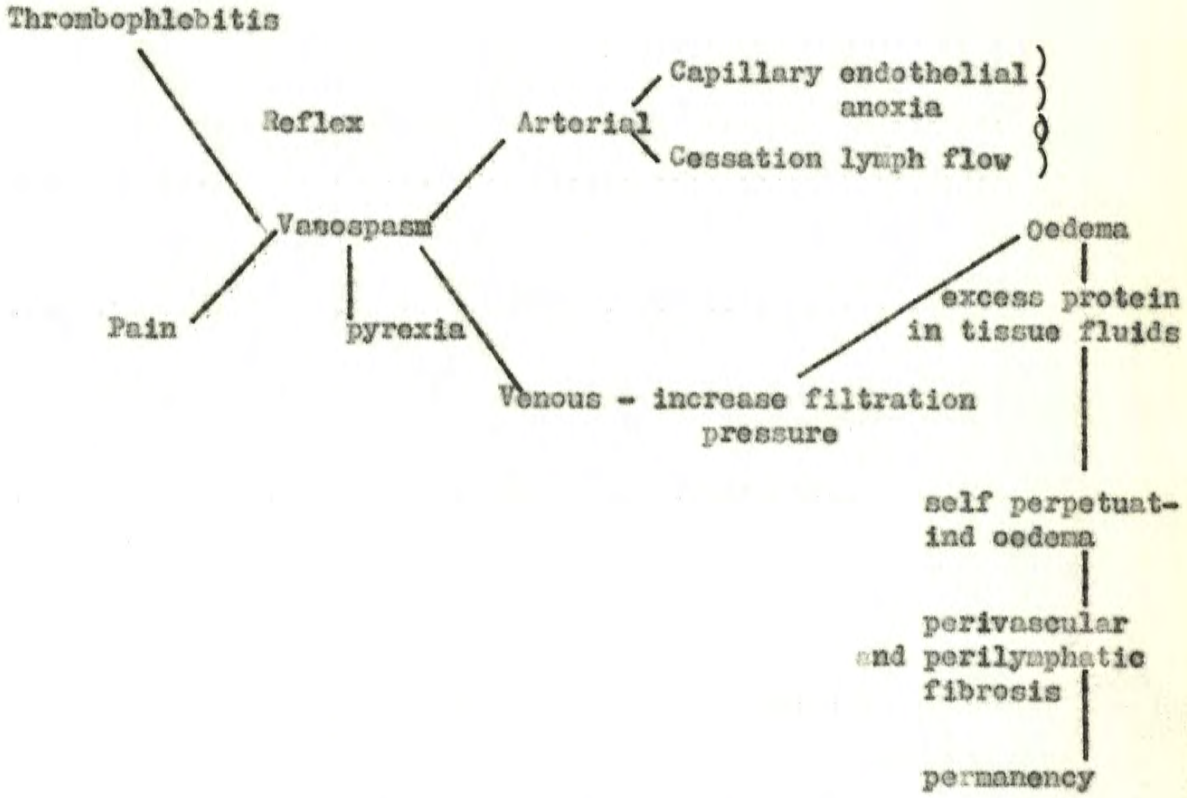


Fig.1. To illustrate the theory of Gschner and DeBakey re : the genesis of the symptoms and signs of thrombophlebitis.

by Haimovici (1950) in which he collected and analysed 27 cases which had proceeded to gangrene, and clearly stated the current views on the cause of the ischaemia.

5. The decade 1949-1959.

Once again, the beginning of a new period was marked by the appearance of a paper of great significance reporting fundamental experimental work. Veal, Duggan, Jamison and Bauersfeld (1951) reported the largest single series over to appear in the literature (eleven cases). In this series of cases they were unable to confirm any useful effect from lumbar sympathetic block. They were, therefore, stimulated to reinvestigate the physiopathology of the condition. In a preliminary series of experiments they confirmed the findings of Fontaine in that they were unable to cause gangrene of the dog's leg by multiple vein ligations. They, therefore, abandoned the femoral vascular bed and used instead, the mesenteric. They produced total venous occlusion in a portion of this bed by ligating a stem vein, and monitored arterial and venous pressures within the involved segment. Their findings are illustrated in Table 1. They noted that over the period of observation the arterial pressure had fallen very little, no more than might be ascribed to general deterioration, but the venous pressure had risen so high that the circulation must have been almost arrested. They adduced

TABLE 1.

Experimental results of Veal et al.

Time Minutes	Venous pressure mm/Hg	Arterial pressure mm/Hg
Zero	4.4	90/80
10	-	90/80
30	62.5	85/70
60	63.2	76/70

these findings as evidence that the circulation can be arrested by venous occlusion and that there is no element of arterial spasm. By corollary, therefore, they discarded sympathetic block as a therapeutic measure and relied on elevation and exercise.

The views of Veal and his colleagues have not gained the wide acceptance given to the earlier opinions of Leriche and DeBakey; but they have made a small impact on the thought of the last ten years. This decade has seen a number of cases reported from North America, and three reports in the British Journals.

Young and Derbyshire (1950) report a case, and quoting DeBakey, ascribe the entire symptom complex to reflex arterial spasm, and in the same year Miles (1950) reported a case successfully treated by thrombectomy and inferior vena caval ligation. Ossius (1951) while still retaining an element of spasm, was the first to agree with Veal that occlusion was the overwhelmingly important factor. He considered the name "Phlegmasia Caerulea Dolens" was objectionable, and suggested "Massive Thrombophlebitis". Ebel, Kaufman and Ehrenreich (1952) subjected their case to sympathetic block and reported this manoeuvre to be without effect. In the same year, Nunez, Milanes, De La Vega, Vazques and Inigo (1952) added another factual case report to the growing literature, as did Myhre and Yvisaker (1954) two years later.

Although the influence of Veal's work can be seen in the preceding reports, there were five observations over the next two years in which the authors considered that arterial spasm played a significant part in the production of the symptom complex. Janes and Hopmans (1953), Halligan, Costello and Lewis (1953), Hershey and Snyder (1953) were the most outspoken proponents of the arterial spasm theory while Manheimer and Levin (1954) discussed at length the role of venospasm.

Mosser, Babin, Cotts and Prandoni (1954) and Mills and Bennetts (1955) reported the only cases in the literature in which attempts were made to apply physiological techniques to elucidate the problems involved.

The three British writers make much less of the "spasm" theory. Turner (1952) reported a case and advised the treatment previously outlined by Veal. Martin (1953) while retaining the concept of "spasm" also advised treatment by elevation and exercise. Finally, Catchpole (1957), heading his paper "Massive Thrombophlebitis" reviews the recent literature and adds five cases of his own. He discards the theory of spasm and advises against antivasospastic treatment and heparin, which he considers increases the risk of capillary rupture, ecchymosis and purpura.

6. <u>The future</u>.

Two very recent articles point the direction in which

future research may make the greatest contributions to the whole question of venous thrombosis. We will see in the course of a clinical review that there are definite indications that this disease occurs in a subject predisposed, because he is in a "hypercoagulable" state. Meek and Maurer (1959) reported the most recent case in the literature. They found in the plasma of this subject a cold-precipitable protein similar to but not identical with cryofibrinogen, and remark on its possible significance.

Marin and Stefanini (1960) have recently published a paper on the experimental production of phlebothrombosis. They found that clotting could be induced much more readily in an animal whose blood had been rendered "hypercoagulable" by the prior infusion of homologous serum. It seems to the author that some such approach to the biochemical aspects of the problem holds the greatest promise of future progress.

CHAPTER 2.

CURRENT CONCEPTS.

SECTION A.

CLINICAL AND PATHOLOGICAL SURVEY.

In striking contrast to the multiplicity of theories advanced as to aetiology, and the unsupported claims made for various therapies, the clinical andpathological pictures are very consistent from case to case. It seems desirable at this stage to recordthese features with some care.

This is a disease of adult life, but is by no means confined to the elderly. There have been many reports of the condition occurring in young adults, and the average age of Haimovici's (1950) series was forty-one. There has been only one case occurring in childhood, reported by Gutzeit (1935) and precipitated by trauma. In the reported series, sex is almost equally distributed.

Preceding Illness.

The onset of the condition like that of phlegmasia alba dolens most frequently occurs in the post-operative, post-partum or post-traumatic state. It is frequently associated with pelvic infections, or malignant disease, and sufferers from ulcerative colitis would seem particularly prone to this complication (DeBakey et al., 1946, Bargen and Barker, 1936, Catchpole, 1957).

However, the syndrome can occur in apparently healthy

people engaged in ordinary activities (Hueter, 1859, Bergendal, 1931, Wertheimer, 1935).

Preceding state of the circulation.

Some authors, notably DeBakey (1946) divide the condition into two distinct types, depending essentially on whether it occurs in a circulation presumably previously normal, or is superimposed in a limb which is known to be the seat of a venous thrombosis. This concept is useful in defining the possible preceding states of the circulation, and to emphasize that in those cases with a previously normal leg, this disease must be entertained in the differential diagnosis of arterial embolism. Apart, however, from this practical value, the concept does not appear to embody a real distinction, for in either case the onset of Phlegmasia Caerulea Dolens is abrupt and with characteristic features.

Several iatrogenic factors appear with uncomfortable frequency in the case reports. A common antecedent is superficial femoral vein ligation performed in the treatment of thrombophlebitis (Veal et al., 1949, Nunez et al., Hershey et al., 1953); varicose vein ligation (Halligan et al., 1953) has been implicated as also has the intravenous infusion of serum (Gregoire, 1938).

Clinical features.

1. The onset is always sudden and dramatic. Whether the limb was previously normal, or already oedematous, there is

never any doubt that some new disaster has occurred.

2. Pain is the outstanding symptom. It is always of very great severity and has a bursting quality, as though the limb is rapidly becoming too big to be contained by its integuments. It is felt diffusely throughout the affected extremity and lacks the localizing quality of the pain of arterial embolism. Although the pain is very diffuse, local tenderness may be elicited over that stretch of the vein where the thrombotic process commenced.

The other symptoms of ischaemia - sensory and motor changes, and a sensation of cold - may also be present and are usually confined to the distal parts of the limb.

3. A bluish discolouration of the skin is perhaps the outstanding physical sign. This characteristically develops with great rapidity, and is present when the patient is first examined. It is a mottled violaceous discolouration which may be associated with purpuric or ecchymotic patches, and has been aptly likened to a limb which has had a venous tourniquet in place for some time. This discolouration commonly involves the entire extremity and reaches the groin, but it may be confined to the leg. It is quite unlike the waxen pallor of the early stages of arterial embolism, and is a useful sign in this differential diagnosis.

4. In these cases, supervening on a known venous thrombosis, oedema precedes the other signs. In those occurring in a previously normal leg, it follows them. In either case, it rapidly becomes extravagant, the affected limb commonly doubling its normal

circumference, and not uncommonly presenting typical "Fracture-blisters".

5. The blue leg is often as warm as its fellow in sharp contradistinction to the limb affected by arterial embolism. The more distal parts of the extremity, however, and particularly those parts which subsequently become gangrenous usually have a lowered skin temperature.

6. In about half the reported cases the arterial pulses were definitely palpable throughout the limb and oscillometric pulsations were recorded. In this event, the venous character of the incident is incontravertible. In the remaining 50%, however, arterial pulsations could not be appreciated.

7. Finally, the rapid sequestration of several pints of blood and of enormous quantities of oedema fluid in the affected extremity can give rise to severe oligaemic shock, and this complication has been a frequent cause of death in the reported cases.

COURSE AND SEQUELAE.

There have now been more than a hundred cases of Phlegmasia Caerulea reported, and the outcome of these cases has been analysed. The information obtained is summarized in Tables 2 and 3. The material has been divided into two groups - 56 cases reviewed by DeBakey (1946) and 45 cases accessible to the author from the recent literature. A very marked discrepancy is apparent in the severity of the gangrenous process. This is to some

TABLE 2.

Outcome of 101 cases of Phlegmasia Caerulea Dolens.

Cases	Deaths	(%)	Major gangrene +	(%)	Minor Gangrene	(%)
Series A * 56	11	(20)	21	(38)	3	(5)
Series B * 45	8	(18)	5	(11)	11	(24)

* A. = cases reviewed by DeBakey (1946)

* B. = cases reviewed by the Author (1946 - 1960)

+ Major gangrene involving the entire foot or hand, or more.

extent due to the fact that the earlier writers resorted to major amputation in the early stages of the disease, and perforce where a major amputation has been performed, the result must be classified as major gangrene. Where a significant difference exists, the more recent series is chosen for discussion.

The overall death rate is 19%, and remains almost unchanged in the recent series. If we restrict the analysis to cases preceding the gangrene, the rate becomes 41%. An analysis of the cause of death is not possible in the older cases and not very rewarding in the more recent series (Table 3). In a number of cases, phlegmasia caerulea dolens supervenes in a patient already dying, and death can be attributed in large part to the primary illness. Of those cases in which Phlegmasia Caerulea is the immediate cause of death, oligaemia and embolism are the factors most commonly responsible.

About 30% of all cases develop gangrene. It will be seen (Table 2) that in the considerable majority this process is of a minor nature, and this is particularly striking in view of the widespread character of the apparent ischaemia.

In quite a high proportion of cases, recovery has occurred without loss of tissue. As a rule the recovery period consists of a slow regression of oedema, and a disappearance of the cyanosis over some days. Pallin (1929) and Martin (1953), however, report cases of great interest in which recovery

TABLE 3.

Cause of death in cases from Series B.

Shock (oligaemia)	2
Pulmonary embolus	2
Extension of thrombosis	1
Primary disease	1
Unknown	2

occurred with a suddenness comparable to that of the onset. Both cases recovered synchronously with the commencement of an incident which in Pallin's case was certainly, and in Martin's probably, a pulmonary embolism.

No account of the course of this disease would be complete without a consideration of pulmonary embolism, which might reasonably be expected to be a frequent and fatal complication. Of the total series of a hundred cases, thirteen suffered a recognizable pulmonary embolus, which was the immediate cause of death in four patients.

The subsequent sequelae affecting the surviving patients are in no way different from those of phlegmasia alba dolens. Neither group is more or less likely to suffer from post-phlebitic oedema or ulceration.

PATHOLOGY.

Morbid anatomical dissections, after death and on post-amputation specimens are now quite numerous, and like the clinical reports, are strikingly consistent from case to case. All the veins of the involved extremity, from the largest to the most minute, are occluded by thrombus. In the more careful studies it is usually apparent that one portion of the clot is old, and the remainder of very recent origin. The older portion may be in themajor veins of the limb, or equally may occupy some smaller channel. There seems no doubt that the onset of phlegmasia caerulea is determined by the sudden propagation of clotting

upwards or downwards, or both, from a preceding smaller thrombus, throughout all the venous system of an extremity. If indeed there is any real difference between "thrombophlebitis" and "phlebothrombosis" it seems to be totally indifferent to which process the primary thrombus conforms. Cases have been reported in the presence of an undoubted primary clot without evidence of inflammation (Bargen and Barker, 1936; Ebel et al., 1952).

Without exception all the reported post-mortem and post-operative studies have demonstrated the complete anatomical patency of the arterial system.

In addition to the studies reported above, some observations of pathological significance have been made on the living at operation. These fall into two groups. A number of authors have explored the femoral vessels at the onset of the condition, usually to exclude arterial embolism. They all report the femoral vein swollen and turgid with clot, but their observations on the state of the artery differ. Bergendal (1931), Gutzeit (1935) and Young, et al., (1950) report a normal artery, while Wertheimer (1935), Gregoire (1938), Audier et al., (1939), Sachenreiter (1940), DeBakey (1946) and Cassius (1950), found the femoral artery reduced in calibre, and beating only feebly.

The second group of observations are those made at amputation by some of the earlier authors (Bergendal, 1931, Wetheimer, 1935), who operated during the acute stage of

of the disease. They again report complete venous occlusion, but are unanimous in noting free arterial and capillary bleeding.

Results of treatment.

In reviewing the published cases of Phlegmasia Caerulea, one cannot fail to be struck, at once by the consistency of the clinical and pathological features, and by the considerable difference of opinion as to how these cases are best treated. This is understandable when one recalls that most of the reports are concerned with only one or two cases, and secondly that the outcome in the untreated cases may vary greatly; spontaneous recovery being by no means rare.

Suggestions for treatment are very numerous but they fall, by and large, into three main groups.

The case for conservative treatment, consisting essentially of elevation and exercise, was firstly clearly stated by Veal et al., (1949). Their series is by far the most impressive in the literature - eleven cases with no deaths, and recovery without gangrene in nine. Good results in smaller series, have been reported by Turner (1952), Moser (1954) and Catchpole (1957), using the same line of treatment.

The second group, by far the largest, contains the antivasospastic measures, advised by those authors who consider reflex arterial spasm to play a large part in determining the ischaemia. The suggestions include lumbar sympathetic block (Wertheimer, 1935, Audier and Haimovici, 1939, Leriche and Geisendorf, 1939, Haimovici and Suffness, 1948, DeBakey and

Oschner, 1946, Ossius, 1950), epidural anaesthesia (Halligan, 1953), periarterial sympathectomy (Gregoire, 1938, Audier and Haimovici, 1939), and the use of acetylcholine (Gregoire, 1938), Hexamethonium (Moser, 1954) and Tolazoline (Martin, 1953). Good results have been claimed in individual cases for all of these measures and particularly for lumbar sympathetic block. There is no doubt that lumbar infiltration relieves pain, but an unbiased appraisal of the subsequent fate of most of these cases entirely fails to confirm any other value for these methods. Of the ten cases reported to have shown a "good" result after antivasospastic treatment a major degree of gangrene supervened in six. Veal et al., (1949) and Ebel et al., (1952) performed lumbar sympathetic blocks on some of their cases, and reported it to be without effect on the course of the disease.

The third group is a miscellaneous group containing two active measures - thrombectomy and vein ligation. The latter method was used with success by Oaks et al., (1948) and Young et al., (1950). On the face of it, this seems an extraordinary method of treatment, but it was, of course, combined with thrombectomy, and possibly this latter measure was more effective in determining a satisfactory outcome. Thrombectomy has been favourably reported in a small series by Ossius (1950) and in individual cases by Leriche et al., (1939) and DeBakey et al., (1946). On the other hand, Nunez et al., (1952) performed it in one case without effect.

SECTION B.

CURRENT THEORIES.

A critical appraisal of the various theories, postulated in exploration of the genesis of the ischaemia will be deferred to a later chapter. However, in order to provide a background against which the present investigation can be seen in perspective, it seems desirable at this stage to summarize as far as possible, contemporary thought on this matter.

1. Venous occlusion.

In the face of the clinical and pathological facts presented above, most modern authors - but not all (Young et al., 1950) - agree that the dominant factor producing ischaemia is pure, widespread venous occlusion - an interruption of what the French term "the circulation of retura".

2. Generalized reflex small artery spasm.

It is almost universally held that this is an essential part of the physiopathology of this condition, and contributes more or less to the clinical picture.

3. Local large artery spasm.

The proponents of this theory envisage an "adventicitis" of a major vein, the seat of a thrombo-phlebitic process, reaching the arterial adventitia and causing a local spasm of the artery.

4. Venous spasm.

Manheimer et al., (1954) postulated that venous spasm administered the coup de grace to an already embarrassed circulation. The reason for this observation is that he noted in his case, oedema of the lower abdominal wall, and later demonstrated the patency of the iliac veins.

CHAPTER 3.

PLAN OF THE INVESTIGATION.

The fundamental question on which opinion remains divided is this - does reflex spasm of the vasculature play any significant part in determining the ischaemia of Phlegmasia Caerulea Dolens; and therefore has spasmolytic therapy any part to play in the treatment of this condition ?

The answer to this question has been sought by way of an experimental investigation using the rabbit as the experimental animal. The basic plan of the investigation can be summarized as follows :

Phase 1.

The measurement of the effect on blood flow in the hind limb, of (a) femoral vein ligation, and (b) chemical irritation the femoral vein and adjacent structures. (This being chosen as the experimental equivalent of the inflammatory irritation of thrombophlebitis.)

Series 1. Using pulse volume as the index of blood flow.

Series 2. Using a heat flow method as the index of blood flow.

Phase 2.

Series 3. The design of a method of producing massive venous occlusion in the rabbit hind limb, and the measurement of blood flow in such limbs.

Phase 3.

An enquiry into the role of reflex arterial spasm in the

experimental "blue" limb.

Series 4. By aortography.

Series 5. By estimating flow before and after total denervation of the limb.

It will be shown in a later chapter that a critical appraisal of the literature suffices to show that the work of Leriche and Kunlin, and of Fontaine and Souza Periera, on which the theory of spasm was based, is suceptible of other explanations. Furthermore, the support that it receives from clinical sources will be seen to rest upon a misinterpretation of the evidence.

The theory rests therefore on the experimental results of DeBakey et al., who reported that chemical irritation of the femoral vein reduced pulse volume (and by inference, blood flow) by 25%. These authors further claimed that this reduction was reversible by sympathetic interruption, and they deduced that it represented a reflex arterial spasm.

This then, seemed a reasonable point of departure, and it was decided to repeat DeBakey's work, in an attempt to confirm his results.

Series 1. Effect of ligature of the femoral vein, and of the intravenous and perivenous application of Sodium Salicylate (40%) on pulse volume.

The measurement of pulse volume was undertaken in the normal leg, and later, after venous ligation, and after the irritation

of the vein lumen with salicylate. Some interesting and significant results were obtained, but it soon became apparent that the method was introducing two very serious sources of error into the results. Briefly this was because pulse volume is influenced by vessel manipulation, and by rising venous pressure, to a degree out of all proportion to their effect on blood flow.

It seemed desirable, therefore, to abandon pulse volume as an index of blood flow and to seek a method better adapted to the circumstances of the experiment.

The so-called direct methods of blood flow estimation (stromuhrs, bubble meter, rotameter, orifice meter etc.) were obviously undesirable when the response of an intact circulation to certain interfering circumstances was under investigation. Two indirect methods were considered because of their relative simplicity and accuracy - venous occlusion plethysmography and calorimetry.

Venous occlusion plethysmography, a method developed by human physiologists is perhaps the best of all methods of measuring blood flow. It has, however, very rarely been used in animal experiments, and a short experience convinced us that it was quite unsuitable for our purposes. Even in the normal hind limb of the rabbit the capacity vessels are so small, that the entire collection period occupied only about one and a half pulse beats. It was obvious, that in the

presence of venous hypertension the collection period would be too short for analysis. Furthermore it has been shown (Loane, 1959), that venous occlusive plethysmography is not entirely reliable in the presence of large changes in venous pressure.

Plethysmography was therefore reluctantly abandoned and we turned out attention to calorimetric methods.

Series 2. Effect of vein ligature and of various chemical irritants applied within the lumen of the vein and to the extravenous tissues. (Calorimetric method of blood flow estimation.)

This series consisted essentially in repeating and expanding the experiments of DeBakey et al., (1939), using a different method of estimating flow.

Series 3. Effect of massive venous thrombosis on blood flow.

The remaining phases of the investigation demanded the design of a method of producing a massive interruption of venous return which would bear a closer resemblance to known pathological processes than the method of Fontaine et al., (1937) of almost totally severing the root of the limb. It seemed that if such an occlusion could be propagated from a single point in the venous circulation, the resemblance to the known pathology of Phlegmasia Caerulea would be reasonably close. Various waxes and types of gelatin were tried in an attempt to propagate a venous occlusion in a retrograde fashion down the femoral vein.

Eventually a technique was developed using Topical thrombin (Parke Davis) with which the venous circulation could be selectively and almost completely occluded.

The blood flow in these limbs was then compared with that in limbs treated in an exactly comparable manner, except for the injection of thrombin.

Series 4. Aortography.

In this series aortograms were performed on animals in which the venous system of one hind limb had been occluded in the manner referred to above, (retrograde injection of thrombin down the femoral vein). Films were made both before and after interruption of the sympathetic chain on the affected side.

Series 5. A comparison was made of the effect of (a) denervation and (b) changes in perfusion pressure, on the blood flow in normal limbs and in limbs in which massive venous occlusion had been produced.

This series of experiments produced some very valuable results and provided a fairly definite answer as to the importance of reflex spasm in the production of the ischaemia of massive venous occlusion.

CHAPTER 4.

EXPERIMENTAL METHODS.

The Animal.

Rabbits were chosen as the experimental animal, mainly because facilities for holding other animals of appropriate size were not available. This animal, while not as popular as the dog for peripheral vascular studies, has been used satisfactorily for this purpose in the past (Kinmonth, Simeone and Perlow, 1949, Barnes and Truetta, 1942, Darian Smith, 1954). As it happened the choice was quite a happy one, because the ready availability and comparative economy of the animal allowed us to plan an investigation in which very few experiments were associated with recovery, and in some stages of which the experimental mortality was necessarily high.

For all stages of the investigation, the common brown wild rabbit was used. Both sexes were used, bucks or does being chosen at random. The rabbits varied in weight from 1.7 kg. to 2.2 kg.

Anaesthesia.

The animals in Series 1 were anaesthetized with intravenous pentobarbitone (Sagatal - May & Baker) 25mgs/Kg., administered via an ear vein. This method provided good anaesthesia, but the animals tended to deteriorate fairly rapidly. Other anaesthetic agents were tried, and eventually

Dial-Urethane (Ciba) was chosen, and used for all the animals in subsequent experiments. The dose used contained diallylbarbituric acid 40mgs./kg., and urethane 160mgs./kg., and was given intraperitoneally, thirty minutes before the commencement of the experiment. This regime provided excellent light anaesthesia lasting about twelve hours.

SERIES 1.

The measurement of the effect of vein ligation, and of intravenous and perivenous stimulation on pulse volume.

Equipment (Figure 2.)

A. The plethysmograph was constructed from a perspex cylinder 18 cm. long and 2.4 cm. in internal diameter. This was closed at one end with a threaded brass plug with an adaptor to accept polythene tubing in an airtight fashion.

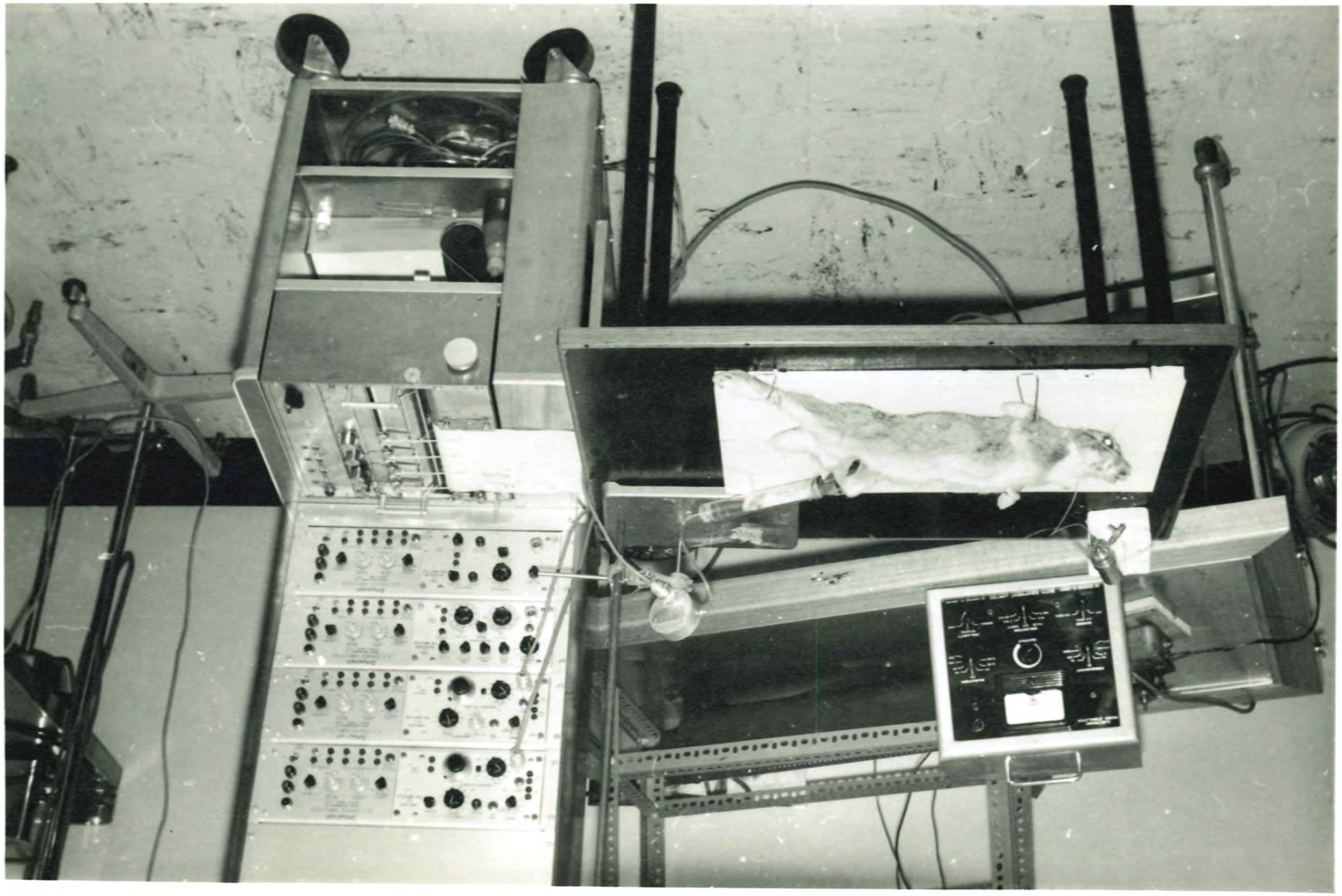
B. The volume transducer.

The volume changes within the plethysmograph were measured with a P.T.5A volumetric pressure transducer (Grass Instrument Company). The P.T.5A developed primarily for digital plethysmography, is designed to measure volume changes while introducing the least possible pressure changes into the system.

When measuring pulse volume, as distinct from whole limb volume, the position of the base line of the recording is not absolutely critical. For this reason the control of the temperature of the air within the plethysmograph-transducer-cavity system need not be quite so rigorous. We were

FIGURE 2.

The experimental lay-out used in recording pulse volume.



fortunate in possessing a room in which environmental temperature remained constant within 1°C. In this room, swathing the system in cotton wool was found to provide sufficient temperature control to maintain a steady base line on the record.

C. The pressure transducer.

A simultaneous measure of systemic blood pressure was obtained by the use of a P 23 A.C. pressure transducer (Statham Instruments Incorporated). This is the complementary instrument to the one described above, designed this time to perceive pressure changes and transduce them to changes in electrical resistance.

D. The polygraph.

The information gathered from the transducers was converted and recorded on a Model 5 Polygraph with a 5 P.I. low-level D.C. pre-amplifier (Grass Instrument Company). The volume transducer was calibrated at the beginning of each experiment by the introduction of a measured quantity of air into the system. The strain gauge was similarly calibrated against a measured head of water. Thereafter throughout the experiments, levels were checked with the electrical calibration signal provided on the polygraph.

E. The electronic nerve stimulator.

Two of the experiments in this series involved stimulation by electrical discharges. For this purpose an Electronic Nerve Stimulator (Both Instrument Company) was used.

Technique.

The plethysmograph contained the foot and leg up to just below the knee. It was fixed in position by making a circumferential incision at the level of the knee joint, and turning a cuff of skin distally over the lip of the plethysmograph and fixing it there with a stout linen ligature.

For the purpose of monitoring the blood pressure, the common carotid artery was exposed by a midline neck incision, and cannulated proximally with No.2 polythene tubing (Allen and Hanbury). At this stage Heparin 2500 I.U. was given into an ear vein.

The femoral vessels in the groin were exposed by a longitudinal incision prolonged up over the lower abdominal wall. To expose these vessels adequately it is necessary to divide the long saphenous neurovascular bundle, and a thin sheet of voluntary muscle which lies anterior to them in the rabbit. Another anatomical difference of importance concerns the high entrance of the profunda femoris vein. Its jundtion with the superficial femoral occurs under cover of Poupart's ligament, and on occasions it was necessary to divide this ligament, to display it.

Dissection around the vessels was kept to the absolute minimum and performed with the greatest care and gentleness. The vein was ligated above and immediately below the entrance

of the profunda, and again 2.5 cm. distally. In some experiments the external iliac and common iliac veins and the inferior vena cava were also ligated. This was performed through a midline suprapubic incision.

Chemical stimulation was provided by the use of 0.5 ml. of a 40% solution of Sodium Salicylate. This was introduced into the lumen of the isolated segment of vein, in some instances with a 25G. needle and in others with a canula of No.7G. polythene tubing.

Electrical stimulation of the various structures was done with a square pulse of 10 m.v. of a duration of 1 m.sec. and with a frequency of 70/sec.

Critique.

In a very general sense it is true that in any given subject under absolutely constant conditions, if the pulse rate remains the same, then the magnitude of the pulse volume change in a part, will bear a proportional relationship to the blood flow through that part. The amplitude and volume of the pulse wave depend however on other factors than the volume flow of blood, chief of which is the elasticity of the arterial walls. This in turn is dependent on many factors including the health of the vessel, the tone of the peripheral circulation, the venous pressure, and the blood volume. Thus it is perfectly possible for the pulse volume to vary markedly without any alteration in total blood flow. This fact very greatly limits the utility of the method even in ordinary circumstances.

In this specific instance, it is apparent that in raising venous pressure (DeBakey, 1946) as has been done, arterial elasticity has been altered also (Burch et al., 1939). It is thus highly dangerous to interpret an alteration in pulse volume in these circumstances, as an alteration in blood flow, particularly if this alteration is a diminution. It may represent nothing more than a damping of the pulse wave by a decrease in the elasticity of the arterial wall. Edhölm, Howarth and Sharpey-Schafer (1951) investigating arterio-sclerotic limbs found that mean blood pressure and flow are not necessarily reduced, but pulse volume is always grossly so.

An equally serious objection to the method, which has been amply demonstrated in our results, concerns the differential effects of traumatic spasm on the pulse volume and on the volume flow. A localised traumatic spasm of a major artery may totally abolish the pulse distally without seriously affecting blood flow. R. T. Whelan (1960) needling the brachial artery with a hand plethysmograph insitu, has noted that on occasions, interference with the artery has abolished the pulse wave on the tracing, but subsequent venous occlusion plethysmograms have shown that flow is unchanged. In our own experiments we have shown that dissection around the vessels in the groin always dramatically reduces pulse volume, while volume flow as measured by other methods is unchanged.

These experimental findings are in accord with the clinical features of some forms of traumatic arterial spasm. It has been the author's experience on several occasions that after the reduction of grossly displaced supracondylar fractures of the humerus, the wrist pulses are imperceptible and may remain so for some days. In the greater number of these cases, however, the peripheral circulation is obviously not seriously impaired, and no sequelae result from ignoring the absent pulses.

These two failings represent a serious indictment of the method, and certainly render it quite unsuitable as an index of blood flow, in the investigation of the effects of venous obstruction.

SERIES 2.

A reinvestigation of the effect of vein ligation and of intravenous and perivenous chemical stimulation on blood flow using the "thermal circulation index", as a measure of flow.

The reasons which led us to abandon the recording of pulse volume and substitute for it a method based on heat flow have been stated previously. It has been repeatedly stressed by physiologists and clinicians that methods of assessing blood flow based on heat and temperature are highly suspect and unreliable. While this is undoubtedly true in the usual clinical circumstances, it does not eliminate the value of the method when applied to carefully controlled experiments in the laboratory. Only very recently

has there been a renewal of interest in these methods. Greenfield (1960) in Belfast has worked extensively with direct calorimetry and reports that the volume flow figures obtained agree very closely with those given by plethysmography and various dye dilution techniques. Direct calorimetry is a difficult technique to apply and would be almost impossible in the case of the rabbit's hind limb. A simpler but equally reliable technique (Catchpole and Jepson, 1955) involves calorimetry with copper-telurium-copper heat-flow discs (Hatfield, 1950). Again, however, the anatomical features of the rabbit hind limb make it very difficult to design any method of ensuring that the outer side of the heat flow disc remains at an even temperature within critically small limits.

We have then in calorimetry an excellent method of assessing flow, but one which presented considerable technical problems in our particular circumstances. The answer to these problems we found in a method described by Burton (1934, 1948) involving the measurement of what he terms the "thermal circulation index". This index is based upon skin temperature, but it also takes into account deep body temperature and the temperature of the environment. The index is such that if the circulation does not change the index remains unaltered even with a changing environment. The index is based on a physical analysis of the flow of heat from the body to the environment. This heat flow is envisaged as occurring down two gradients, the physiological -

from the body core to the skin - and the physical - from the skin to the environment.

The flow down these gradients can be expresses as :

(a) $H^1 = C^1 (T_c - T_s)$

(b) $H = C (T_s - T_e)$

when H = heat flow ($cals/cm^2/sec$)

T_c = core temperature

T_s = skin temperature

T_e = environmental temperature

C = thermal conductivity of the environment

C^1 = thermal conductivity of the tissues

The thermal conductivity of the tissues depends on many factors including the proportion of fat and water in the tissues, the thickness of the skin, and the length of the pathway from tissues at the core temperature, to the skin. However, the only factor governing C^1 which will alter during the course of an experiment is blood flow. The measurement of C^1 will therefore provide an index of volume flow and is the closest we can come, by observations of skin temperature, to a direct measurement of peripheral blood flow.

Now in the steady state, the amount of heat reaching the skin must clearly equal that leaving it. In other words $H^1 = H$. Eliminating H we are left with $\frac{C^1}{C} = \frac{T_s - T_e}{T_c - T_s} = r$ (the thermal circulation index.)

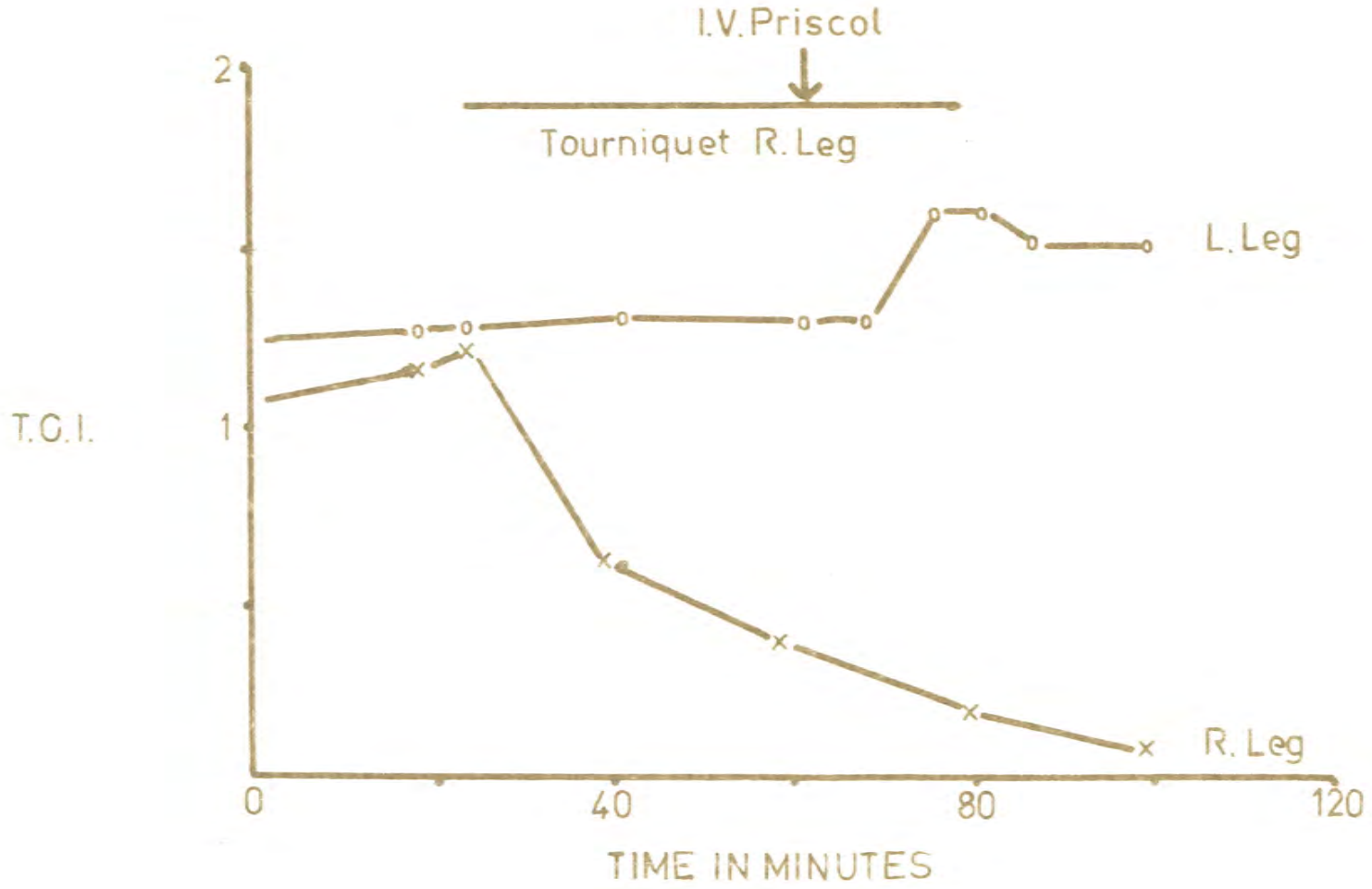


FIG. 3 To illustrate the response of the T.C.I. to changes in blood-flow

Under experimental conditions, the physical factor C can be kept reasonably constant. Changes in the value of the index will then reflect changes in the conductivity of the tissues; i.e. they will be indicative of changes in the peripheral circulation. The absolute level of the index has no quantitative meaning, but a change in the index by some factor (say twice) means that flow must have increased at least by that factor (at least twice), (Burton,1948).

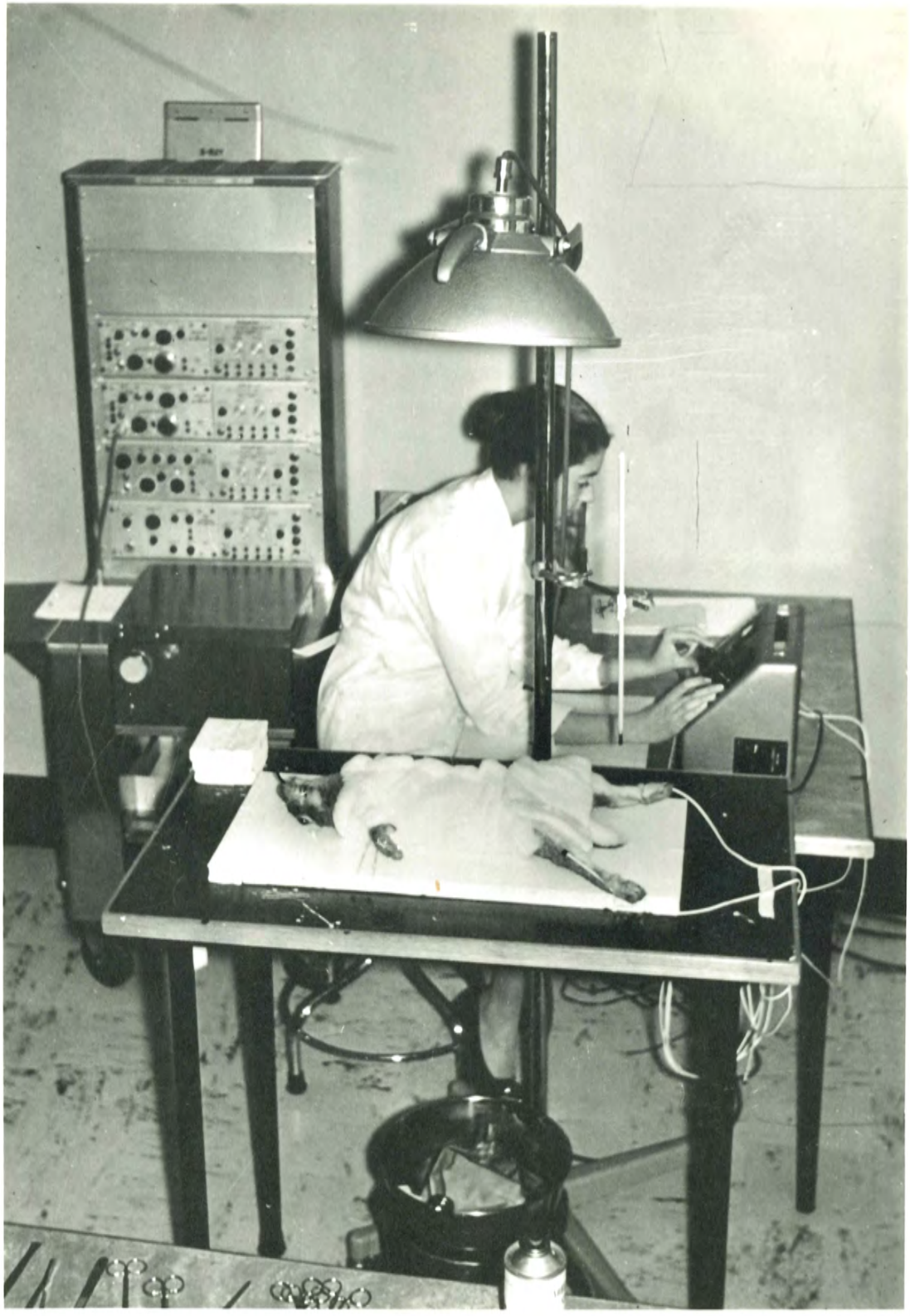
In other words the assumption is made that flow in mls/min = Kr where K is a constant. The value of K can be deduced from direct flow measurements in the rabbit hind limb to have been approximately one, in our experiments.

Burton (1948), as a result of many measurements found that the temperature difference between bilaterally symmetrical areas on the body has a mean of 0.02°C with an S.D. of 0.3°C. By statistical criteria therefore a difference of 0.9°C is significant at the 5% level. Thus, measurements made on two legs simultaneously are roughly comparable, a lower temperature indicating a poorer flow.

Some cautions are necessary in interpreting these results in terms of blood flow. Firstly, it is not known in what porportion skin flow and muscle flow contribute to the result. As changes may occur independently in these tissues, we are observing the algebraic sum of unknown proportions of the two variables. From the point of view

FIGURE 4.

The experimental lay-out used in recording the "thermal circulation index".



of our experiments, this is not a disadvantage. Secondly, our equation applied only to the steady state, and while temperatures are changing, the quantitative aspect of the index does not apply. Thirdly, as with all heat and temperature recording methods, there is a "thermal lag": that is, temperature alteration follows some minutes after the alteration in blood flow which caused it. In these experiments, the response to diminution in flow was almost immediate (within two minutes) while temperature increase in reponse to a rising flow, did not usually commence for four to six minutes and took ten to twelve minutes to reach a maximum and resume the steady state. Again this is no disadvantage in the present context in which we are looking for sustained alterations. The type of reaction observed is illustrated in Figure 3.

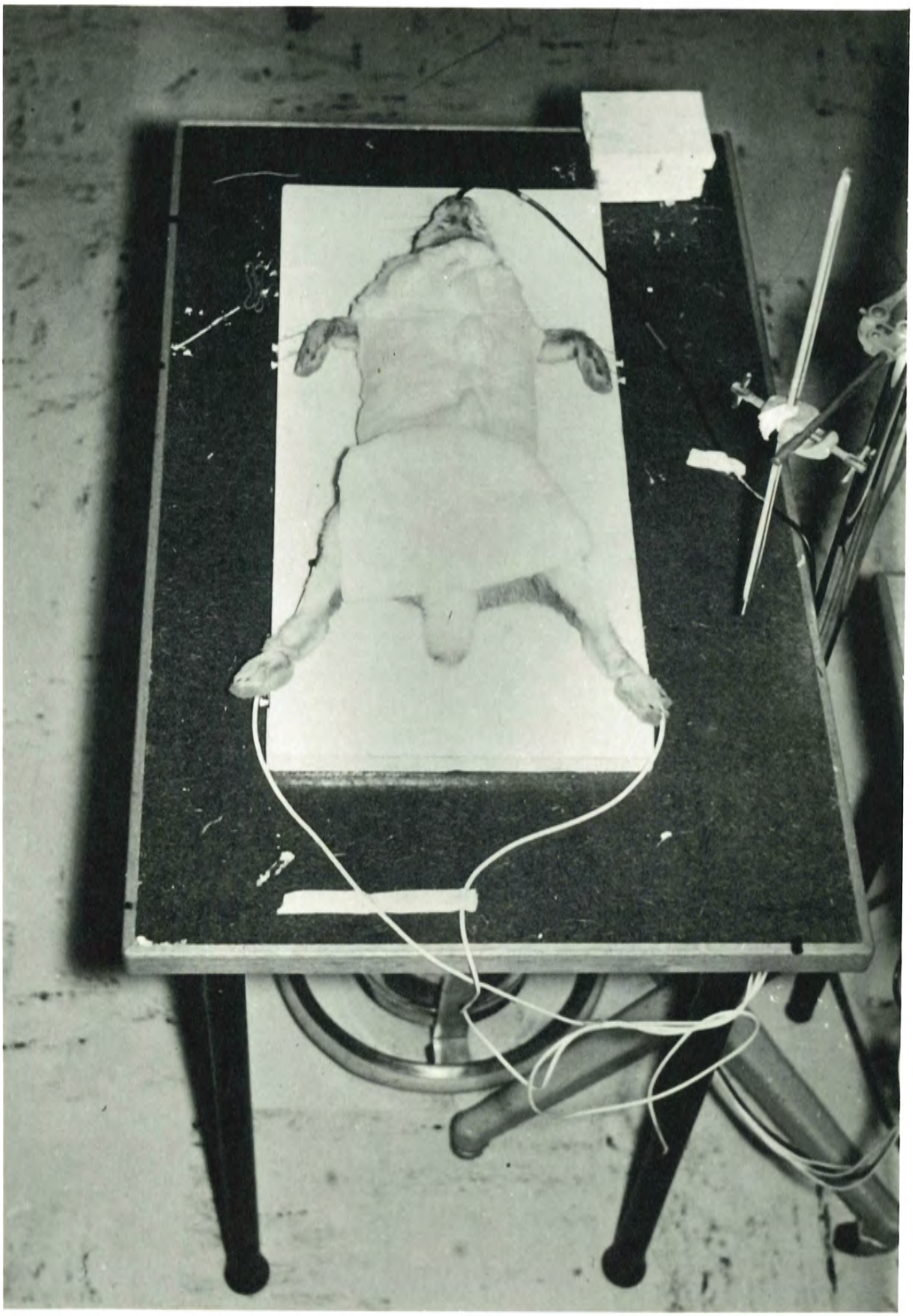
Equipment. (Figures 4, 5, 6.)

All experiments involving the recording of temperature were performed in a room where the environmental temperature remained constant within 1°C and usually within 0.5°C during the course of the experiment. The mean temperature during most of the experiments was 24°C. Environmental temperature was measured by a mercury thermometer graduated in 0.1°C and recorded every two minutes.

Other temperatures were measured with Model 1 G.P.O. Electric Thermometer (Light Laboratories). This is a

FIGURE 5.

The animal prepared for the recording of the "Thermal circulation index". Note the swathe of cotton wool, and the probes in position.



thermistor (resistance thermometer) in which the operating principle is as follows : a current generated by a battery is made to flow around a circuit, part of which is incorporated in the sensing probes. This portion of the circuit is constructed from a metal (lead foil) in which the change of resistance with change of temperature is large. This is a very convenient instrument, having several advantages over the more usual thermocouple. Firstly, since we are not entirely dependent on a small Emf generated at the wire junction, recording is much easier and can be accomplished with a less sensitive galvanometer. Also unlike the thermocouple and thermopile, the relationship between temperature and resistance is linear at all levels, making complex calibration unnecessary.

The model used was equipped with probes adapted for recording skin temperature and also bougie type probes, with which oesophageal or rectal temperature could be measured. The working range was from 20°C to 40°C and the accuracy obtainable was equal to or better than $\pm$ 0.2°C.

Technique.

With the animal anaesthetized, the skin probes were fixed to the outer side of the legs, below the knee by the use of Norbecutane (Evans), and a bougie type probe was passed down the oesophagus until it was judged to be just above the cardia. The left common carotid artery was then cannulated for blood pressure monitoring and the animal heparinized as previously

described.

The femoral vein was exposed and tied in the groin as described in the previous section. A fine polythene cannula was then introduced into the isolated segment of vein. Temperature observations were commenced and taken every two minutes for a minimum period of thirty minutes. This period was continued if necessary until the skin temperatures were stable.

At the end of this period the chosen chemical irritant - in this series, either Sodium Salicylate 40%, saturated Sodium Chloride solution, Dextrose 50% - was introduced into the lumen of the vein, via the cannula which had been introduced previously so as to isolate the effect of irritation from that of trauma. The effect of this manoeuvre was also observed for thirty minutes.

Perivenous irritation was then provoked by injecting the irritant into the tissues surrounding the vein as in Series 1.

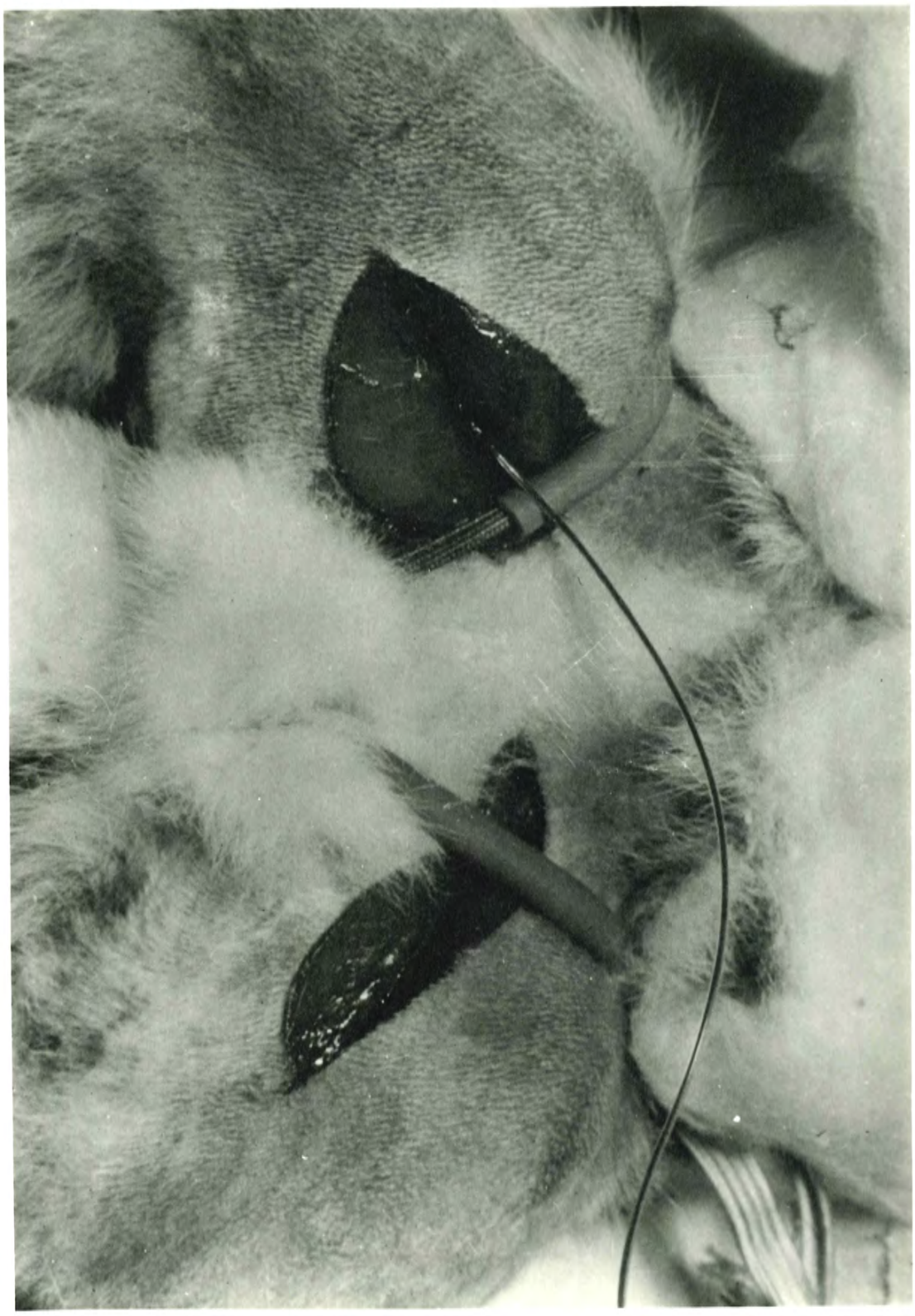
Great care was taken during these experiments to prevent extraneous factors altering the environment. In particular, the entire procedure was carried out by the light provided by fluorescent tubes in the ceiling, and theatre of spot lights of any kind were not allowed. Solutions injected or applied to the groins were kept at 24°C.

SERIES 3.

Measurement of the effect of massive venous occlusion upon

FIGURE 6.

The tourniquets in position prepatory to the injection of thrombin.



blood flow in the rabbits hind limb, as indicated by thermal circulation index records.

The greatest technical problem of the investigation resulted from an attempt to design a method of producing massive venous occlusion, which would in some degree peproduce the pathological features of phlegmasia caerulea dolens. Eventually a method was developed consisting in the retrograde injection of thrombin down the femoral vein. Thrombin administered into the circulation is an extremely lethal drug and it was essential to confine it within the treated leg until it had been fixed by thrombus, and also to flood the rest of the circulation with heparin. On the other hand, of course, heparin is an anti-thrombin and it was equally necessary to exclude it from the treated leg, until the thrombus had formed. A tourniquet was used to subserve both these purposes. In order to keep vessel damage to a minimum, soft sewing "elastic" was used and threaded through rubber tubing where it lay over the front of the thigh. In the rabbit it is not possible to keep a tourniquet in position in the groin unless it is hooked over the ischial tuberosity behind. Five minutes was found to be the minimum time which would allow thorough fixation of the thrombin and survival of the animal after removal of the tourniquet. This period of application was therefore used as a routine.

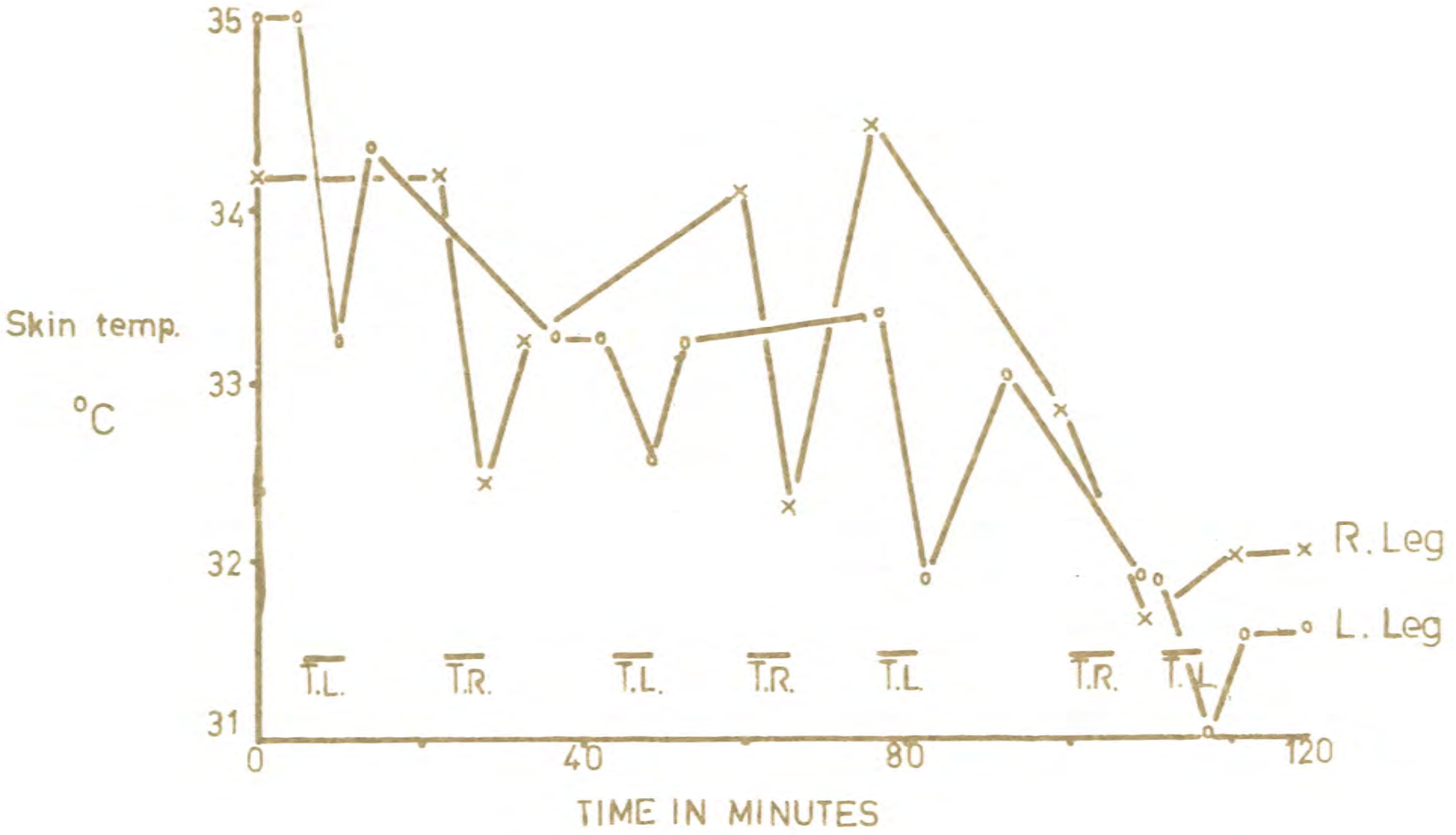


FIG 7 Showing the effect of a tourniquet, in place six minutes, on skin temperature

The — indicates a tourniquet in place

An experiment was performed to see what would be the effect of a tourniquet applied in the manner specified above. A portion of the graph of results obtained is shown in Figure 7 and a summary of the result in Table 5. The application of the tourniquet regularly resulted in a precipitate drop in skin temperature and in T.C.I. (thermal circulation index) commencing within two minutes. Release allowed a recovery commencing usually within two minutes, always within four, and reaching a maximum within ten minutes.

Recovery was complete, in sense of a return to the pre-tourniquet level in only one case, but considering the general downward trend of the temperatures throughout the experiment, it was probably better than the mean 70% calculated from the results.

The magnitude of the tourniquet drop varied directly, as might be expected, with the height of the temperature at the time of application.

The application of a tourniquet then might be expected slightly but not seriously to affect flow subsequent to its removal. To further minimize this possible source of error, tourniquets were applied in a comparable manner to both the treated and control legs.

By this technique it was possible to produce animals which were alive and in good condition at the end of the procedure. Furthermore all the treated legs had suffered a serious interference with venous return as could be judged from the

TABLE 5.

Showing the effect on subsequent blood flow of a soft tourniquet applied for five minutes. (T.C.I. = Thermal circulation index.)

Experiment No.	Initial Temp.C°	Initial T.C.I.	Maximum fall Temp.C°	Maximum fall T.C.I.	Time Mins.	Maximum recovery Temp.C°	Maximum recovery T.C.I.	% Recovery	Time Mins
1	35.0	4	33.2	2.1	6	34.3	3.2	61%	6
2	34.1	3	32.4	1.6	6	33.3	2.3	53%	6
3	33.2	2.4	32.7	2.0	4	33.1	2.5	100%	6
4	34.0	3.8	32.2	1.8	6	34.4	4.0	120%	10
5	33.4	2.7	31.8	1.6	6	32.7	2.3	57%	10
6	32.5	2.0	31.3	1.3	10	31.8	1.5	70%	6
7	31.8	1.5	31.0	1.2	6	31.5	1.5	70%	6
8	31.2	1.4	30.2	1.0	8	30.6	1.1	40%	8

massive oedema (white leg) developing in those animals who survived twelve hours or more (Figures 8 and 9). In about 60% of cases a true "blue leg" was produced. This was not accepted unless the skin colour of the treated limb was distinctly blue, and this was verified by at least one observer who was unaware which leg had been treated (Figures 10 and 11). A clear distinction is made between the results obtained from the "white" and "blue" legs.

That the pathological process at work in those legs was a massive venous occlusion involving virtually all the veins of the limb, with preservation of the arterial system was demonstrated in the following ways. Dissection of the limb during life constantly showed that every vein large enough to be seen was filled with clot which could be expressed from them in the form of work-like casts. By contrast free bleeding occurred from severed arteries (Figure 12.). Post-mortem dissection was performed on most of the animals used. Again the veins were constantly found full of clot. In addition, where limited survival had occurred, oedema was very obvious, and extravasations of blood were seen here and there in the muscles (Figure 13).

Finally, aortography was performed on a number of animals in this series. The technical details were similar to those in a later series, and will be discussed then. It was a constant finding that arterial filling was adequate in

FIGURE 8.

A leg treated with thrombin twelve hours previously, showing massive oedema.

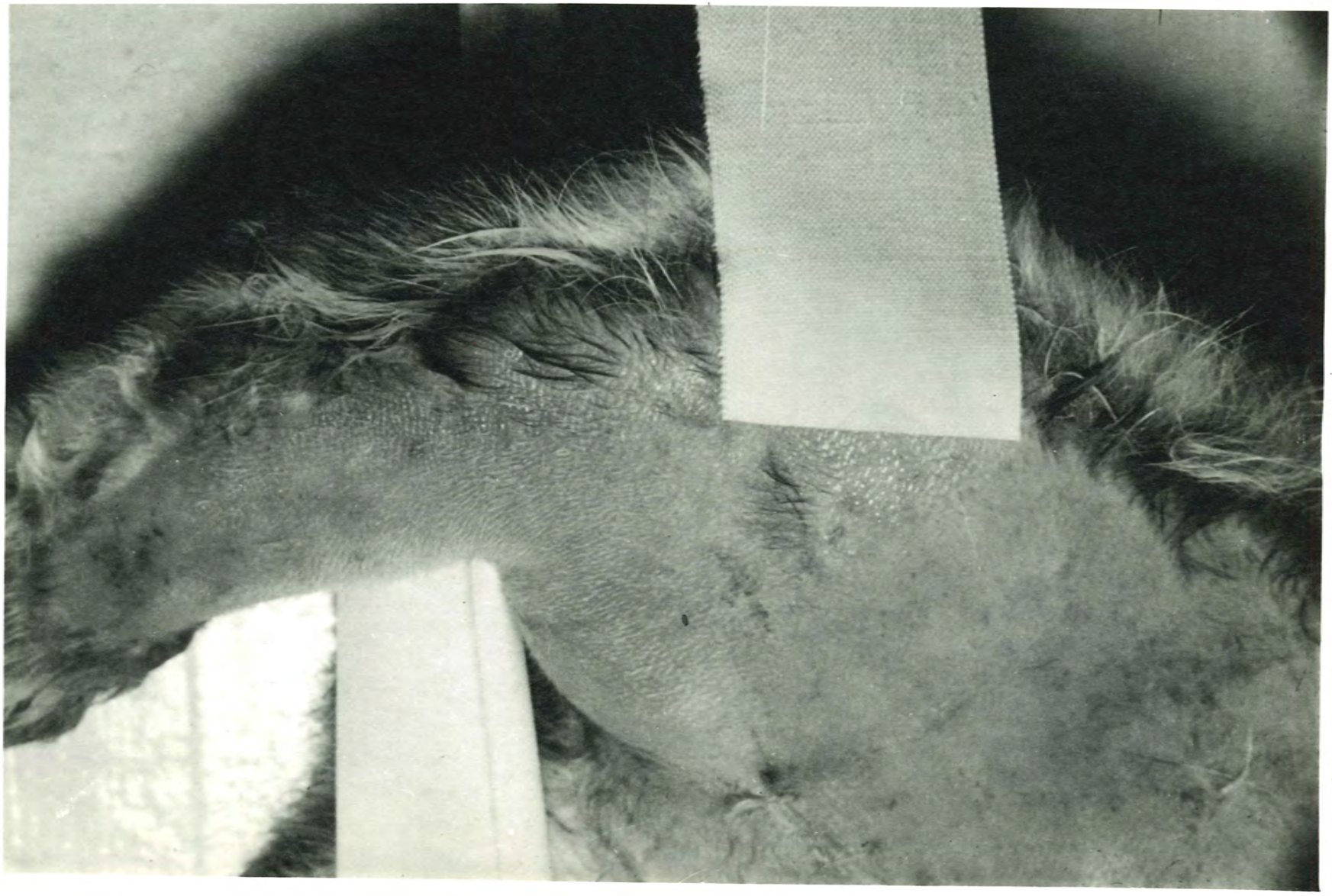
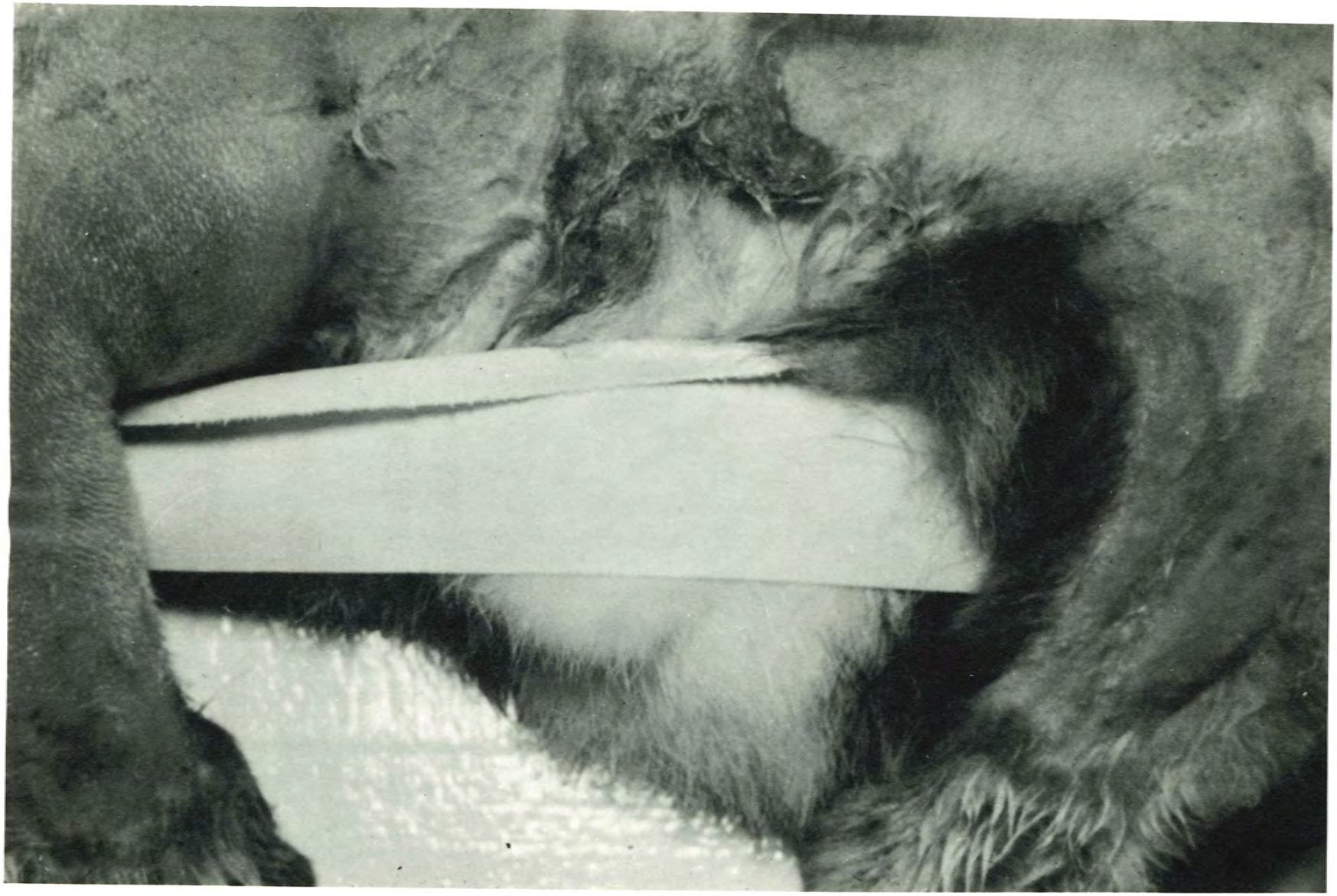


FIGURE 9.

A leg showing massive oedema contrasted with the normal control leg.



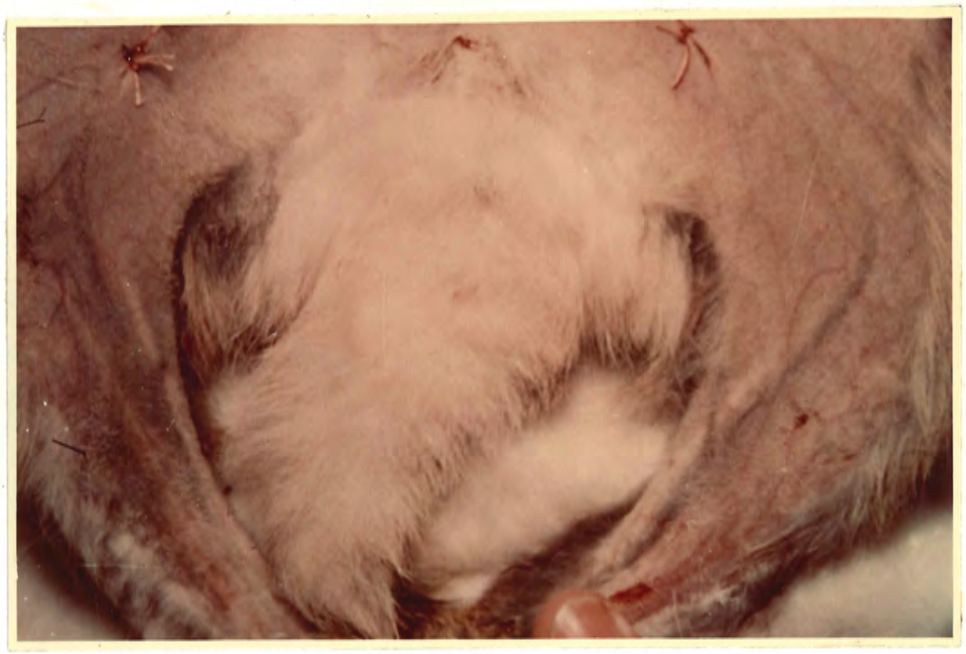


FIGURE 10.

The right leg has been treated with thrombin and shows the violaceous colour change.

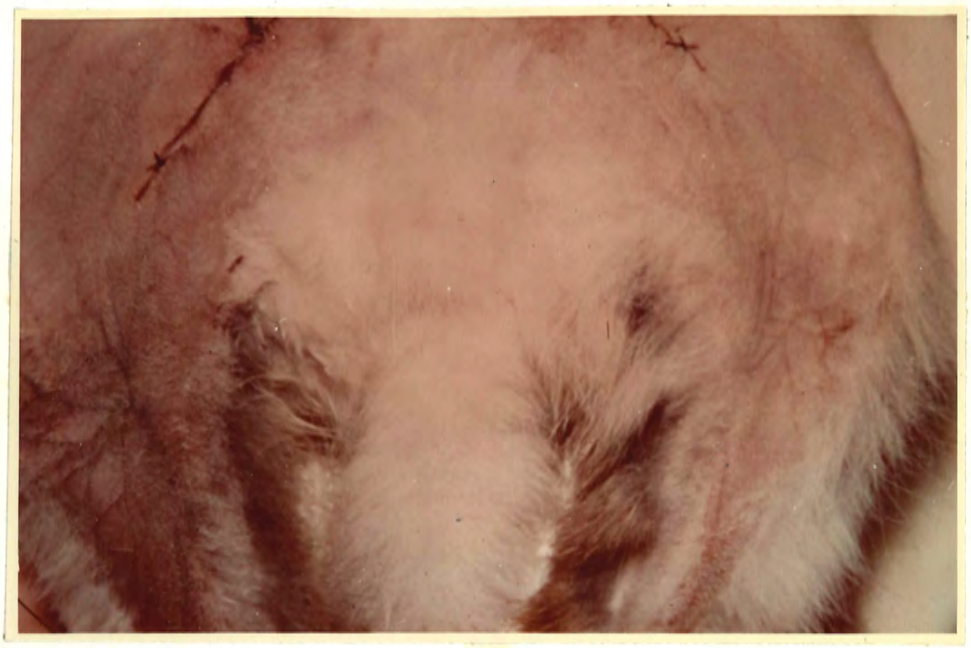
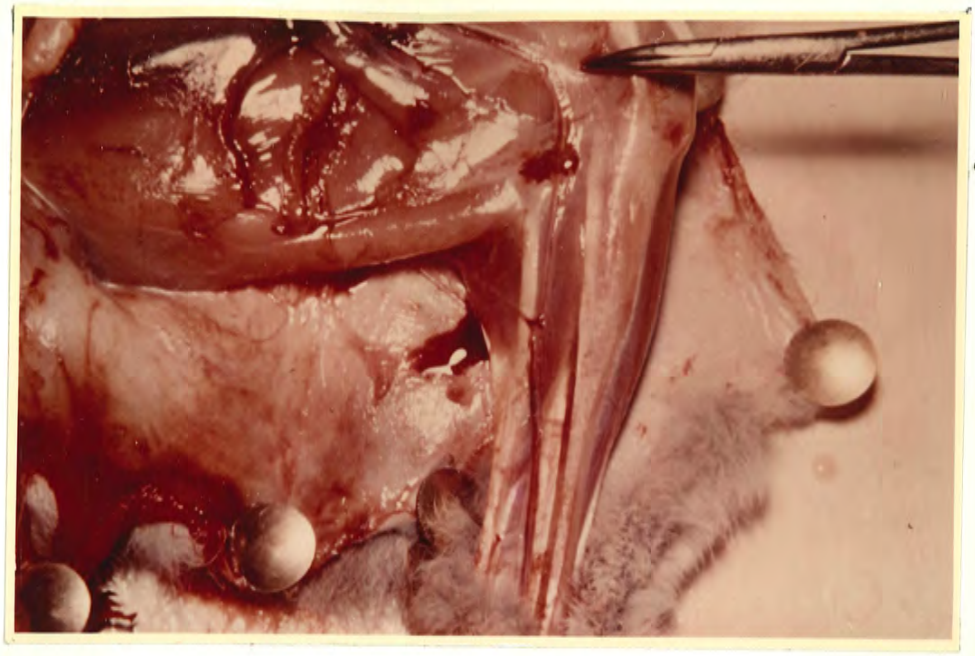


FIGURE 11.

Another example of the experimental blue leg.



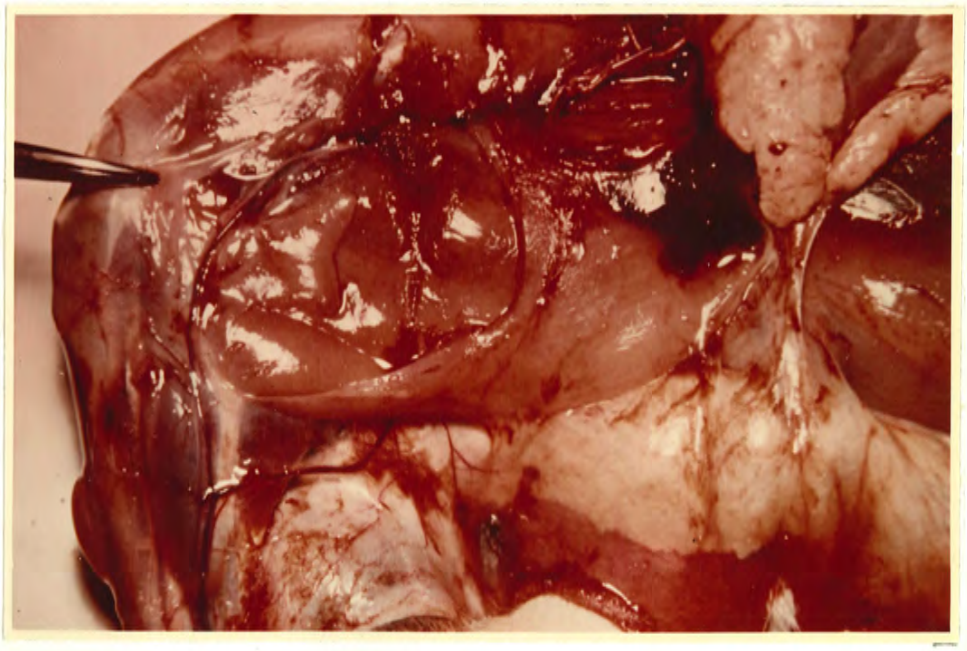
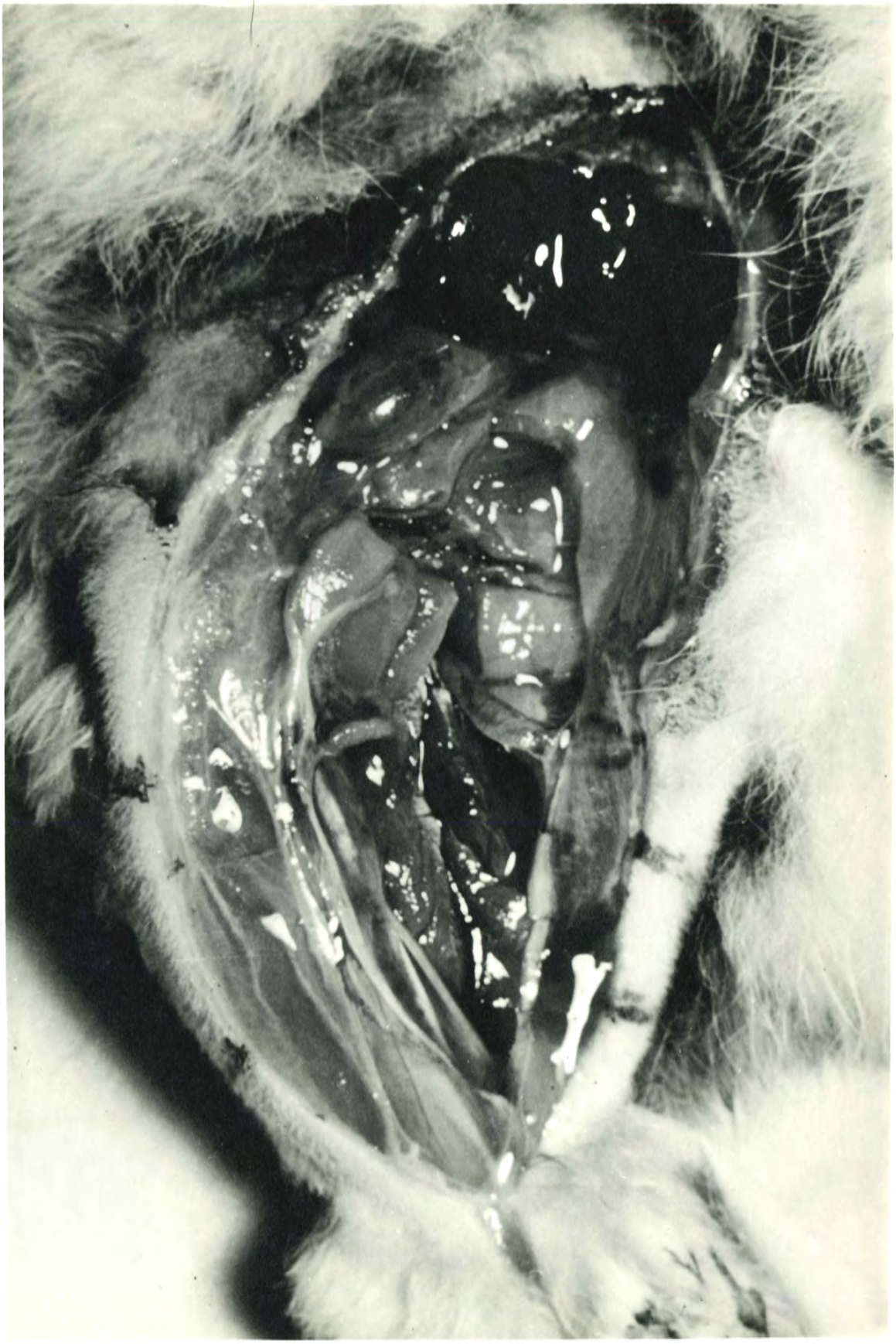


FIGURE 12.

The upper photograph illustrates a normal leg flayed during life. The lower photograph is of a blue leg similarly treated. Note the clotted veins, and fresh arterial and capillary bleeding.

FIGURE 13.

Post mortem dissection of a blue leg. Note the oedematous muscle planes and extravasations of blood.



both legs, but, although venous filling could be demonstrated easily in the control leg, no venous dye was seen in the treated legs in more than thirty aortograms (Figure 14).

Technique.

Because this procedure was a very traumatic one, and because, as we have seen, recovery of skin temperature after the application of a tourniquet, is poor in a deteriorating animal, every effort was made to keep trauma to a minimum, and to prevent unnecessary loss of body heat. For this reason, trusting to the fact that there is a control leg, we abandoned the recording of systemic blood pressure. For this reason also the animal was swathed in cotton wool throughout the experiment.

Thermistor probes were fixed to the skin and introduced into the oesophagus as discussed in the last section. Environmental conditions were controlled and measurements taken in the same way as previously.

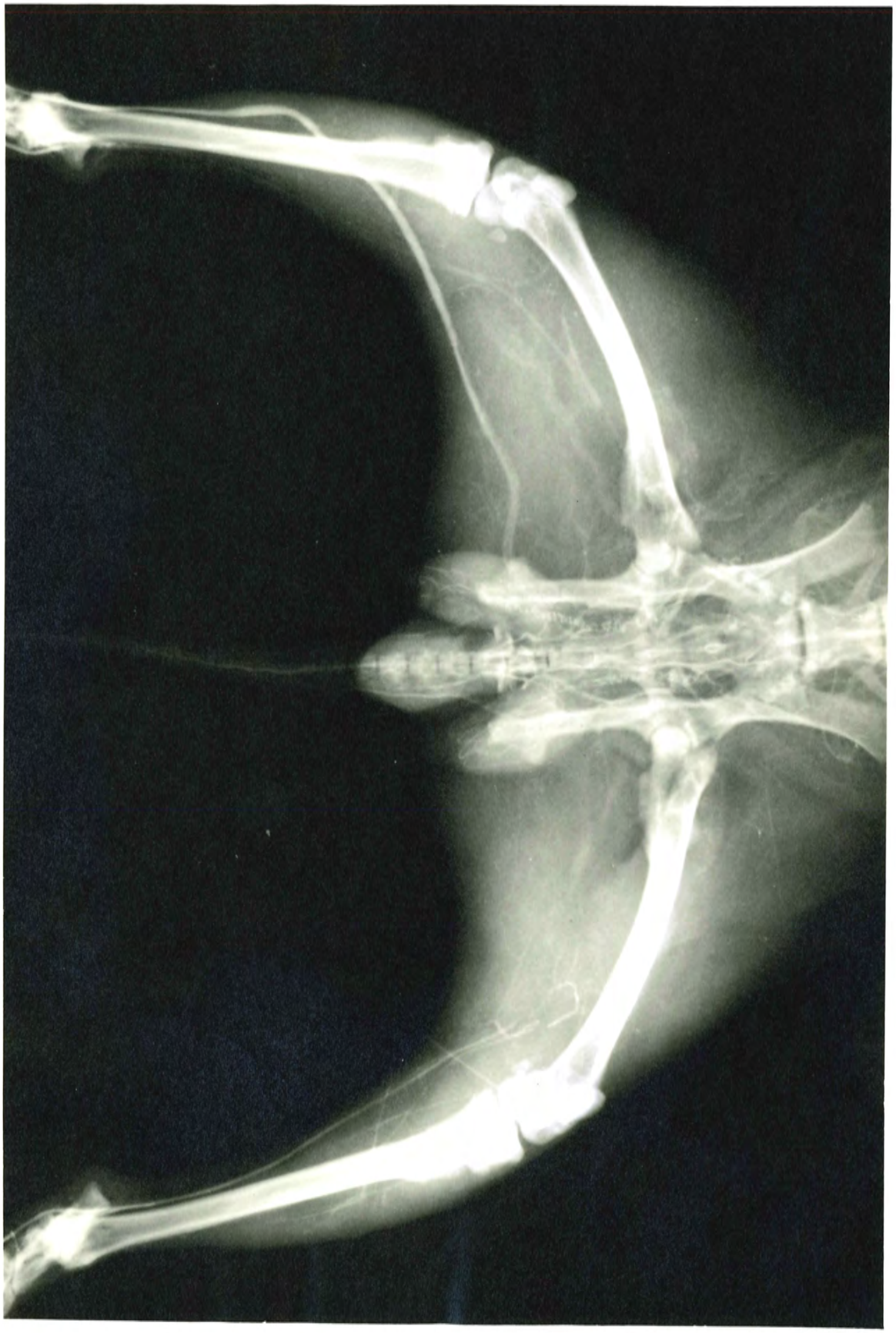
After a period of observation had ensured a steady state, the femoral vessels were exposed in both groins and the veins tied as previously described. A fine polythene catheter was introduced into the distal segment of femoral vein, in one leg only. (In some experiments the control leg was left normal.)

After a further period of observation tourniquets were placed and tightened about both legs. Immediately 500 I.V.

FIGURE 14.

A late film from a series of aortograms of a blue leg.

On the left (control) a large vein is seen filled. On the right (blue) arterial filling persists but there is no evidence of contrast medium in the veins.



Heparin was injected into an ear vein, and 5 ml. of a solution of Topical thrombin (500^{u}) was injected into the femoral vein cannula.

Five minutes later the tourniquets were removed, and temperature recordings were continued for at least a further sixty minutes.

SERIES 4.

Visualization of the arterial circulation in the presence of massive venous occlusion, before and after lumbar sympathetic block.

Technique.

The animals were prepared in a manner very similar to that discussed in the previous section. Because it is impossible to cannulate the femoral vein in the rabbit without provoking a localised arterial spasm apparent in the radiograms, the vein was cannulated on both sides, and in the control leg the injection of thrombin was replaced by an injection of 5 ml. of N. saline. Thus apart from the effects actually attributable to thrombin, conditions are identical in both legs, and it seems reasonable to assume that any differences in the angiograms can be attributed to the agency of massive venous occlusion.

In addition, through a loin incision removing the twelfth rib, a right nephrectomy was performed and the renal artery cannulated for the later introduction of the dye.

This was necessary because in the heparinized rabbit, needling of the aorta provoked a rapidly exsanguinating haemorrhage.

Aortograms were made on these animals at times varying from thirty minutes to six hours after the production of the venous occlusion. Standard 17" x 14" "Kodak Blue" brand films were used in a manually operated cassette changer. An exposure of 50 K.V., 10 Mas at 40" was employed with Paterson par speed screens.

Five ml. of Diatrizoate Sod. (Hypaque, Winthrop) was injected into the arterial cannula as rapidly as possible. Three films constituted a series. The first was exposed during the injection of the final 0.5 ml. of dye, the second as rapidly as possible, and the third, for venous filling, after four seconds.

A right lumbar sympathetic block was then performed using 8ml. of 1% lignocaine in four injections of 2 ml. each. The technique is similar to that used in the human, but much simpler. The initial insertion of the needle, striking and passing above the transverse process, and angling to strike the side of the vertebral body is identical. In the rabbit, the psoas major is a massive muscle and reaches a more anterior plane than the front of the lumbar bodies, which therefore lie in a gutter which is readily palpable through the anterior abdominal wall of the anaesthetized animal. After some practice

on the eviscerated cadaver, therefore, it is possible to introduce the needle point with great precision to lie alongside the vertebral body and just dorsal to the inferior vena cava. Of the animals in which this technique was practised, most were later sacrificed and the adequacy of the block checked by dissecting the needle track which in the heparinized animal was usually easily discovered.

Twenty minutes were allowed to elapse for the block to exert its maximum effect, and the series of films was repeated utilizing the same technique.

SERIES 5.

A comparison of the effects of (a) denervation, and (b) changes in perfusion pressure on the blood flow in normal limbs, and in limbs in which a massive venous occlusion had been produced. The "thermal circulation index" was again used as a measure of flow.

Denervation in the manner described herafter can be expected to completely interrupt the sympathetic innervation of the limb with the exception of that supplied via the periarterial plexus to the proximal femoral artery and vein. This is made abundantly clear by the work of Woolhard (1926), Moore and Moore (1933) and Kinmonth (1952), referred to elsewhere, which limits the periarterial sympathetic supply to the major vessels in the groin.

Technique.

The anaesthetized animal was positioned on its back

in the usual way, and the femoral and sciatic nerves on both sides exposed. The femoral nerve was approached through a longitudinal incision similar to that previously described for the exposure of the femoral vessels. To obviate the necessity to turn the animal after the thermistor probes were fixed in position, a lateral approach to the sciatic nerve was devised. This can be readily accomplished in the rabbit by a half inch incision along the posterior border of the greater trochanter. There is no fleshy glutous maximus to obstruct this approach, and after dividing a fascial attachment to the bone, an intermuscular plane, between the lateral septum and adductor magnus anteriorly and the hamstrings posteriorly can be opened up very easily. The nerve is readily identified and a thread was passed around it to ensure rapid and easy identification later.

A massive venous thrombosis was then provoked in the right hind limb using the technique previously described; and finally the right carotid artery was cannulated to allow the blood pressure to be continuously recorded. Our interest was in the mean pressure available to perfuse the hind limbs, and an electrical damping device on the polygraph allowed direct recording of mean arterial pressure.

A blue leg was produced in all the animals in this series and as soon as it was apparent that this had been

accomplished, the thermistor probes were placed as previously described and temperature recording begun. After a steady state had been observed for an average of thirty minutes, the femoral and sciatic nerves were divided bilaterally. Observation was continued until, under the influence of time and trauma, the mean blood pressure had fallen to 50-70 mm Hg. The pressure was then restored to 100 mm Hg. by an infusion of Dextran 6% (Intradex - Glaxo) and temperature observations were continued until the pressure began to fall again.

TABLE 6.

Showing the results obtained in the individual experiments in Series 1.

Manoeuvre	% change in pulse volume.							
	Exp.1.	Exp.2.	Exp.3.	Exp.4.	Exp.5.	Exp.6.	Exp.7.	Exp.8.
Vessel dissection				- 60	- 25	- 80	-T40	- 16
Ligation common femoral vein	0	0	0	- 10	0	0	- 25	- 16
Ligation common iliac vein					0	0	- 25	
Ligation external iliac vein						0		
Ligation inferior vena cava						0		
Intravenous Sodium Salicylate 40%	- 50*	- 60	- 70		- 80			- 25
Femoral nerve stimulation						+ 50	+ 40	
Femoral artery stimulation						0	0	
Femoral vein stimulation						0	0	
Crural muscle stimulation						0	0	

Note: In this and the following tables, the signs + and - indicate an increase or decrease in pulse volume. The percentages quoted are not cumulative. The steady state obtaining before each new manouevre is taken as zero.

CHAPTER 5.

RESULTS AND ANALYSIS.

Series 1. (Table 6)

From the viewpoint of result analysis, this first series, which as we saw earlier concerned itself with the effects of various manoeuvres on the pulse volume, falls into four parts.

1. The effect of dissection in the groin.

In the early experiments it soon became apparent that it was impossible to carry out the operative procedures associated with exposing the femoral vessels, without profoundly affecting pulse volume. For this reason, in the later experiments the operative steps up to and including the placing (but not tying) of the femoral vein ligatures, was performed as a separate step, and its effect quantitatively assessed. (Table 7). It constantly produced a profound fall in the pulse volume, which varied presumably with the trauma of the operation, but which averaged 50%. This change is statistically significant ($p = 0.01 - 0.02$). There is no reason to imagine that this is in any way a reflex phenomenon. It is well known (Kinmonth, Simeone & Perlow, 1949) that traumatic spasm is easily provoked in the rabbit femoral artery, and indeed the diminution of calibre in the vessel during the dissection is easily appreciated by the naked eye. In view of the findings of Whelan (1960) and Edholm, Howarth and Sharpey Schaffer (1951) referred to previously, such a diminution in pulse volume is to be

TABLE 7.

Showing the effect of various manoeuvres on pulse volume.

Manoeuvre	No. of observations	Mean % change in pulse volume	Range	Significance. P
Vessel dissection	6	- 49 %	16 - 80	Less than 0.02.
Ligation of common and superficial femoral vein	8	- 5%	0 - 16	Less than 0.1.
Ligation common iliac vein	4	+ 2%	0 - 25	
Ligation external iliac vein	1	0		
Ligation inferior vena cava	1	0		

expected in the presence of traumatic spasm, and I believe this to be the explanation of this result.

2. The effect of venous ligation.

As can be seen from Table 7 ligation of both the common and superficial femoral veins produced a mean diminution in pulse volume of a further 5% in eight experiments. In Table 6, however, it can be seen that in five of these experiments, the vein ligation was without any effect on the pulse volume, and the alteration is not significant ($p = 0.10 - 0.05$). In those three cases where it was associated with a small fall, it seems reasonable to attribute the fall in all probability to the trauma of tying the ligatures, knowing from the results discussed above, the extreme sensitivity of the pulse volume to traumatic arterial spasm. This impression is strengthened by the absence of any effect on pulse volume, of extending the vein tie progressively to the external and common iliac veins and even to the inferior vena cava. (Table 6 and 7).

3. The effect of chemical irritation. (Table 8).

The attempt to deliver a 40% Solution of Sodium salicylate into the lumen of an isolated segment of femoral vein was regularly associated with a considerable depression of pulse volume, averaging 57%. This result is highly significant ($p = 0.01 - 0.001$). As it was quite apparent that introducing the irritant with a needle always resulted

TABLE 8.

Showing the effect of certain chemicals on pulse volume.

Manoeuvre	No. of observations	Mean % change in pulse volume	Range	Significance P.
Intravenous Sodium Salicylate 40%	5	- 57 %	+ 25 - - 80	Less than 0.01
Intravenous Sodium Salicylate - with care to prevent spillage	1	- 5%		

in spillage, an attempt was made to deliver it via a polythene cannula. Introducing a cannula, however, was productive of so much trauma that the pulse tracing was abolished.

In a single experiment, polythene sheeting was placed between the vein and the other tissues, and the irritant introduced with a needle. In this case the depression of pulse volume was 5%. Such a small deviation cannot be accepted as significant, and in any case could be attributed to the trauma of the manipulations.

To further test the hypothesis that extravenous leakage was responsible for the effect of the salicylate, two experiments were performed using electrical stimulation in place of chemical irritation.

4. The effect of electrical stimulation. (Table 9).

Stimulation of the femoral artery or vein has no effect on pulse volume. Neither has stimulation of the muscle tissue in the thigh.

Stimulation of the intact femoral nerve, of either the ipsilateral or contralateral leg increases pulse volume an average of 45%. Some of this increase may perhaps be attributed to increased muscle tone improving venous return and diminishing arterial elasticity, but the fact that it can be provoked by stimulation of the contralateral nerve, suggests that it may be in part at least, a reflex inhibition of vasomotor tone.

TABLE 9.

Showing the effect of electrical stimulation on various structures in the groin.

Structure	No. of observations.	Mean % change in pulse volume	Range
Femoral nerve (intact)	2	+ 45%	+ 40 - + 50
Femoral artery	2	0 *	
Femoral vein	2	0	
Thigh muscle	2	0	

* See text.

In the summary, the following conclusions seem to be warranted from the first series of investigations.

(a) Ligation of the common femoral vein has virtually no effect on pulse volume. In view of the enormous available venous collateral pathway at the root of the thigh, so beautifully demonstrated in the dog by Fontaine and Souza Pereira (1937) this result is not unexpected. It is, however, completely at variance with the results obtained by DeBakey, Burch and Oschner (1939) in the dog. It seems unlikely that this is a species difference, and we believe that the explanation lies in the fact that DeBakey and his colleagues did not differentiate the effect of the vein tie, from that of the trauma of tying, to which, as we have demonstrated, pulse volume is very sensitive.

(b) In common with DeBakey we found that the injection of a chemical irritant into the lumen of an isolated segment of femoral vein reduced pulse volume very markedly. One other group of observers (Freeman, Shumacker and Radigan, 1950) have reported similar findings. All these experiences, however, are sharply at variance with what is known of large vein innervation from the work not only of physiologists but also of anatomists. Woolhard (1926) in a classical and beautifully designed investigation reported that the nerve supply to large vessels was wholly by way of the periarterial plexus and wholly sympathetic, while the innervation of smaller vessels was

partly sympathetic and partly afferent and travelled via adjacent somatic nerves. This anatomical picture has been many times confirmed from a functional viewpoint. Moore and Moore (1933) and Moore and Singleton (1933) report great pain sensibility of arteries, residing wholly in the smaller vessels and not at all in the larger. The sensibility can be abolished by posterior root section but not by sympathectomy. Lynn and Simeone (1952) distending a femoral vein segment with a variety of irritants failed to demonstrate any effect on pulse volume. In the light of all these facts, these authors attributed the results of DeBakey and Freeman to spillage of the irritant outside the vein lumen.

As suggested earlier, we had independently come to a serious suspicion that spillage was influencing our results. The few experiments that we performed with electrical stimulation which can be accurately confined to the structure under investigation, tended to confirm this suspicion. Before this question could be thoroughly investigated, we had become dissatisfied with the method of pulse volume recording, and had decided to repeat all these previous experiments using the "thermal circulation index" as a measure of flow.

Series 11. (Table 10). Figure 15 and 16.

Skin temperature, and any index of flow derived from it, tends to vary from moment to moment in a much more erratic fashion that does blood flow itself. In the present state of

TABLE 10.

Results of individual experiments in Series 2.

% change in Thermal Circulation Index.

Manoeuvre	EXPERIMENT. 1	2	3	4	5	6	7	8	9	10	11	12
Vein dissection	0	0	0	- 20	0	0	0	0	+ 59	- 5	0	0
Vein tie	0	0	0	+ 42	+ 100	+ 14	0	0	+ 12	- 8	0	0
Intravenous Sodium Salicylate 40%	0	0	0	+ 67	0	0	0					
Topical Sodium Salicylate 40%	+ 75	+ 87	+ 33	0	+ 71	+ 50	+175					
Intravenous Saline (Saturated)								0	0	0		
Topical Saline (Saturated)								0	+ 12	+ 50		
Intravenous Sucrose (50%)											0	0
Topical Sucrose (50%)											+ 30	0

Note: In this and the following tables, the signs + and - indicate an increase or decrease in "Thermal Circulation Index". The percentages quoted are not cumulative. The steady state obtaining before each new manoeuvre is taken as zero.

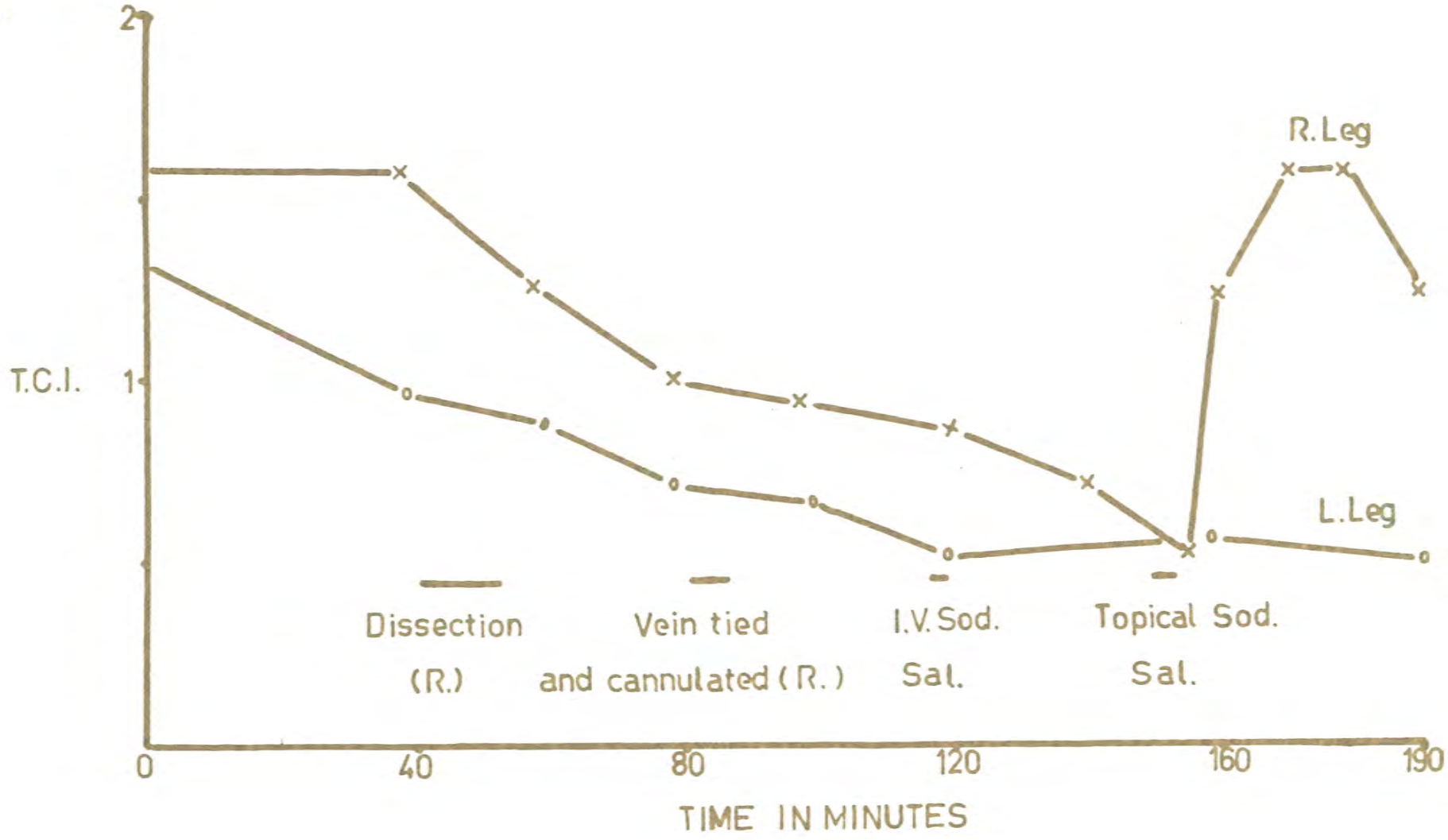


FIG. 15 Typical graph from SeriesII [Exp. 2]

knowledge, such small variations remain unexplained and are regarded as "spontaneous". In addition to these random variations, there is usually over the course of several hours a slow erratic downward drift of skin temperatures which can be only partially attributed to a lessening of blood flow. It is due to a general cooling of the entire animal, and also in part to a diminution in cardiac output and systemic blood pressure.

Results in experiments such as these, must then be interpreted with considerable care. Firstly, changes in the index based on a temperature alteration of less than $1^{o}C$ are not accepted as significant. Secondly, any change to be acceptable must clearly deform the preceding pattern, and must moreover occur in the right form and with the right time relation to the stimulus which provoked it. Figure 17 shows a specimen graph illustrating these points. If we simply took the figures for the T.C.I. at the commencement of the vessel dissection and again at the end of a period of observation thereafter, we would see a decline in apparent flow of 18%. A glance at the graph, however, shows that the pattern is entirely unchanged, and it would be folly to interpret the alteration as significant. Again, the response to tying the vein consists only of a slight accentuation of a preceding pattern and although this is probably significant, it is not certainly so.

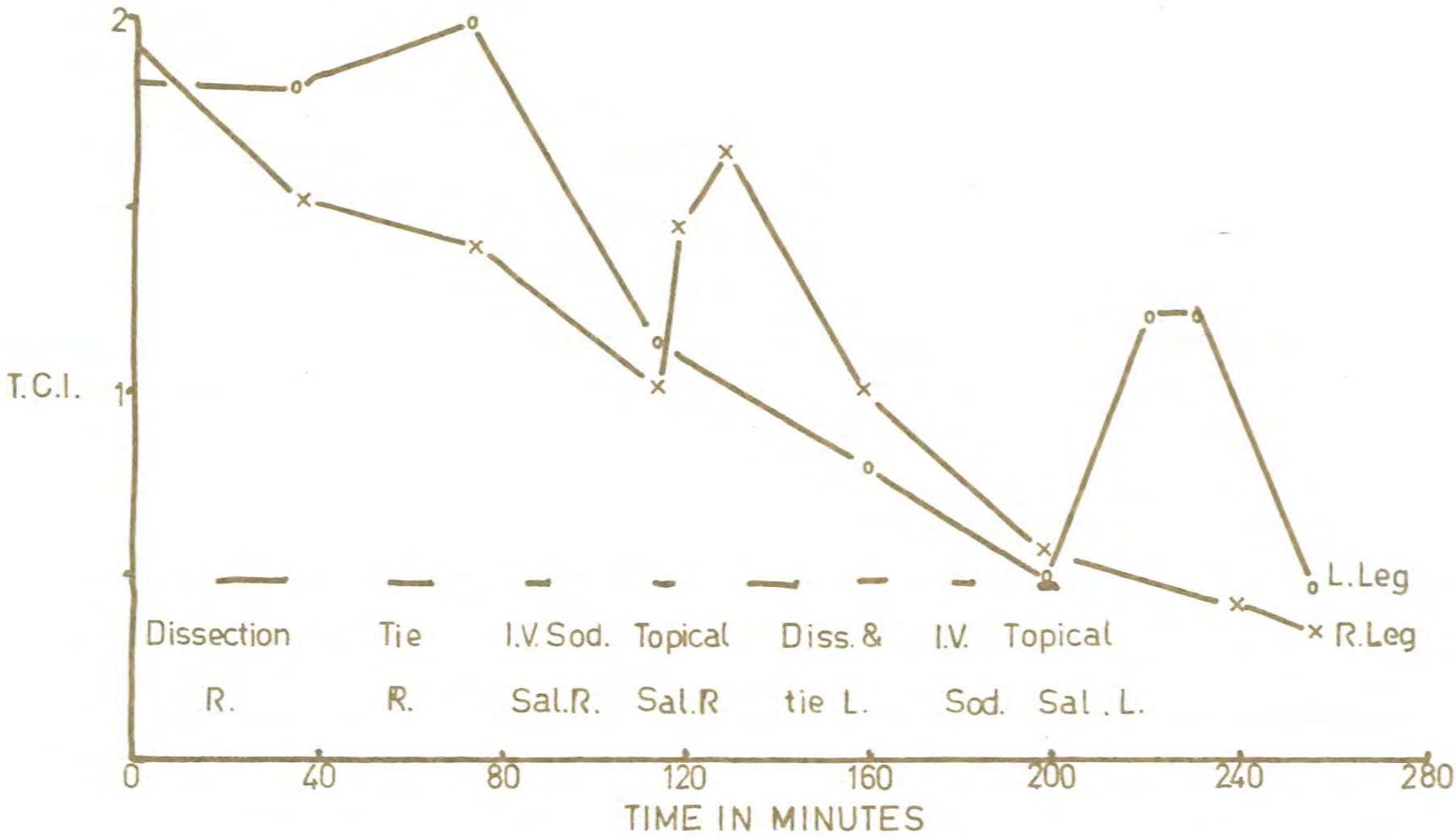


FIG. 16 Typical graph from SeriesII [Exps. 6 & 7]

When sodium salicylate is applied to the tissues however, there can be no doubt that a profound alteration in the pattern is casually related.

Interpreted in this way, the results of this series of experiments is summarized in Tables 10 and 11.

1. Dissection of the femoral vessels in the groin is usually without any effect on the T.C.I. Occasional variations were encountered in both directions. These vagaries do not constitute a significant variation from the normal ($p = 0.6 - 0.7$). A fall was interpreted as showing a profound traumatic spasm due to an inept dissection. A rise was probably contributed to by the warmth of the operator's body and possibly in part consequent on the division of those branches of the femoral nerve lying in front of the vessels.

These results are very different from those obtained in the first series. We interpret this as strong confirmation of two facts mentioned previously - viz. traumatic spasm need not seriously interfere with blood flow, and secondly that pulse volume is a poor flow index.

2. Tying both common and superficial femoral veins does not as a rule affect blood flow. On four occasions, however, thia manoeuvre produced a rise in TC.I. This can probably be attributed to the fact that it brings the operator's hands very close to the leg, and they will usually be $5^{\circ} - 6^{\circ}$C warmer than the skin temperatures being measured. There is some evidence, however,

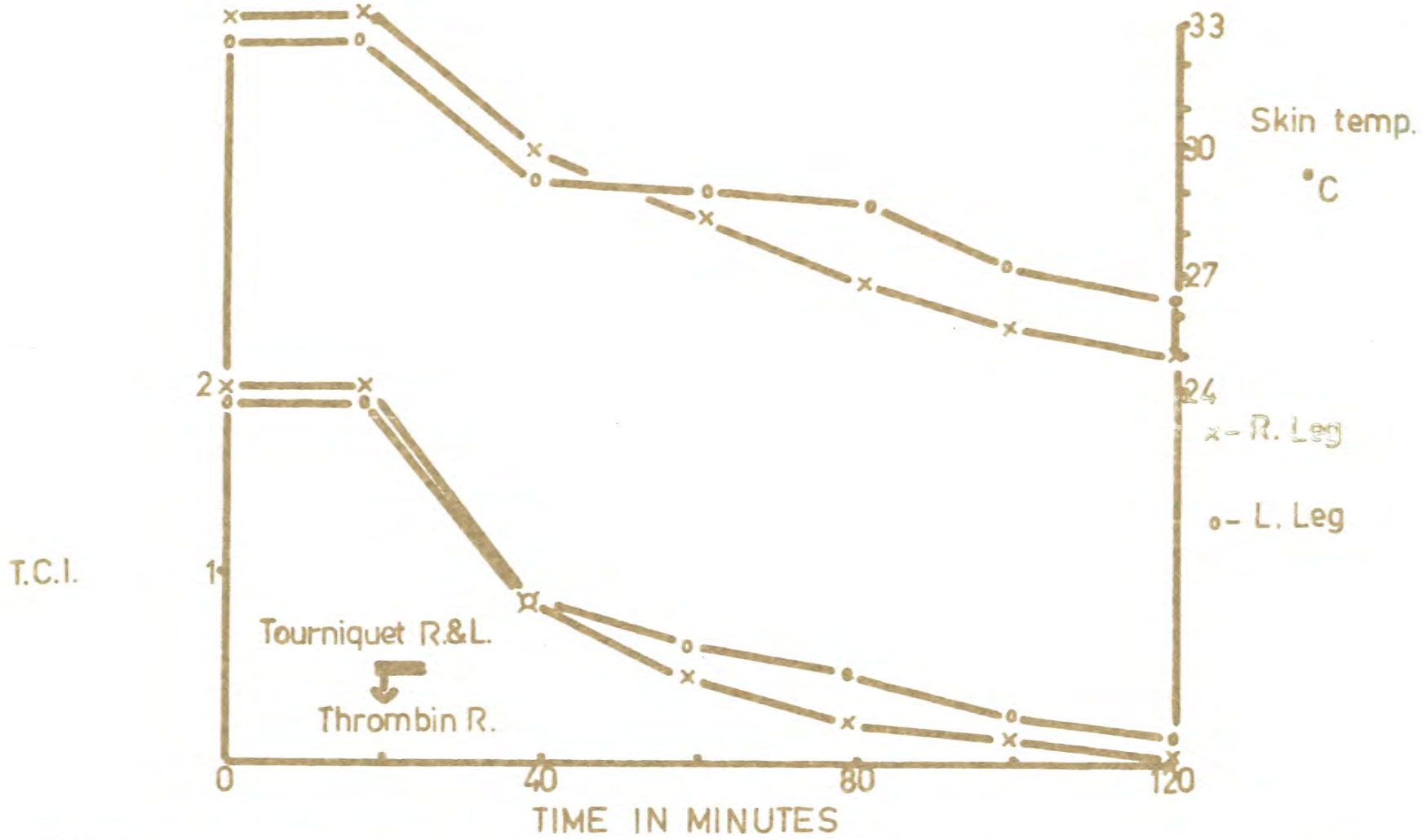


FIG. 17 A graph from Series III [Exp. 7] comparing the parameters, skin temp. & T.C.I.

Note a steady fall throughout with "recovery" on the L., seen better in the temp.-graph

that a rise in venous pressure, providing sufficient venous channels remain patent, may lower peripheral resistance and improve flow (Read, Kuida and Johnson, 1958). The variations however are not statistically significant ($p = 0.2 - 0.1$).

These results are totally at variance with those of DeBakey et al., and serve to confirm the impression generated in the first series, that DeBakey's findings were due to the effect of local trauma on the pulse volume.

3. The introduction of a chemical irritant into the lumen of an isolated segment of femoral vein has no effect on blood flow. One experiment shows an apparent exception to this result, but looking at the results as a whole it is quite obvious that this exception was due to spillage.

4. The topical application of a chemical irritant to the tissues of the groin regularly resulted in a marked rise in the T.C.I. averaging 70% in the case of salicylate. This rise is statistically significant ($p = 0.02 - 0.01$).

These two results taken together entirely confirm the opinions of Lynn and Simeone (1952) quoted earlier, and make it apparent that the 25% reduction claimed by DeBakey as the result of intraluminal salicylate, was firstly the result of spillage and secondly a direct "traumatic spasm" effect on pulse volume, and the inference of these authors that blood flow was affected similarly was mistaken.

TABLE 11.

Showing the effect of various manoeuvre on Thermal Circulation Index.

Manoeuvre	Mean % change in Thermal Circulation Index	Range	No. of Experiments	Significance P.
Vessel dissection	+ 4	- 20 - + 59	11	0.70 - 0.60
Vein tie	+ 14	- 8 - + 100	12	0.20 - 0.10
Intravenous Salicylate	0		6	
Topical Salicylate	+ 70	+ 33 - + 175	6	0.02 - 0.01
Intravenous Saline	0	-	3	
Topical Saline	+ 20	0 - + 50	3	0.40 - 0.30
Intravenous Sucrose	0	-	2	
Topical Sucrose	+ 15	0 - + 30	2	

It is interesting to speculate on the mechanism of the increase of T.C.I. in response to chemical irritation. The possibilities appear to be as follows:

(a) local paralysis of the tone of the femoral artery. In view of its well documented effect on pulse volume this explanation would appear invalid.

(b) absorption into the general circulation and transference thence to the tissue cells. The salicylate ion is a powerful metabolic stimulant at the cellular level, and would doubtless cause a temperature rise if absorbed in this way. The fact that this effect is confined to the ipsilateral leg excludes this explanation.

(c) absorption into the femoral artery and thence selectively into the tissues of the ipsilateral leg. Prima facie, this seems unlikely and is made more so by the fact that the same affect, less only in degree, can be obtained with a saturated saline solution which is not a metabolic stimulant.

(d) a true reflex inhibition of vascular tone. That this is not an unlikely explanation is apported by the similar results obtained by nerve stimulation in series 1. It has been well known for many years (Sampson Wright, 1955) that stimulation of a peripheral nerve (unless it be very powerful and unphysiological stimulation) produces a reflex inhibition of vasomotor tone in the extremity concerned.

In summary then we have shown that neither vein ligature nor intraluminal irritation affect blood flow, and that irritation of the extravenous tissues in a manner somewhat similar to that which may be expected to result from a thrombophlebitis, usually increases rather than decreases flow.

SERIES 3.

A summary of the results of this series, which is concerned with the estimation of blood flow in a limb in which massive venous occlusion has been produced, is shown in Table 12. It has been pointed out previously that our technique of producing venous occlusion usually produced a "blue" leg, but not uncommonly only a massive oedema was produced. In the latter case virtually no alteration in blood flow was detected (mean fall - 10.25%). When a "blue" leg was produced however, there was universally a disastrous decline in blood flow as indicated by the thermal circulation index (mean fall - 57.75%). The difference of these means is highly significant ($p = 0.01 - 0.001$). (Figure 18). Apart from this formal series of experiments, "blue" legs were produced on more than twenty occasions, and a grave degree of ischaemia was always evidenced both by the skin discolouration and by the palpable coldness of the limb.

Evidence has been adduced in a previous section, that the "blue" legs which we have produced bear a reasonable pathological resemblance to spontaneous phlegmasia caerulea dolens. We have now added evidence that our "blue" legs suffer a serious degree of ischaemia.

TABLE 12.

Showing the effect of massive venous occlusion on blood flow.

Experiment No.	"Blue" or "White" Leg	T.C.I. as % of that in the control limb
1	Blue	50%
2	Blue	58%
3	Blue	31%
7	Blue	30%
Mean		42%
4	White	89%
5	White	100%
6	White	70%
8	White	100%
Mean		90%

The difference of the means is significant ($p \simeq 0.01 - 0.001$.)

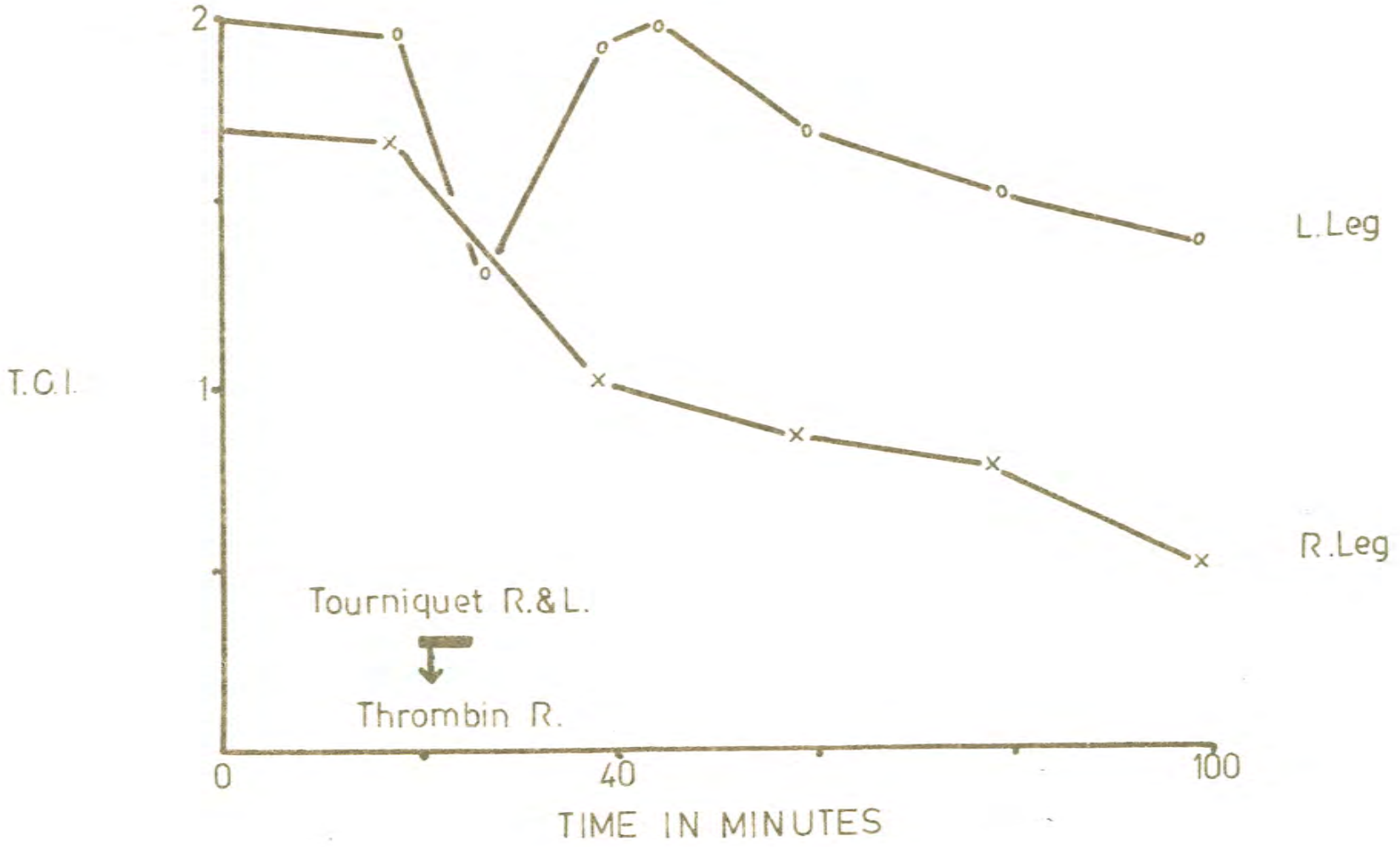


FIG. 18 Typical graph from Series III [Exp. 3]

In summary, therefore, these results are suggestive that massive venous occlusion can apparently cause serious interference with blood flow, and the factor which appears to determine the appearance of ischaemia is the completeness of the venous occlusion. That is, if sufficient venous channels remain patent, to support an adequate circulation, only a "white" leg will result. If, however, sufficient channels do not remain, then ischaemia will result, on the simple principle that what cannot get out of a given circulatory system, cannot get in (excepting the replacement of an increase in fluid filtered from the capillaries into the extracellular space). In an attempt to adduce more conclusive proof of these contentions, two further series of experiments were performed seeking to demonstrate the precise role of reflex spasm in the production of the ischaemia evident in our experimental "blue" legs.

SERIES 4.

The results of this series comprise fifty-four aortograms in eighteen series of three films each. These eighteen were performed in nine animals, ten before and eight after lumbar sympathetic block. Of the nine animals, the clotted leg was preclassified as "blue" in five cases and as "white" in four. The films were studied to determine the differences between the pattern seen in the clotted leg, and that in the control leg which had received similar treatment, except for the thrombin.

TABLE 13.

Features seen in individual aortograms of clotted limbs.

Experiment No.	White or Blue Leg	Time period between clotting and angiography	Reduction in calibre of major vessels	Reduction in small vessel filling	Circulatory slowing	Venous filling	Effect of sympathetic block
1	White	6 hours	Slight	Marked	Marked	Absent	Present
2	Blue	3 hours	Slight	Marked	Marked	Absent	Absent
3	White	30 minutes	None	Marked	Marked	Absent	Present
4	Blue	2 hours	None	Marked	Marked	Absent	Absent
5	White	4 hours	Slight	None	Marked	Absent	-
6	Blue	4 hours	Slight	None	Marked	Absent	Absent
7	White	2 hours	Slight	None	Marked	Absent	Absent
8	Blue	30 minutes	None	Marked	Marked	Absent	Absent
9	Blue	4 hours	Marked	Marked	Marked	Absent	Absent

1. Slowing of the arterial flow was the most marked effect of the treatment with thrombin and was seen in every case (Table 13). In the first film it was usual to see dye approaching the foot in the control leg, while it had not yet reached the knee in the treated limb. That this did not represent an organic arterial block was apparent from the later films in which filling had always progressed further.

2. The other feature regularly noted was the total absence of venous filling in the treated leg although it was regularly seen in the control.

3. In 80% of the "blue" legs and 50% of the "white" it was clear that small vessel filling was seriously interfered with in comparison with the control limb (Table 14).

4. The calibre of the major vessels of the limb was not affected in any constant manner. In one case only was the arterial diameter grossly reduced on the treated side, but in two-thirds of the animals there was a very minor and scarcely perceptible narrowing on this side. In this respect, it did not seem significant whether the limb had been classified as "blue" or "white", but a fairly definite correlation can be seen between the presence of narrowing, and the duration of the venous occlusion (Table 13). This suggests that oedema may in a purely mechanical fashion affect vessel diameter. At all events, the calibre was never affected by sympathetic interruption and so presumably is not a reflex effect.

TABLE 14.

A comparison of the angiographic features in "white" and "Blue" limbs.

% of cases showing various angiographic features.

Nature of Pathology	No. of cases.	Reduction in calibre of major vessels	Reduction in small vessel filling	Circulatory Slowing	Absence of venous filling	Response to sympathetic block
"White" Limbs	4	75	50	100	100	75
"blue" Limbs	5	60	80	100	100	0

5. In most cases sympathetic block produced an increase in collateral filling about the root of the limb, above the site of previous application of the tourniquet. This was a most useful objective check as to the adequacy of the block. Apart from this, none of the "blue" legs were in any way affected. Two-thirds of the "white" legs however showed obvious changes. This was always in the direction of more small vessel and collateral filling. The calibre of the major vessels was never affected, and the speed of the circulation scarcely altered.

Specimen aortograms demonstrating these changes are shown in Appendix 4.

In summary then, it appears that any serious degree of venous occlusion will adversely affect blood flow, the "blue" leg standing at the extreme end of the range. In all cases arterial filling is preserved albeit diminished, but the minute circulation is probably much more seriously affected. Although arterial calibre is not uncommonly diminished, this is susceptible of mechanical explanations, and the postulate of arterial spasm remains unproved.

The affect of sympathetic interruption is interesting. Apparently ifsufficient venous channels are patent and capable of supporting any increase in blood flow, then a lumbar block will produce its expected result. In the "blue" legs, however, the venous system might be expected to be already taxed to its limit, and in fact, the abolition of vasomotor tone

does not result in any apparent increase in the circulation.

This must be regarded as strong evidence in favour of the mechanical origin of the ischaemia, and particularly strong evidence against the conception of venospasm as a factor in its production.

SERIES 5.

In this last series of eight experiments, the response of blood flow to (a) denervation of the limb, and (b) a change in perfusion pressure was compared in normal and "blue" legs. The results obtained show a very similar pattern in all cases, and that there are highly significant differences to compare, can be seen by reference to the specimen graphs (Figures 19 and 20).

(a) The response to denervation is summarized in Table 15. In the normal leg the abolition of vasomotor tone regularly results in a marked increase in flow, averaging 100%. In marked contrast, in the "blue" leg, there was either no change (five cases) or an increase markedly less than that in the corresponding control limb (average 13%). This difference is highly significant ($p < 0.001$).

This would seem to be proof positive that in the ischaemic limbs which we have produced, reflex vasomotor spasm plays no part in the production of the ischaemia. If spasm were a factor, then denervation of the limbs could be expected to allow an increase in flow greater on the affected side.

TABLE 15.

Showing the effect of denervation on blood flow.

Experiment No.	Increase in blood flow in response to denervation.			
	Normal leg		Blue leg	
1	0.13 K. ml.	250%	0.06 K.ml.	50%
2	0. 15 k.ml.	50%	0 ml.	0%
3	1.8 k. ml.	150%	0 ml.	0%
4	0.7 k. ml.	66%	0.05 k. ml.	25%
5	0.4 k. ml.	35%	0.01 k. ml.	5%
6	1.5 k. ml.	160%	0 ml.	0%
7	0.6 k. ml.	9%	0 ml.	0%
8	1.0 k. ml.	30%	0.3 k. ml.	0%
Mean	0.79 k. ml.	94%	0.06 k. ml.	113%

The difference of the means is highly significant (p = less than 0.001).

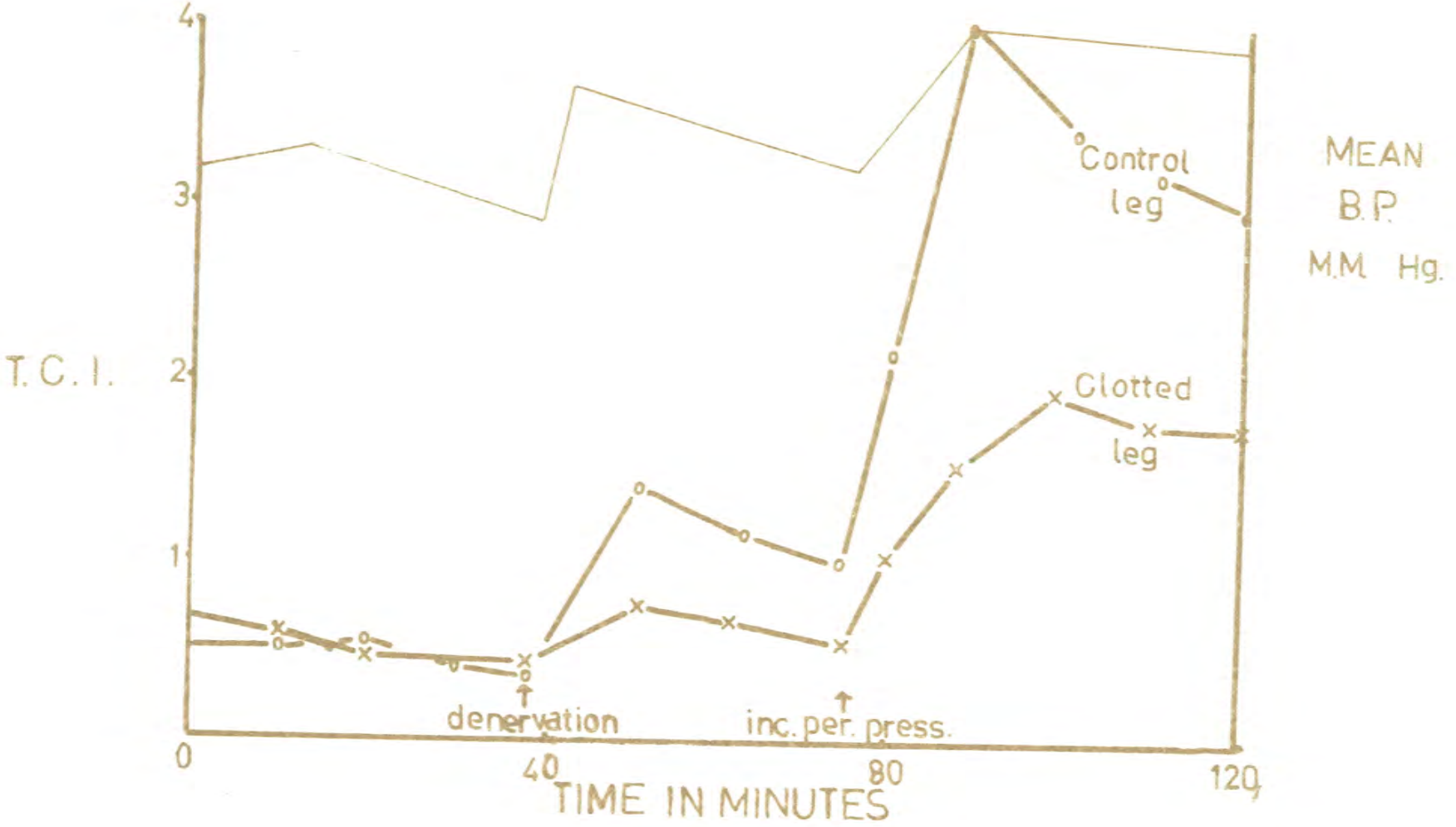


FIG.19 Showing the effect of denervation of the limbs on subsequent blood flow. [Series V. Exp. 8.]

The fact that a much lesser increase has been observed, not only rules out the possibility of spasm, but further suggests that some purely mechanical factor is preventing even the normal rise associated with the abolition of vasomotor tone. Presumably this factor is the absence of a sufficient cross-section of patent venous bed to support any increase in the circulation.

(b) The formal part of this investigation was concerned with observing the response of the denervated circulation to an increase in perfusion pressure of 30 mm Hg. In both the control and the "blue" limb this produced a significant increase in blood flow (Table 16). Reference to the graphs will show that this increase was markedly smaller and slower to develop in the "blue" limb. The difference between the mean rise in the control limb (181%) and in the "blue" Limb (71%) is significant ($p = 0.02. - 0.05$). It can also be seen, although this was not specifically elicited, that flow in the "blue"leg was abnormally sensitive to a falling perfusion pressure.

These results are of interest in two respects. Firstly, they indicate the grave local consequences of hypotension in phlegmasia caerulea dolens, and by contrast, the considerable improvement that can be effected in the local condition by restoring an adequate blood pressure.

Secondly, they allow us to speculate on the nature of

TABLE 16.

Showing the effect of an increase in perfusion pressure of 30 mm.Hg. on blood flow in the denervated limb.

Experiment No. Increase in blood flow.

	Normal Leg		Blue Leg	
1	0.07 k. ml.	180%	0.1 k. ml.	50%
2	1.1 k. ml.	90%	0.5 k. ml.	50%
3	2.6 k. ml.	110%	0.4 k. ml.	40%
4 *		Experiment unfinished		
5	2.7 k. ml.	400%	1.2 k. ml.	40%
6	1.7 k. ml.	110%	0.5 k. ml.	60%
7	1.2 k. ml.	100%	0.2 k. ml.	80%
8	2.9 k. ml.	280%	1.3 k. ml.	180%
Mean	1.8 k. ml.	181%	0.6 k. ml.	71%

The difference of the means is significant ($p = 0.02 - 0.05$).

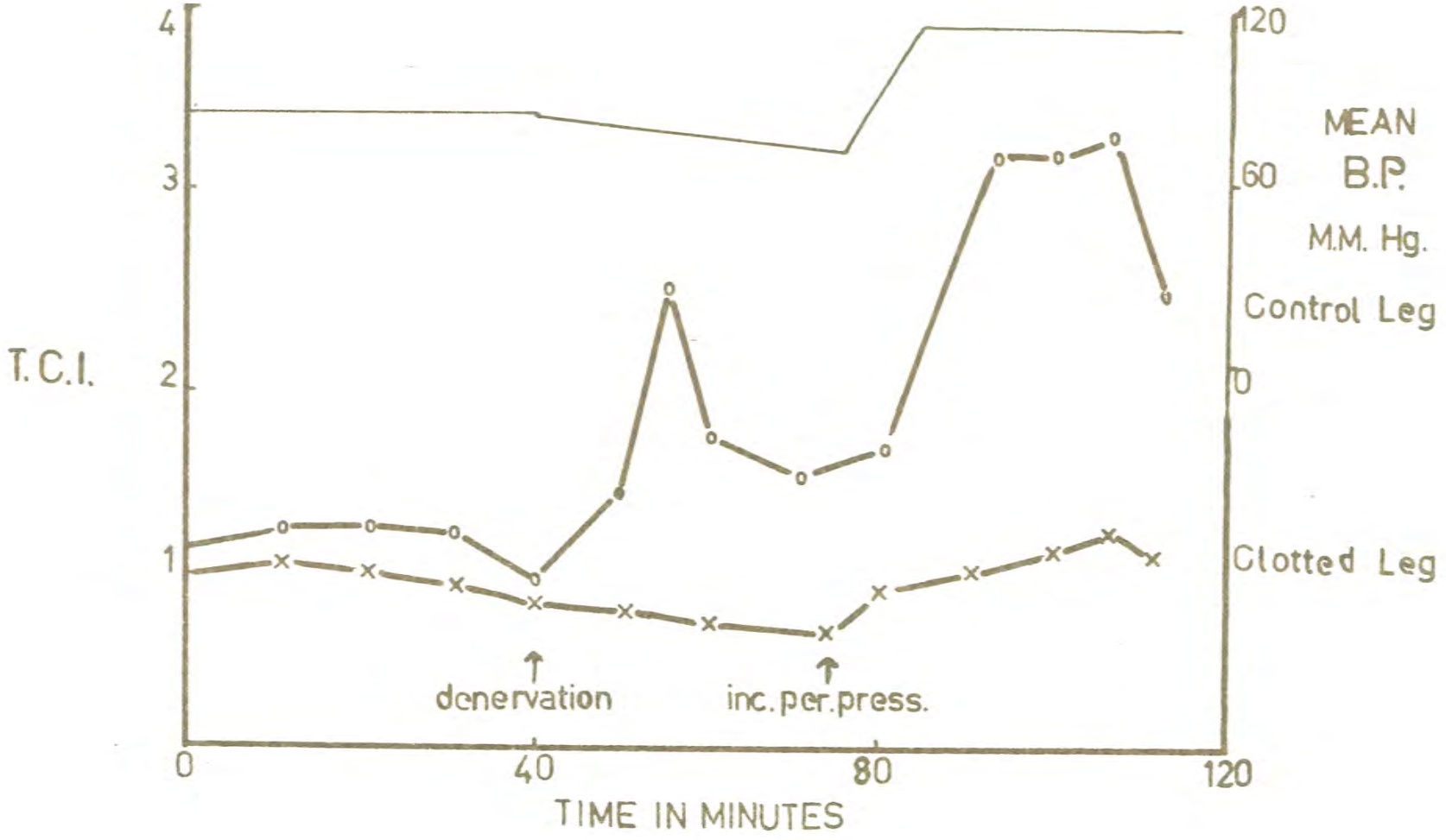


FIG 20 Showing the effect of denervation of the limbs on subsequent blood flow. [Series V. Exp. 6.]

the peripheral resistance in these limbs.

In the otherwise normal, but denervated limb, an increase in perfusion pressure has its expected result. The peripheral resistance is flaccid, the vessels passively dilate, and a considerable increase in flow is achieved.

In the "blue" limb by marked contrast, the increase in flow is much less. This can only be interpreted as indicating that the peripheral resistance is no longer responsive to reflex control, but is mechanically fixed. It seems reasonable to assume that it no longer resides in the arterioles, but is now sited in the venous side of the circulation, and is dependent on the mechanical blockage of these channels by clot.

SUMMARY.

1. Ligature of the common femoral vein does not significantly affect arterial input.

2. Massive venous occlusion may produce ischaemia.

3. This degree of occlusion can be produced by propagating a clotting process retrogradely down the femoral vein.

4. In such a limb, reflex spasm of either arteries or veins plays no part in determining the ischaemia.

5. Stimulation of major vessels does not give rise to reflex effects.

6. Stimulation of perivascular tissues, and presumably

also of smaller vessels does give rise to reflex vasomotor effects. Stimulation of the intensity which might be expected to occur due to thrombophlebitis, is more likely to produce vasodilation than vasoconstriction.

7. Local traumatic spasm of a major artery does not necessarily reduce flow to a significant or serious degree.

CHAPTER 6.

DISCUSSION.

The relevant literature contains four separate explanations which have been offered from time to time, to account for the ischaemia associated with venous thrombosis in cases of phlegmasia caerulea dolens.

They are :

(i) the mechanical theory

(ii) the theory of reflex small artery spasm

(iii) the theory of major artery spasm

(iv) the theory of venospasm

Various combinations of these suggestions have been advanced by different authors, but the consensus of opinion is that both mechanical factors and reflex spasm play a significant part.

We are now in a position to review these theories in the light of the clinical and experimental findings which we have collected.

1. The mechanical theory.

This explanation is the first to appear in the literature, having been mentioned by Hunter (1859) and clearly restated by Bergendal (1931). It envisages the venous circulation so embarrassed by massive thrombosis that it is unable to support a flow sufficient to maintain the viability of the tissues in its drainage area. Now it is clear that if

blood cannot leave a given circulation no new blood can enter it. The blood continues to pulse at a normal pressure in the arterial system, but capillary circulation is restricted to replacing that volume of blood per unit time, to which the venous system can still give exit, plus the volume of fluid which leaves the capillaries to give rise to oedema. In addition, this extravagant oedema which develops very rapidly, no doubt further disturbs the minute circulation by compression of the small vessels.

This theory has the great virtue of simplicity. Furthermore, the whole clinical picture, dominated by oedema and a violaceous discolouration suggests a venous circulatory failure, and in no way, an arterial one. Indeed the peculiar skin discolouration observed in this condition has been aptly likened to that produced by a venous tourniquet, with which, of course, it is exactly comparable.

The autopsy findings of a venous circulation, which as far as the eye and the microscope can appreciate, is totally occluded, offer strong evidence in support of this view. Equally, convincing are those reports in which, at amputation free arterial and capillary bleeding was seen. This can only be interpreted as evidence that the input circulation free of the necessity of returning its blood via the veins, was operating in a normal unobstructed manner.

Finally, from the therapeutic viewpoint, the good

results claimed from conservative measures (Veal et al., 1949) and the occasional successes from thrombectomy (Ossius, 1951) offer supporting evidence in favour of this mechanical conception.

The cases reported by Pallin (1929) and Martin (1953) in which sudden and dramatic local improvement occurred synchronously with the onset of a pulmonary embolism, must be considered relevant in this regard. The most reasonable interpretation of these reports is surely that a mechanical disobliteration of sufficient venous channels had occurred, to allow the input circulation to resume a level adequate to prevent clinical ischaemia.

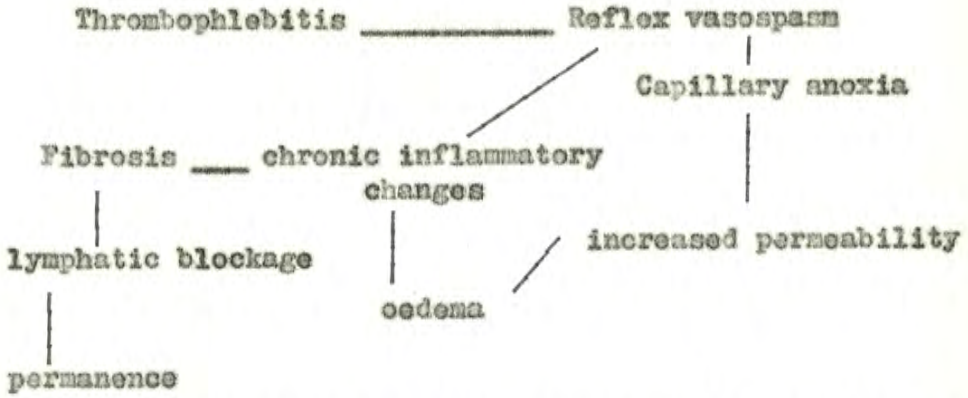
Only two attempts have been made to produce ischaemia experimentally, by interference with the venous circulation. Fontaine and Souza Pereira (1937) produced gangrene in the dog's hind limb by severing and resuturing all the tissues of the thigh, sparing only the femoral artery and the femoral and sciatic nerves. In this investigation we have pfoduced proven ischaemia by propagating thrombus throughout the venous system. Thus these two attempts to produce ischaemia by mechanical venous occlusion have been successful.

There is, therefore, a considerable body of evidence in favour of this view. There is no direct evidence against it, except that which has been adduced in favour of the other theories and this will be discussed in connection with them.

2. The theory of reflex spasm.

The view that small artery spasm is responsible in a significant degree, for the ischaemia of phlegmasia caerulea dolens is very widely held. In its simplest form this idea envisages a thrombophlebitic process stimulating afferent nerve endings either in the vessel wall, or in the extravenous tissues, and giving rise thereby to a reflex increase in vasomotor tone.

This conception of the role of reflex spasm in thrombophlebitis was first postulated to explain the long term oedema of the post-phlebitic syndrome. A number of French surgeons in the 1930's became interested in this subject, and in 1931 Leriche and Jung reported that they were unable to produce a permanent oedema in the dog by multiple vein ligations. They postulated, therefore, the operation of a cycle of events.



This concept gained clinical support (Leriche and Kunlin, 1934) from reported good results in thrombophlebitis, from treatment with sympathetic blocks. Finally, Fontaine and

Souza Pereira (1937) confirmed and extended the experimental basis when they were unable to produce a lasting oedema, in dogs, by multiple venous ligations or chemical obliterations, even when combined with lymphatic ligation.

There is much that is still obscure about the physiopathology of chronic oedema and gravitational ulceration, but in the light of modern knowledge we can see that these experimental results are easily susceptible of a simple mechanical explanation.

In retrospect these authors failed to appreciate the paradox that it is not the mild transient venous hypertension associated with vein occlusion that is responsible for post-phlebitic oedema but rather the much more severe permanent venous hypertension due to recanalization of a venous system lacking competent values. Furthermore, the effect of man's erect posture is so great in this connection, that animal experiments are of limited value.

However at the time the views of Leriche gained almost universal acceptance at least in France and America. It will be recalled that at this time there was an upsurge of interest in the condition of phlegmasia caerulea dolens in these two countries, and the concept of spasm as an integral part of the physiopathology of thrombophlebitis was immediately seized upon to explain the ischaemia seen in phlegmasia caerulea dolens.

Two clinical findings were advanced to support these contentions. Firstly, the operative reports of a femoral artery reduced in diameter (Wertheimer, 1935; Gregoire, 1938; Audier and Haimovici, 1939; Sachenreiter, 1940; DeBakey, 1946; Ossius, 1950) were misinterpreted by the earlier authors as evidence of reflex spasm. The brilliant work reported by Kinmonth, Simeone and Perlow (1949) and again by Kinmonth (1952) has very clearly demonstrated that major arteries are not affected by sympathetic stimulation. What these operators observed was certainly a local myogenic spasm, coupled no doubt with the effects of an oedematous, exudate-filled arterial wall. These findings cannot therefore be adduced as evidence of reflex spasm.

Secondly, the results of antivasospastic treatment, particularly lumbar sympathetic block, were advanced as evidence in favour of this theory by many authors enumerated in Chapter 2. On analysis, these good results appear to consist in nothing more than the transient relief of pain, presumably by a simultaneous effect of the anaesthetic on the lumbar somatic nerves. Despite the fact that lumbar infiltration was occasionally repeated many times (Leriche and Geisendorf, 1939, report nineteen daily blocks on one patient) the major amputation rate in these patients was 60% compared with 38% over all cases in the same period. A critical analysis, therefore, fails to confirm antivasospastic

measures as a useful line of treatment, or as evidence for the participation of reflex spasm in the physiopathology of the condition.

As evidence for reflex spasm then we are left with the experimental results of DeBakey et al., (1939) showing a reduction of pulse volume associated with the introduction of salicylate into the lumen of an isolated segment of femoral vein. We consider that our results clearly demonstrate that this was a direct effect of spillage of the irritant affecting the femoral artery locally in the groin. Further we have demonstrated that the effect of such spillage on the pulse volume is not in any way a reflection of its effect on blood flow, and indeed we suggest that if a mild chemical stimulation has any reflex effect on blood flow, it is probably by way of an increase rather than a decrease.

Now it is our contention that, within the limits imposed by an experimental investigation, the pathology which we have provoked by the injection of thrombin into the femoral vein parallels quite closely the path logy of spontaneously occurring phlegmasia caerulea dolens. Two differences are however immediately apparent. The first is that the occluding agent in our experiments is pure clot, caused by a physico-chemical reaction between the excess thrombin added and the fibrinogen of the blood plasma. It therefore differs in constitution from a true thrombus. It is, however, apparent

from the histological studies made in the spontaneous disease that the initiating thrombus is of comparatively minor extent, and that it is the widespread propagation of clotting from this thrombus that determines the disease picture (Hueter, 1859; Bargen et al., 1936; Ebel et al., 1952). In this respect then the difference is not great.

If indeed there is any real distinction between "thrombophlebitis" and "Phlebothrombosis", other than a difference in the stage of organization, then herein may lie a second difference. There is good evidence, however, that thrombophlebitis, so-called, is not a necessary basis for the production of spontaneous phlegmasia caerulea, for the condition has been reported in the absence of any inflammatory reaction (Hueter, 1859, Bargen et al., 1936, Ebel et al., 1952). Furthermore, the dramatic onset, in the light of what we know about the histopathology, suggests that the ischaemia is associated, not with the initiating inflamed thrombus but with the sudden widespread propagation of clot. If this parallelism is accepted, and it would seem reasonable to do so, at very least in those cases without phlebitis, then our conclusive demonstration in Series 4 and 5 of the absence of significant reflex spasm becomes very meaningful.

The clinical investigation of Moser and his colleagues (1954) is also relevant here. These workers, using skin

temperature and oscillometry as indices, measured the effect of hexamethonium, in one case. They report a small rise in temperature and oscillometric recordings consequent on the exhibition of the drug, exactly equal in the "blue" and the normal limb. This must be taken as evidence that there was no abnormal degree of vasomotor tone operating in this spontaneous "blue" limb. The fact that the rise was equal is slightly at variance with our results reported as Series 5, and suggests perhaps, that the degree of venous occlusion was less in this spontaneous case of phlegmasia caerulea dolens, than in our experimental limbs.

Before leaving this question of generalized arterial spasm, we must notice in passing that recently Gaskell and Burton (1953) advanced the theory that rising venous pressure in itself provoked arteriolar spasm. They came to this conclusion after observing an "after drop" in the plethysmographic records from dependent fingers, and Burton later attempted to confirm his opinion by a series of experiments perfusing isolated rabbits ears (Burton and Rosenberg, 1956). This "after drop" has since been conclusively shown to be a mechanical consequence of the emptying of veins beneath the collecting cuff, and the results obtained by Burton and Rosenberg are unsatisfactory and not generally accepted (Greenfield, 1960).

Summarizing, therefore, it would seem that the theory

of reflex spasm was postulated on incorrect premises, and obtains no real support from the clinical picture. There is no doubt that ischaemia can be produced by pure venous occlusion under circumstances in which it is possible to demonstrate conclusively that reflex spasm does not appreciably contribute. Finally, stimulation of afferent nerve ending in the perivenous tissues and presumably in the smaller vessels, of a degree comparable with that which might result from "thrombophlebitis" does not give rise to vasoconstrictor reflexes. There is, therefore, no reason to suppose that reflex spasm contributes to the clinical picture of phlegmasia caerulea dolens.

3. The theory of local large artery spasm.

There seems to be no doubt, on the basis of the reports quoted previously, that a diminution in calibre of the femoral artery is a common but not invariable concomitant of phlegmasia caerulea dolens. The work of Kinmonth et al., (1949) makes it clear that this must be a local, probably myogenic effect and does not in any way represent reflex spasm. The same authors claim that such a spasm, providing it remains localized, does not seriously prejudice distal blood flow. The observations of Whelan (1960) previously mentioned, support this contention, as do our own results. It is, therefore, unlikely that this diminution in the calibre of the femoral artery plays any

significant part in the production of the ischaemia, or at least does so only very exceptionally.

In any case, whether it does or does not, it remains a local phenomenon and is quite unaffected by any sympatheticolytic measures including periarterial stripping (Kinmonth, 1952). For this reason, its importance as a practical problem is not great.

4. Venospasm.

This has been advanced as a significant contributing factor to the ischaemia of phlegmasia caerulea dolens by only one group of authors (Manheimer et al., 1954). There is no doubt that the venous system is just as responsive to vasomotor impulses as is the arterial system, and that venous spasm can occur. There is, however, no real evidence that it does occur in this condition, and the evidence already adduced against the presence of reflex arterial spasm applies equally if referred to reflex venous spasm.

It is an everyday clinical observation that veins dilate markedly in response to raised venous pressure. It seem reasonable to expect that any small channels which escape occlusion will, in the face of the very high venous pressure which obtains in the blue leg, be maximally dilated rather than reduced in calibre.

On the available evidence, both clinical and experimental, therefore, it seems most reasonable to ascribe

the ischaemia seen in phlegmasia caerulea dolens to the mechanical effects of massive venous occlusion. Those theories involving reflex spasm of the vasculature do not stand a critical analysis of the reasons for their introduction, and are not in accord with the evidence furnished by this investigation.

CHAPTER 7.

THERAPEUTIC IMPLICATIONS.

At the present time, it remains general though not universal opinion, that the mainstay in the treatment of phlegmasia caerulea dolens, is some form of sympatheticolysis. The results of this investigation would seem to have deprived this therapy of any rational basis; and indeed a disinterested analysis of the results obtained fails to confirm its value.

In addition to an absence of any positive value, this type of therapy suffers from the theoretical objection that the abolition of normal vasomotor tone in a "blue" limb will subject the capillaries to a further rise in what is already a dangerously high internal pressure. This in turn will facilitate oedema formation and capillary rupture.

It seems worthwhile to examine anew the question of treatment, without preconceived ideas, utilizing what is known of the physiopathology, and of the results of reported cases.

Fundamentally, treatment has four aims :

(i) to promote venous return via any channel still patent; for any increase in arterial input must be proportional to, and a consequence of an increase in venous output.

(ii) to minimize the formation of oedema fluid, and so prevent the strangulation of what little circulation remains.

(iii) if possible to remove clot.

(iv) to prevent the extension of the thrombotic process and to prevent embolism.

For achieving the first two of these objectives, there seems little doubt that the conservative regime outlined by Veal et al., (1949) offers the most logical available method. It has been used with success in a large series by Veal and his colleagues, and favourably reported in smaller series by many other authors (Turner, 1952; Moser, 1954; Catchpole, 1957).

The method consists in high elevation of the affected limb, and active exercise by way of alternate dorsiflexion and plantarflexion of the foot. The patient should be persuaded to perform this exercise as often, and for as long periods as he can tolerate, and preferably almost continuously. Heavy analgesia will be necessary before the patient will be willing to move at all, and regular injections of morphia will best provide this.

The rationale of the method is that elevation and the use of the calf-pump, will increase venous return if any channels remain open, and even a small increase in blood flow may save a limb from gangrene. In the normal course of events nature makes its own provisions by developing collateral flow, and the danger period does not as a rule extend beyond twenty four or forty eight hours. If the viability of the limb can be tided over this period recovery will occur without gangrene.

Active exercise of a limb, the seat of recent widespread clotting, theoretically increases the danger of embolism, but this has not been a feature of the reported cases. It seems reasonable to accept this small theoretical risk in view of the obvious benefits obtained from the therapy.

The results of thrombectomy have been favourably reported by several authors (Ossius, 1950, Leriche et al., 1939, DeBakey et al., 1946). On the same basis that even a small increase in the number of available venous channels may be sufficient to avert gangrene, this therapy is logical. It has not yet received a reasonable clinical trial and in the only series of cases reporting its use (Ossius, 1950), the results seem very favourable.

The spontaneous recovery associated with embolism reported by Pallin (1929) and Martin (1953) might be interpreted as further evidence that thrombectomy may be a useful adjunct to conservative treatment. It has up to date always been the practice, after performing thrombectomy, to ligate the vein above and below the venotomy opening. This, of course, is for the twofold reason, firstly to prevent embolism, and secondly, because subsequent thrombosis of the damaged vein is almost inevitable. It is striking, however, that even in the presence of massive venous occlusion, free bleeding can usually be provoked both

distally and proximally after as much clot as possible has been extracted. As we have remarked earlier, if an extra venous channel can be persuaded to remain patent for twenty-four hours, this may be sufficient to avert gangrene. It seems to the author that it would be reasonable in these cases to accept the added risk of embolism and to close the vein by lateral suture. The concomitant administration of human fibrinolysin might help to maintain its lumen over the critical period. Even if thrombectomy is decided upon, it should not replace, but merely precede, the conservative regime.

The question of anticoagulation poses a difficult problem. In these limbs with a high capillary pressure, and usually evidence of widespread capillary rupture in the way of purpura, and haemorrhagic blebs, there is an obvious theoretical danger in rendering the blood incoagulable. Catchpole (1960) has reported a case in which following heparinization, a widespread bloody infiltration of the tissues occurred, itself contributing to the eventual necrosis. Furthermore, there have been several reports in which progression of the thrombotic process has occurred while the patient was apparently adequately anticoagulated.

On the other hand, there can be little doubt that anticoagulation is indicated on general grounds. A

reasonable compromise is to withhold heparin during the critical early days, and commence it as soon as the vitality of the limb is assured by the disappearance of the blue discolouration.

No special reference has been made to resuscitative or supportive measures. They may of course be of life-saving importance, and I have referred elsewhere to their importance in the preservation of the limb.

Finally, the additive experience of many case reports, is that gangrene, if it occurs, is likely to be of minor extent compared with the widespread nature of the initial pathology, and to be relatively superficial, affecting the skin more than deeper structures. This suggests that our attitude to venous gangrene should be conservative in the extreme; waiting for demarkation and commencing separation before resorting to surgical debridement: and that we should think in terms of debridement and resurfacing, rather than of amputation.

As this condition becomes more widely recognized larger series will undoubtedly be seen, particularly in units with an interest in vascular surgery. When this occurs it is hoped that adequate clinical trials of the various features of treatment will be carried out. In the meantime we must shape our treatment to what seems

most reasonable in the light of the underlying physiopathology of the condition, and the regimen detailed above represents an attempt to do this, in the light of information gathered during this investigation.

ACKNOWLEDGEMENTS.

I wish firstly to acknowledge my debt to Professor R.P. Jepson for suggesting the initial direction of this research, and for the considerable help and encouragement he has given me during the course of the work.

Professor R.J. Whelan was kindness itself and proved of very great assistance on the occasions when I sought his help.

Mr. L.J. Opit and Mr. B.N. Catchpole were ever ready and very patient sources of ideas and advice.

The very high technical standard of the aortograms is due entirely to the skill and adaptability of Mr. G. Tidswell and Mr. G.H. Haines, of the Radiology Department, Queen Elizabeth Hospital, Woodville. I am very greatly in their debt.

Mr. D. Darian Smith very kindly undertook a great deal of photographic copying work. The author however is solely responsible for any technical shortcomings.

Mr. G. Lehmann and my wife shared the labour of translating German and French articles, and for this help I am most grateful.

My most constant co-workers, to whom I am very greatly obligated as much for their patience and untiring application as for their skilful technical assistance, were Miss K. Rumbold and Miss B. Hogg.

Finally, I wish to record my appreciation of the invaluable secretarial help which I received from Miss K. Brock and Miss E. Aird.

REFERENCES.

AUDIER, M. and HAIMOVICI, H. (1939), Press med., 2, 1403.

BARGEN, J.A. and BARKER, M.W. (1936), Arch.intern.Med., 58, 17.

BARNES, J.M. and TRUETTA, J. (1942), Brit. J. Surg., 30, 74.

BERGENDAL, S. (1931), Acta chir.scand., 68, 529.

BERGERET, A., GUILLAUME, A.C. and DELARUE, J. (1932),
Ann.d'Anat.Path., 9, 536.

BURCH, G., DeBAKEY, M. and SODEMAN, W. (1939),
Proc. Soc.exp. Biol., N.Y., 42,858.

BURTON, A.C. (1934), J.Nutrition, 7, 497.

BURTON, A.C. (1948) in "Methods in Medical Research"
(Potter, V.R.(Editor) Chicago : Year Book
Publishers Inc.), 1, 146.

BURTON, A.C. and ROSENBERG, E. (1956), Amer.J.Physiol.,185,465.

CATCHPOLE, B.N. (1957), Lancet, 1, 343.

CATCHPOLE, B.N. (1960), Personal communication.

CATCHPOLE, B.N. and JEPSON, R.P. (1955), Clin.Sci., 14, 109.

DARIAN SMITH, I. (1954), Thesis for degree M.D. presented to
the University of Adelaide.

DeBAKEY, M., BURCH, G.E. and OSCHNER, A. (1939),
Proc.Soc.exp.Biol., N.Y., 41, 585.

DeBAKEY, M. AND OSCHNER, A. (1946), Surg., 26, 16.

DECOULX, P. and BASTIEN, P. (1939), Ann.d'Anat.Path., 16, 353.
(quoted by Haimovici, 1950).

EBEL, A., KAUFMANN, M. and EHRENREICH, T. (1952),
Arch.intern.Med., 90, 402.

EDHOLM, D.G., HOWARTH, S. and SHARPEY SCHAFER, E.P. (1951),
Clin.Sci., 10, 361.

EDWARDS, E.A. (1937), Amer.Heart J., 14, 428.

FAVRE, M., ROCHET, PRIEH, and GODINOT, C. (1940),
Lyon Chir., 36, 723.
(quoted by Haimovici, 1950).

FONTAINE, R. ISRAEL, L, and DeSOUZA-PEREIRA, A. (1936),
J.de chir., 47, 928.
(quoted by Haimovici, 1950).

FONTAINE, R. and DeSOUZA-PEREIRA, A. (1937), Rev. de Chir.,
Paris, 75, 161.

FONTAINE, R. and FORSTER, E. (1946), Lyon chir., 41, 173.
(quoted by Haimovici, 1950).

FREEMAN, L.W., SHUMACKER, H.B., Jr., and RADIGAN, L.R., (1950),
Surgery, 28, 274.

GAILLARD, L. (1894), Bull.et mem. Soc.med.d.hop.de Paris,11,315.
(quoted by Haimovici, 1950).

GASKELL, P. and BURTON, A.C., (1953), Circulation Res., 1, 27.

GREENFIELD, A.D.M. (1960), in "Methods in Medical Research
(Bruner, H.D. Editor : Chicago :
Year Book Publishers Inc.) 8,293.

GREGOIRE, R. (1938), Presse med., 2, 1313.

GUTTERMUTH, W. (1942), Deutsche med.Wchnschr., 68, 486.
(quoted by Haimovici, 1950).

GUTZEIT, R. (1936), Munchen med. Wchnschr, 83, 1628.

HAIMOVICI, H. and SUFFNESS, G. (1948), Amer.J.Med.Sci.,215,278.

HAIMOVICI, H. (1950), Circulation, 1, 225.

HALLIGAN, E.J., COSTELLO, J.L. and LEWIS, T.F. (1953),
Ann.Surg., 137, 543.

HATFIELD, H.S. (1950), J.Physiol., 111, 10P.

HERSHEY, C.O. and SNYDER, R.E. (1953), Surgery, 34, 297.

HUETER, (1859), Virchows Arch., 17, 482.

JANES, E.C. and HOPMANS, C.C. (1953), Canad.med.Ass.J.,68,156.

KINMONTH, J.B., SIMEONE, F.A. and PERLOW, V. (1949),
Surgery, 26, 452.

KINMONTH, J.B. (1952), Brit.med.J., 1, 59.

LERICHE, R. and JUNG, A.V. (1931), J.de Chir., 37, 481.
(quoted by Haimovici, 1950).

LERICHE, R. and KUNLIN, J. (1934), Presse med., 2, 1481.

LERICHE, R. and GEISENDORF, W. (1939), Presse med., 2, 1301.

LOANE, R.A. (1959), J.appl.Physiol., 14, 411.

LYNN, R.B. and SIMEONE, F.A. (1952), Amer.J.Physiol., 169,471.

MANHEIMER, L.H. and LEVIN, L.M. (1954), Angiology, 5, 472.

MARIN, H.M. and STEPHANINI, M. (1960), Surg.Gynec.Obstet.,
110, 263.

MARTIN, P. (1953), Brit.med.J., ii, 1351.

MEEK, J.R. and MAURER, J.J. (1959), Amer.J.Surg., 97, 104.

MILES, R.M. (1950), Surgery, 30, 718.

MILLS, E.S. and BENNETTS, R.C. (1955), Canad.Med.Ass.J., 72, 917.

MORALES-APARICIO, L. (1944), Rev.espan.de cir.traumat.y.ortop., 1, 218.
(quoted by Haimovici, 1950).

MOORE, R.M. and MOORE, R.E. (1933), Amer.J.Physiol., 104, 259.

MOORE, R.M. and SINGLETON, A.O. (1933), Amer.J.Physiol., 104, 267.

MOSER, M., BABIN, S.M., COTTS, G.W. and PRANDONI, A.C. (1954), Ann.intern.Med., 40, 361.

MYHRE, J. and YVISAKER, R.S. (1954), Arch.Surg., Chicago, 69, 732.

NUNEZ, A.N., MILANES, B., De la VEGA, L.M., VAZQUES, G. and INIGO, J.R. (1952), Angiology, 3, 385.

OAKS, W.W. and HAWTHORNE, H.R. (1948), Ann.Surg., 127, 1247.

OSCHNER, A. and DeBAKEY, M. (1940), J.Amer.med.Ass., 114, 117.

OSSIUS, E.A. (1951), Arch.Surg., Chicago, 65, 19.

PALLIN, G. (1929), Acta Chir Scand., 65, 558.

PRINGLE, J.H. (1938), Glasgow med.J., 129, 126.

PONS, H. (1905), Bull.et mem.Soc.anat.de Paris, 80, 645.
(quoted by Haimovici, 1950).

READ, R.C., KUIDA, H. and JOHNSON, J.A. (1958), Amer.J.Physiol., 192, 609.

REYT. (1897), Thesis in Medicine, Paris.
(Quoted by Haimovici, 1950).

SACHENREITER, G. (1940), Presse med., 2, 575.

SALMON, M., AUDIER, M., JOUVE, A. and HAIMOVICI, H. (1938), Bull et.mem.Soc.de chir de Marseille,12,1. (quoted by Haimovici, 1950).

SWARTLEY, W.B., WEEDER, S.D. and McLAUGHLIN, E.F. (1940), Ann.Surg., 116, 184.

TILLEY, J.H. (1938), Amer.J.Obstet.Gynec., 36, 157.

TREMOLIERE and VERAN (1929), Bull.Med. Paris, 43, 1101.

TURNER, D.P.B. (1952), Brit.med.J., ii, 1183.

VEAL, J.R., DUGGAN, T.J., JAMISON, W.L. and BAUERSFELD, R.S. (1949), Surgery, 29, 355.

WERTHEIMER, P. and FRIEH, P. (1935), Presse med., 1, 1004.

WHELAN, R.J. (1960), Personal communication.

WOOLLHARD, H.H. (1926), Heart, 13, 319.

WRIGHT, S. (1955), "Applied Physiology" (Oxford University Press, Lond.), 9th Ed., p.312.

YOUNG, R.L. and DERBYSHIRE, R.C. (1950), Ann.Surg., 131, 252.

NOTE 1.

For the early historical information I am indebted to the following works :

METTLER, C.C. "History of Medicine" (Philadelphia : The Blackiston Co., 1947).

GARRISON, F.H. "An Introduction to the History of Medicine" (Philadelphia : W.B. Saunders Co., 1929).

BARNETT, A.J. and FRASER, J.R.E. "Peripheral Vascular Disease" (Melbourne University Press, 1955 - Stawell Memorial Prize Essay, 1952).

AUDIER, M. and HAIMOVICI, H. (1939), Presse med., 2, 1403.

NOTE 2.

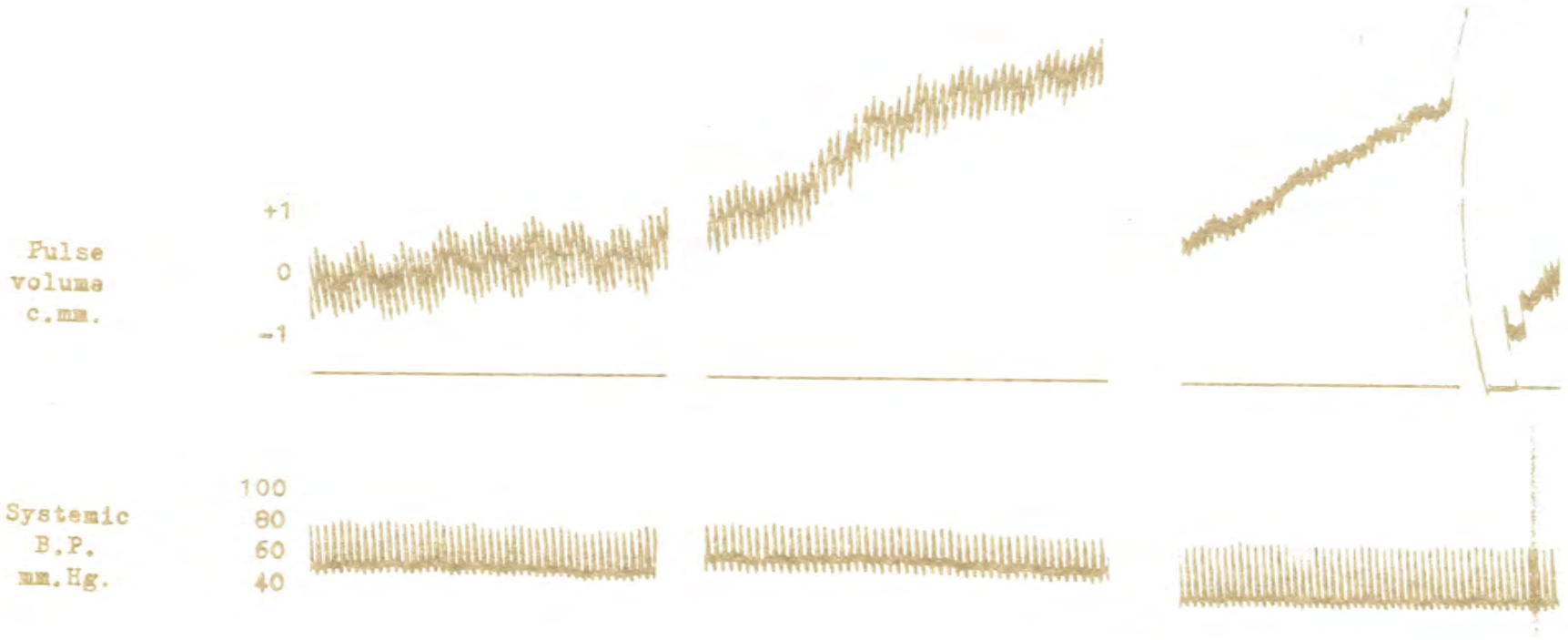
A proportion of the recent literature is not available in Australia.

Where indicated I am indebted for my information to the review of Haimovici (1950).

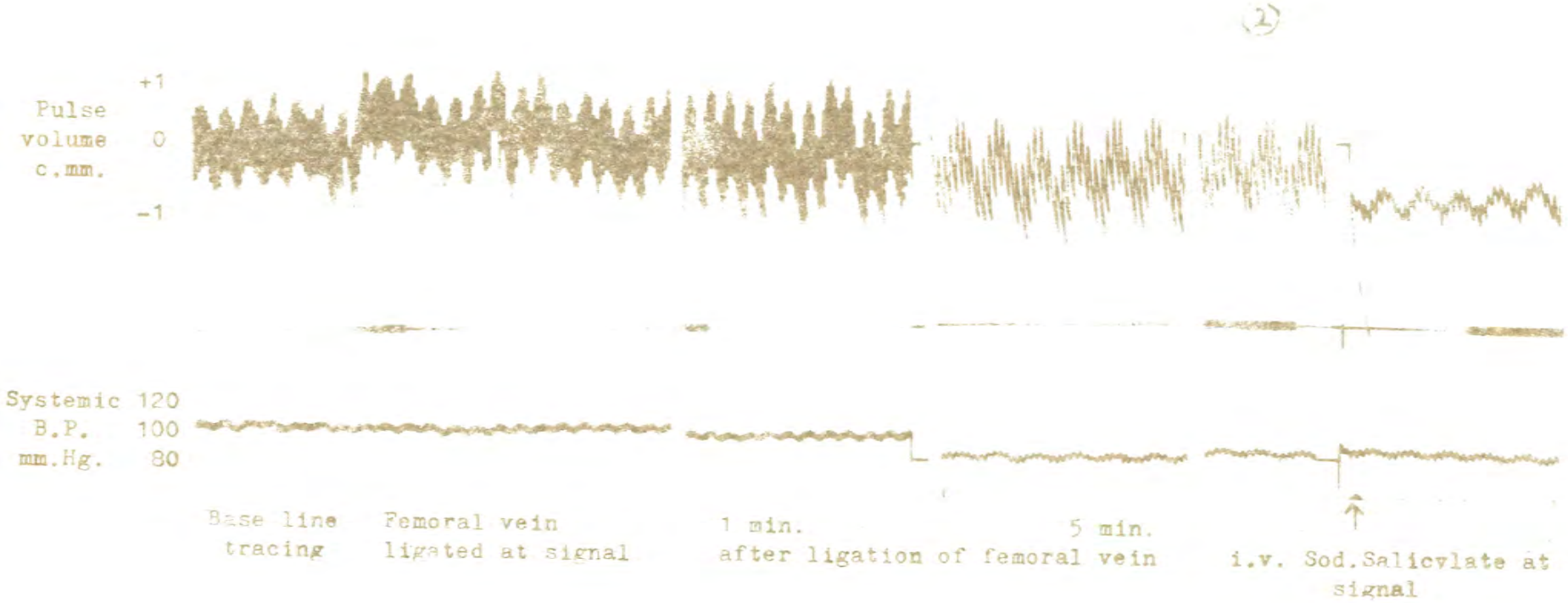
APPENDIX 1.

Representative tracings of pulse volume and systemic blood pressure taken from the experiments constituting Series 1.

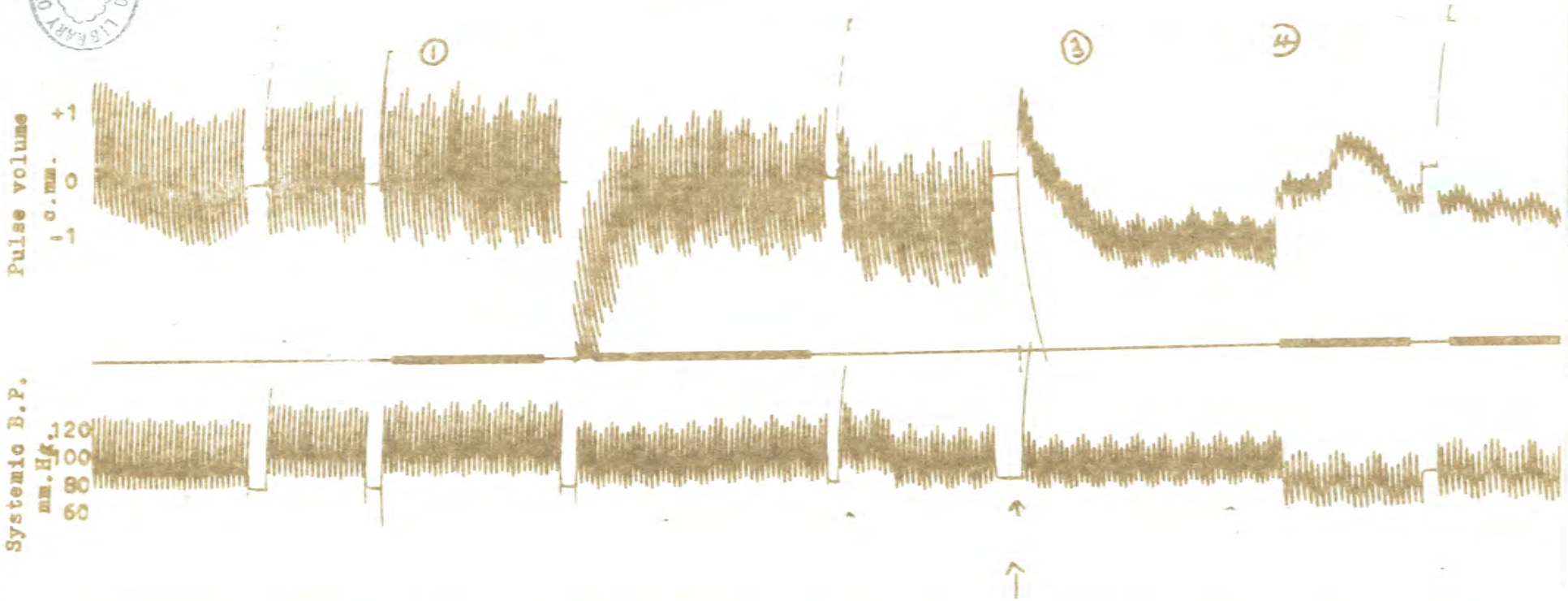
EXPERIMENT 1



EXPERIMENT 3



EXPERIMENT 4



Base line tracing

1 min. after ligation of superficial femoral vein

5 min.

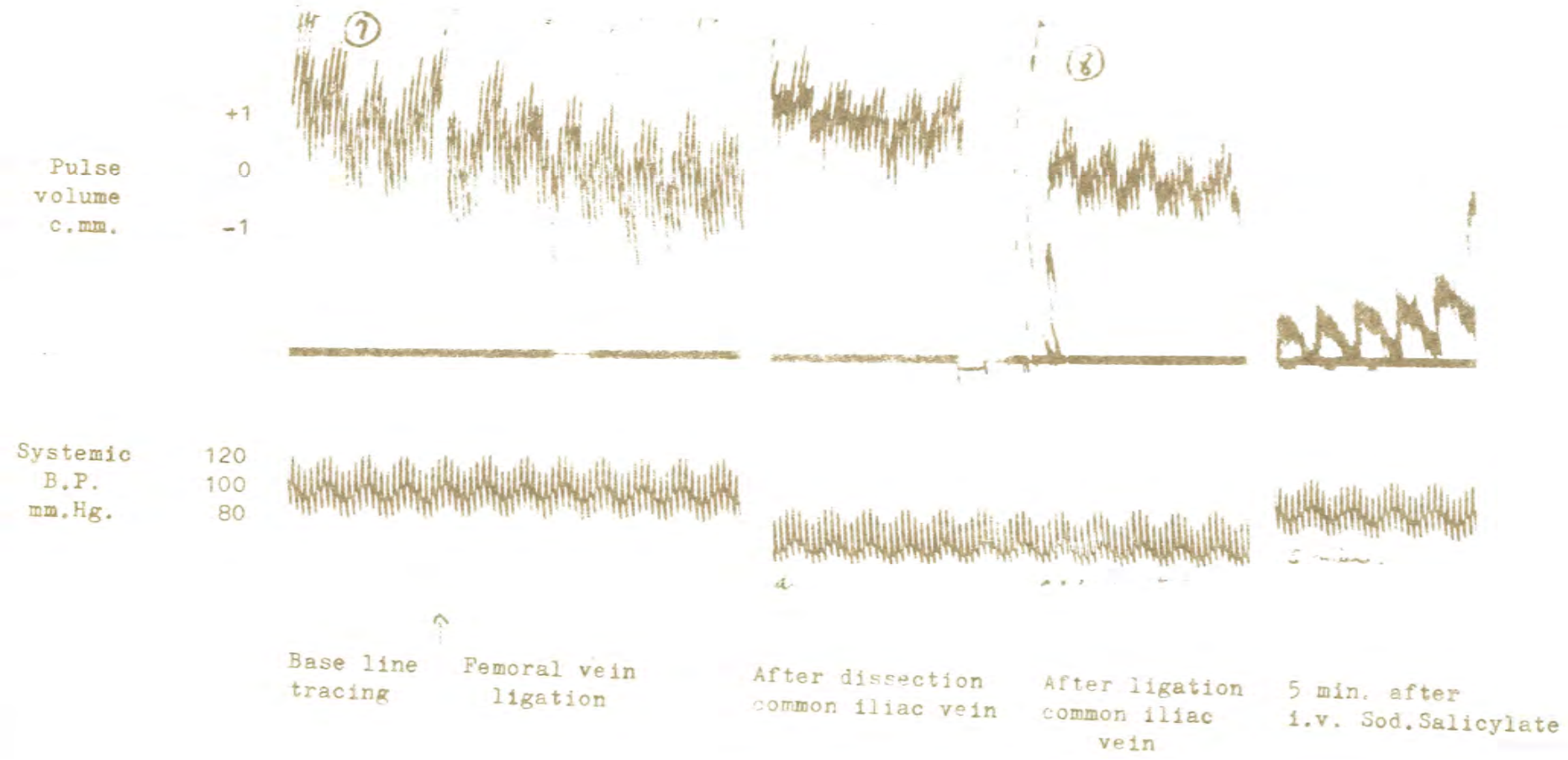
Ligation common femoral vein

5 min. after ligation

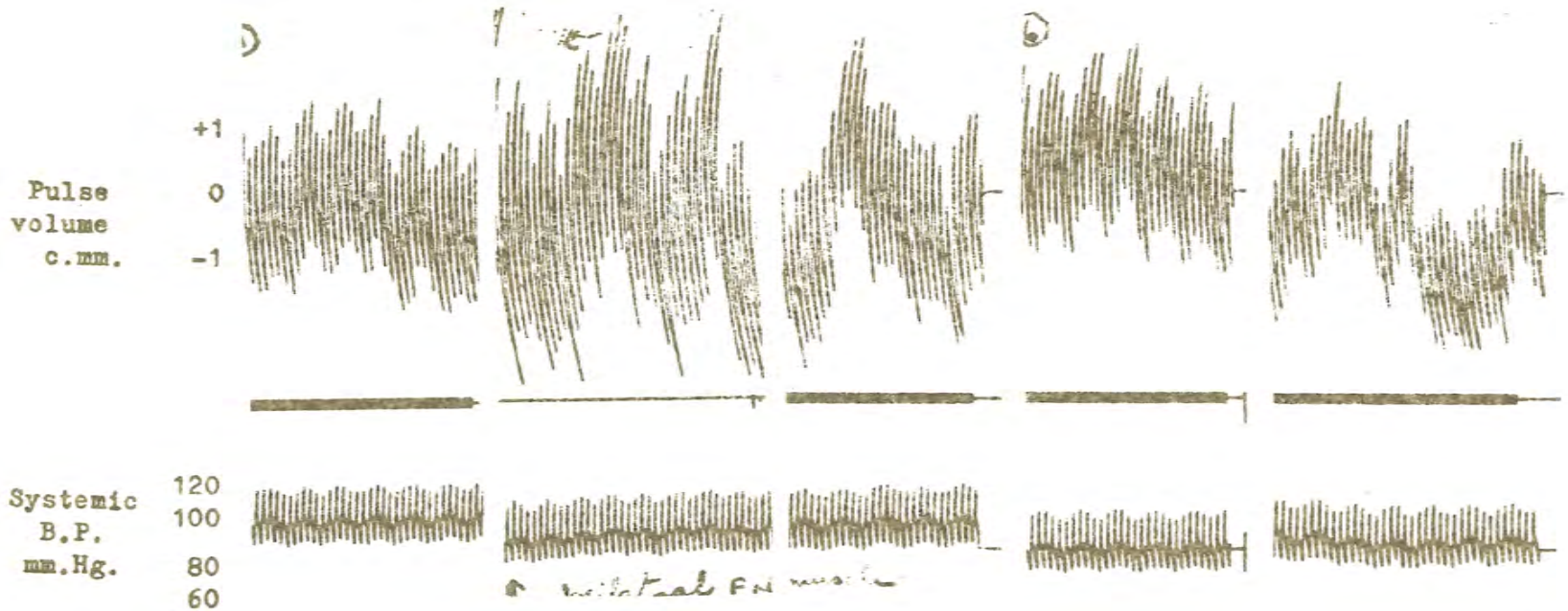
Further dissection of the vessels

5 min. after i.v. Sod. Salicylate

EXPERIMENT 5

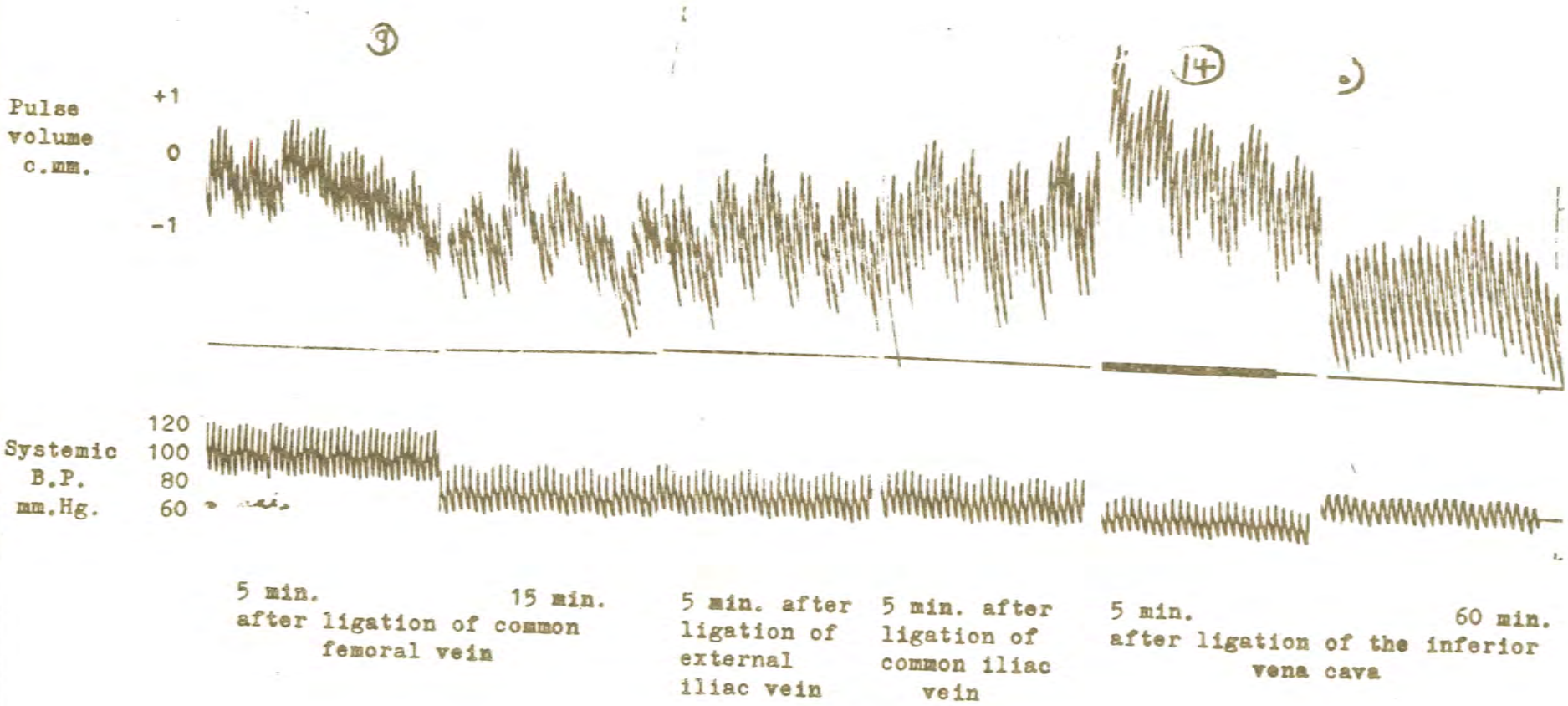


EXPERIMENT 6



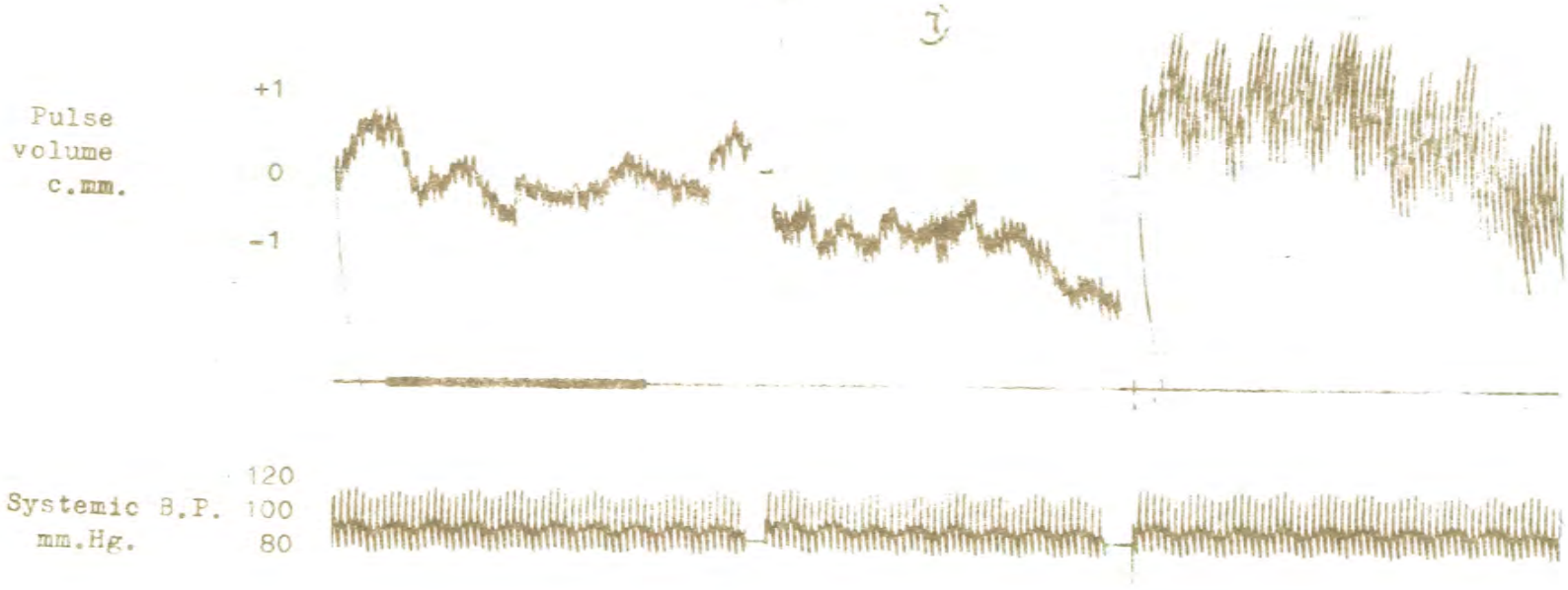
(Details of voltage, frequency etc. in text)

EXPERIMENT 6 (cont.)



EXPERIMENT 6 (cont.)

Illustrating the effect of traumatic arterial spasm on pulse volume.



APPENDIX 2.

Graphic representation of results from the experiments constituting Series 2.

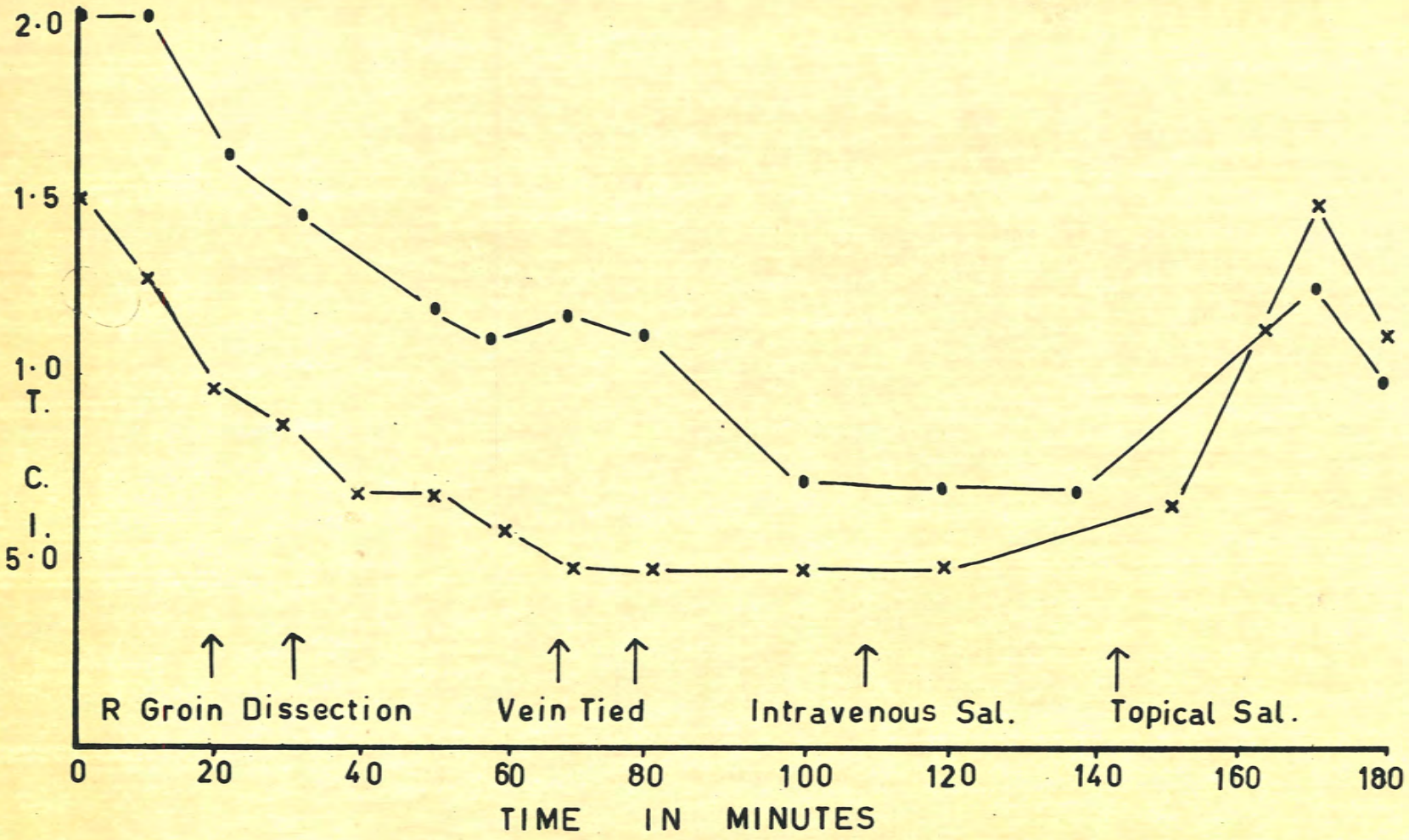
Abbreviations :

T.C.I. Thermal circulation index.

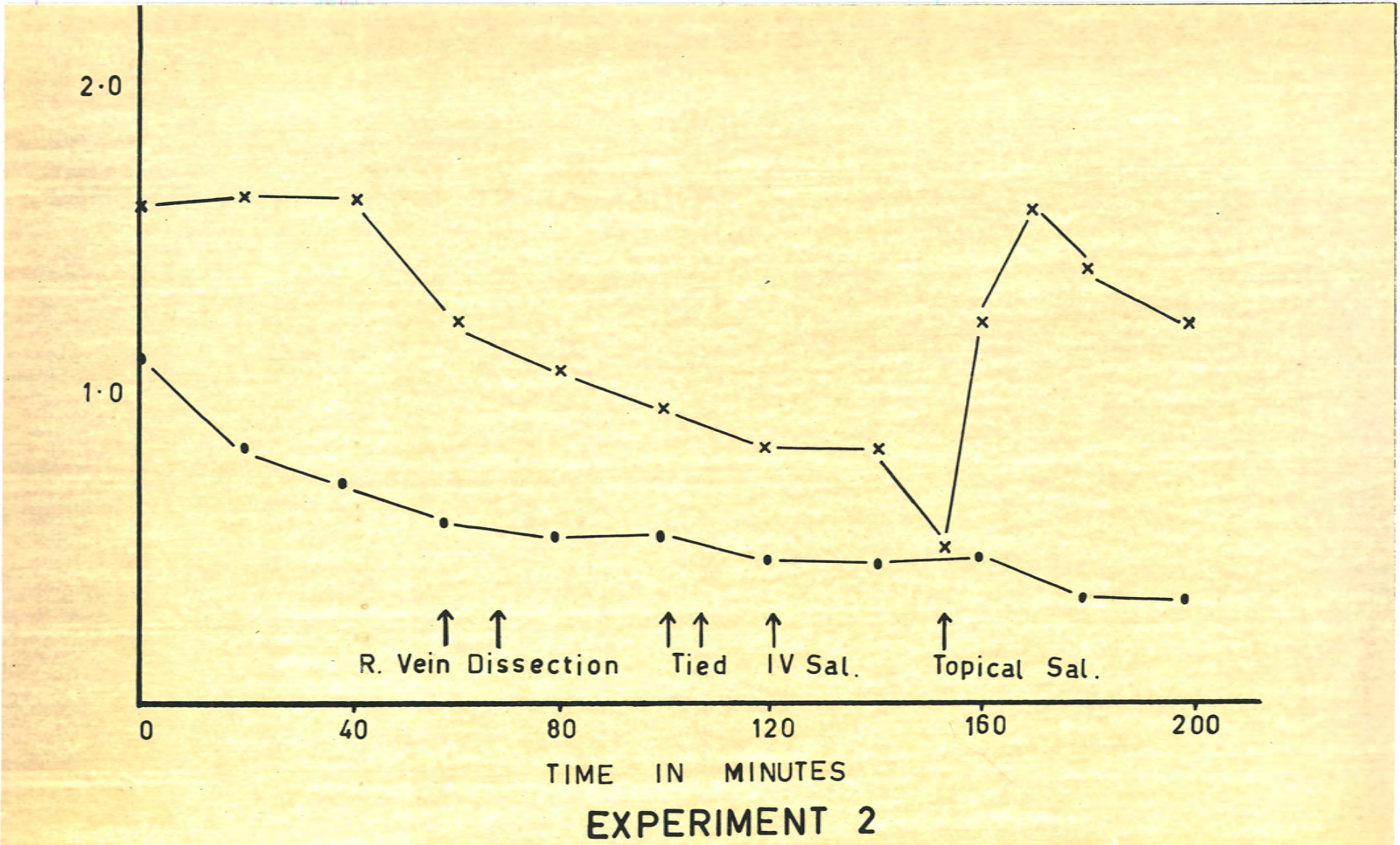
Sal. Sodium salicylate solution (40% w/v).

I.V. Intravenous

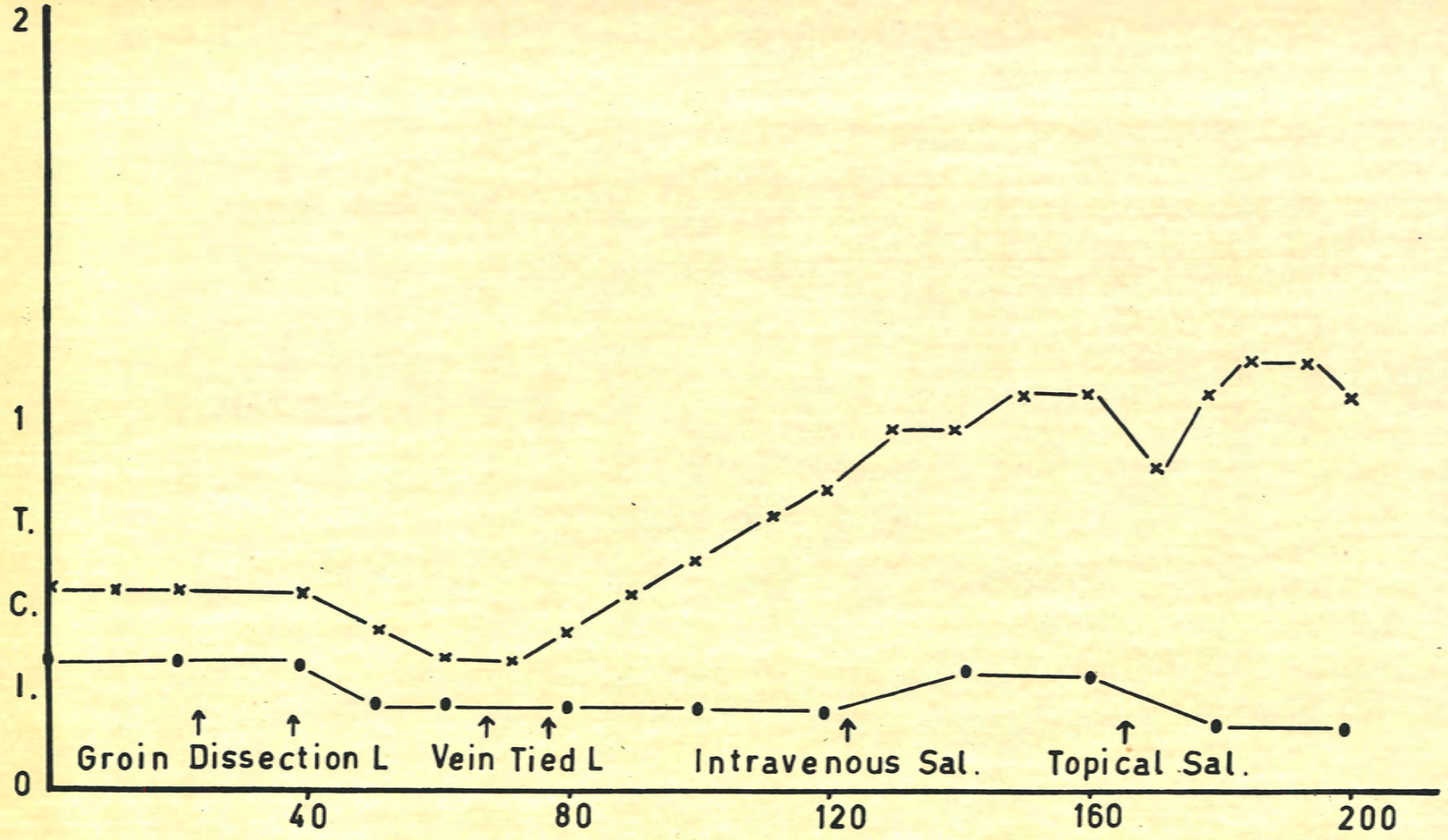
Top. Topical


2·0
1·5
1·0
T.
C.
I.
5·0
R Groin Dissection
Vein Tied
Intravenous Sal.
Topical Sal.
0
20
40
60
80
100
120
140
160
180
TIME IN MINUTES

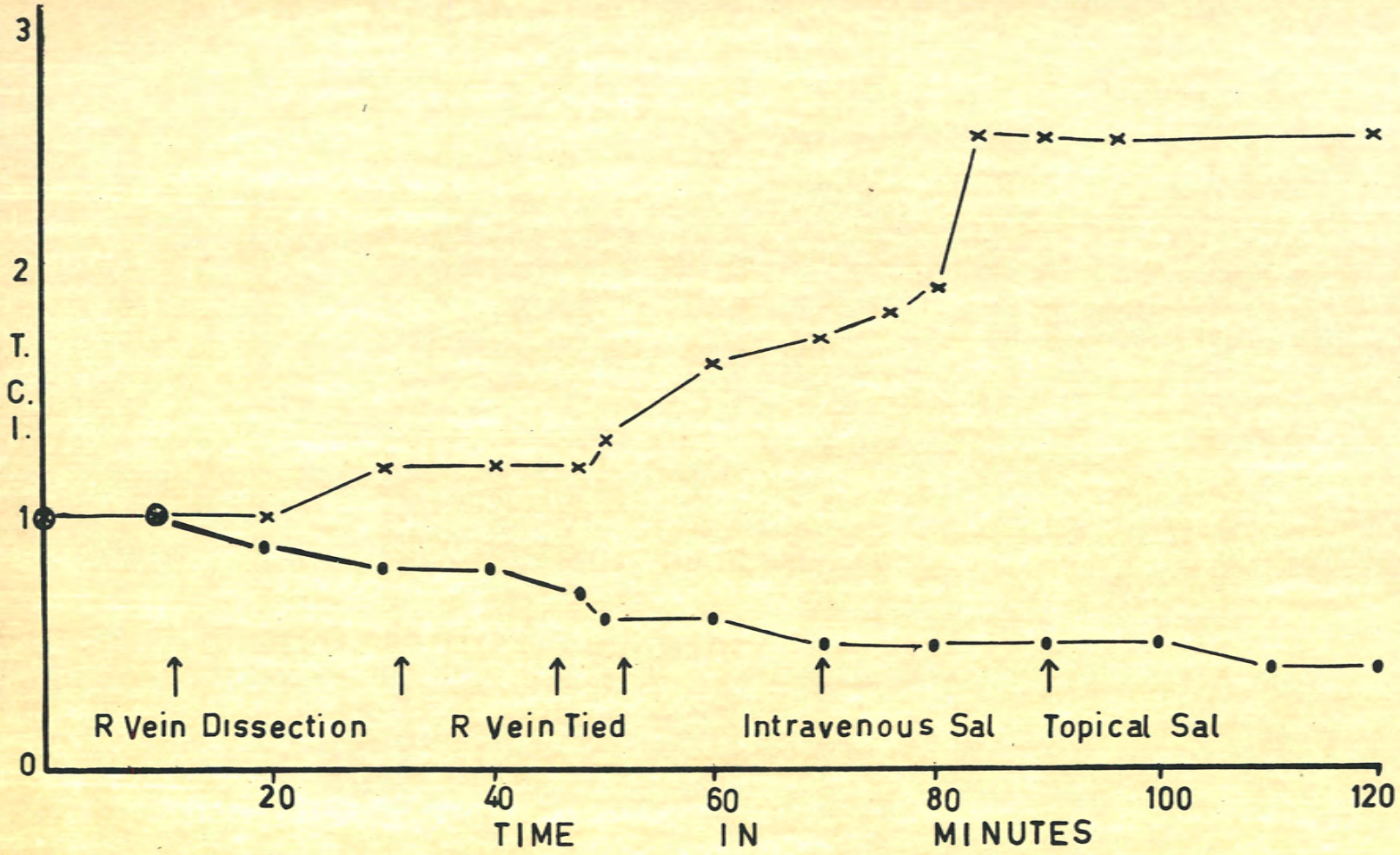
EXP. 1



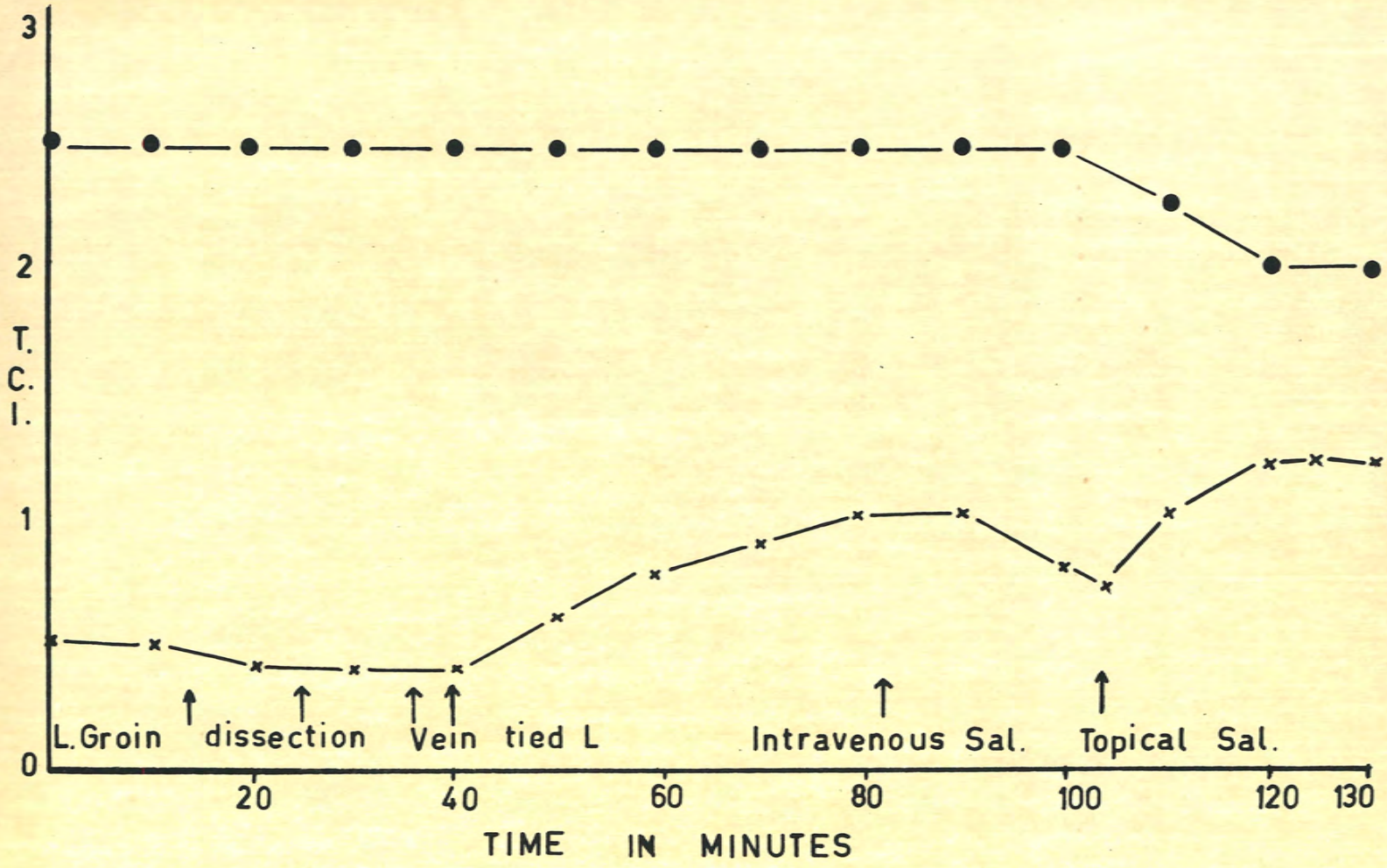
EXPERIMENT 2


2
1
T.
C.
I.
0
Groin Dissection L
Vein Tied L
Intravenous Sal.
Topical Sal.
40
80
120
160
200
TIME IN MINUTES

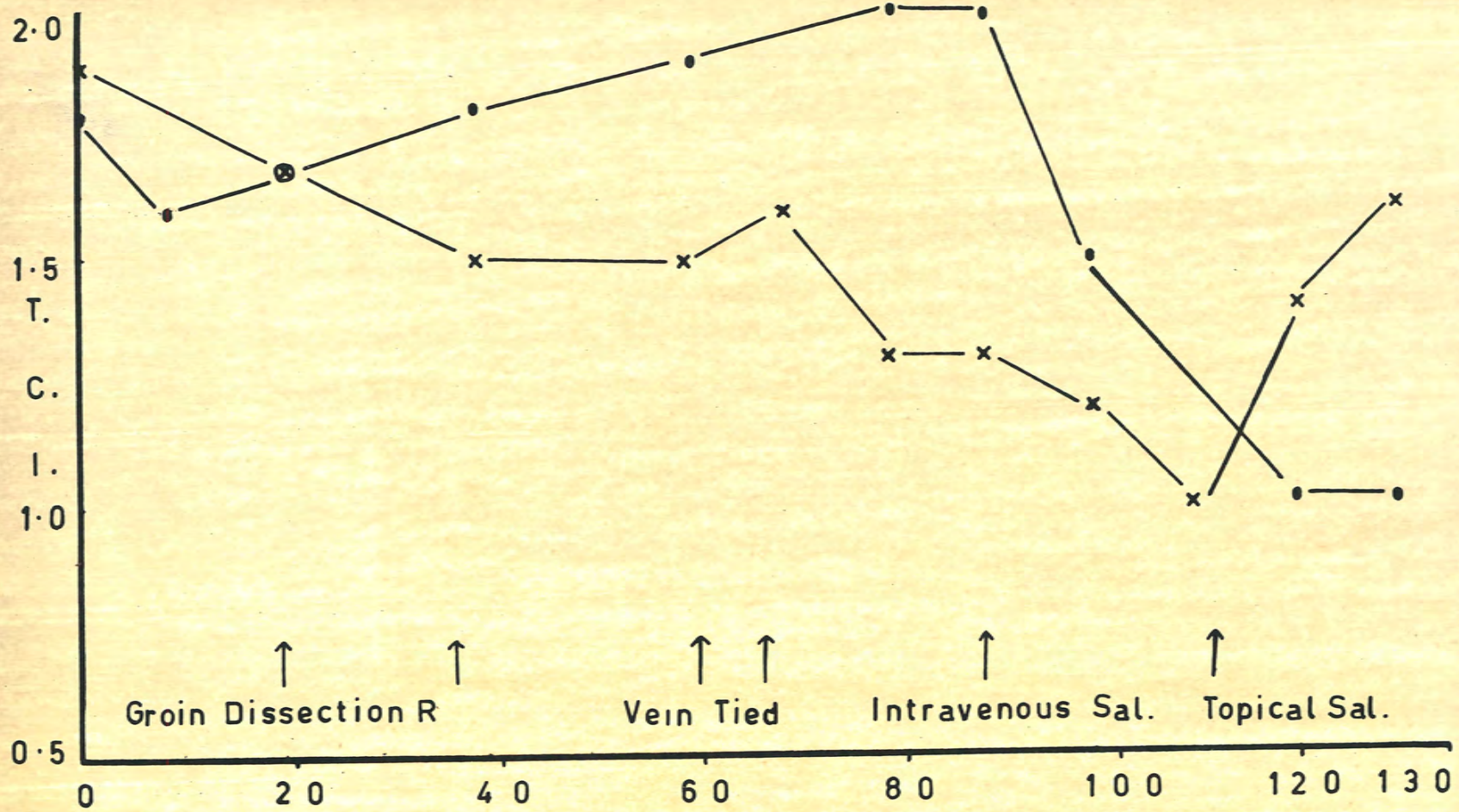
EXP. 3


3
2
T.
C.
I.
1
0
R Vein Dissection
R Vein Tied
Intravenous Sal
Topical Sal
20
40
60
80
100
120
TIME IN MINUTES

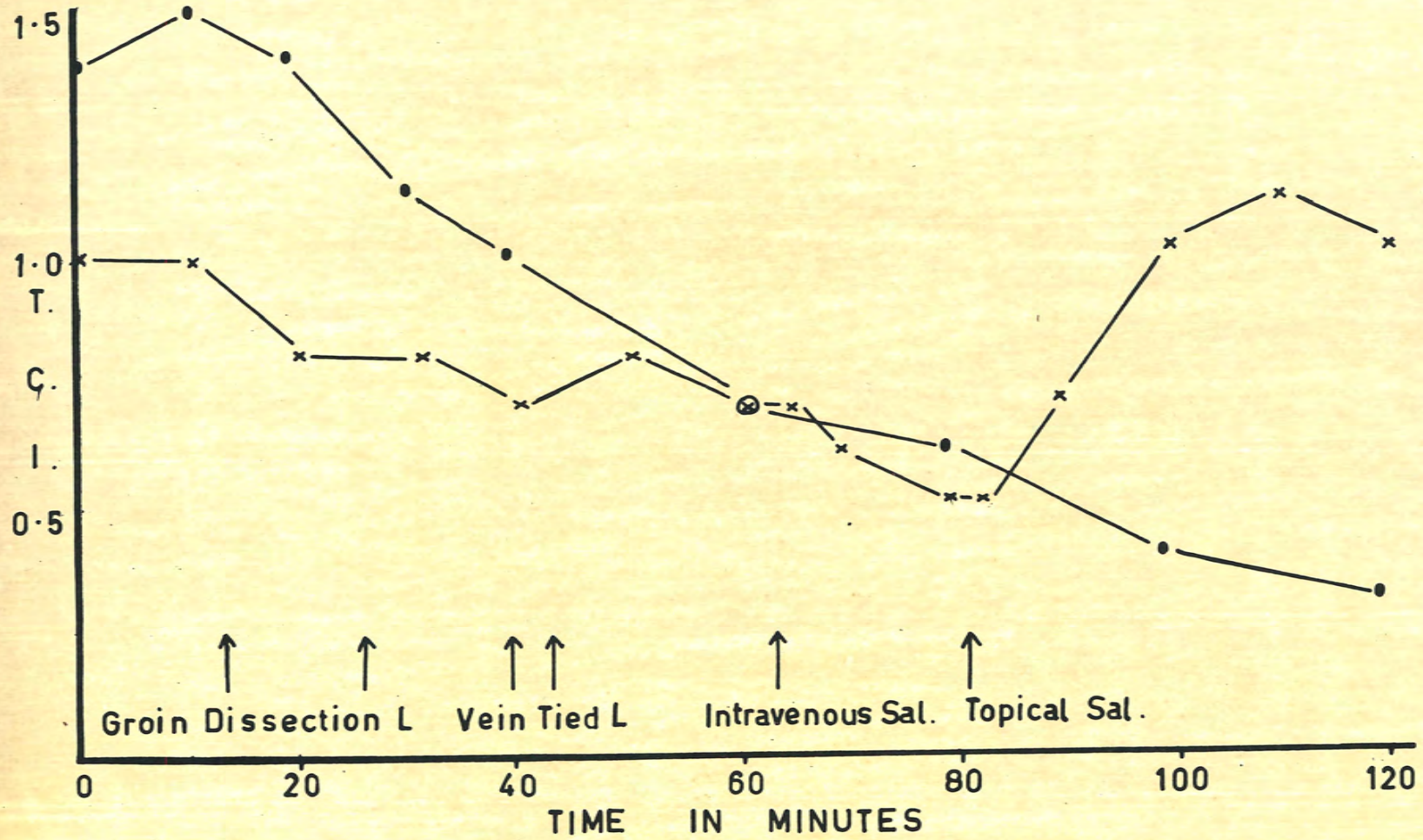
EXP. 4


3
2
T.
C.
I.
1
0
L.Groin
dissection
Vein tied L
Intravenous Sal.
Topical Sal.
20
40
60
80
100
120
130
TIME IN MINUTES

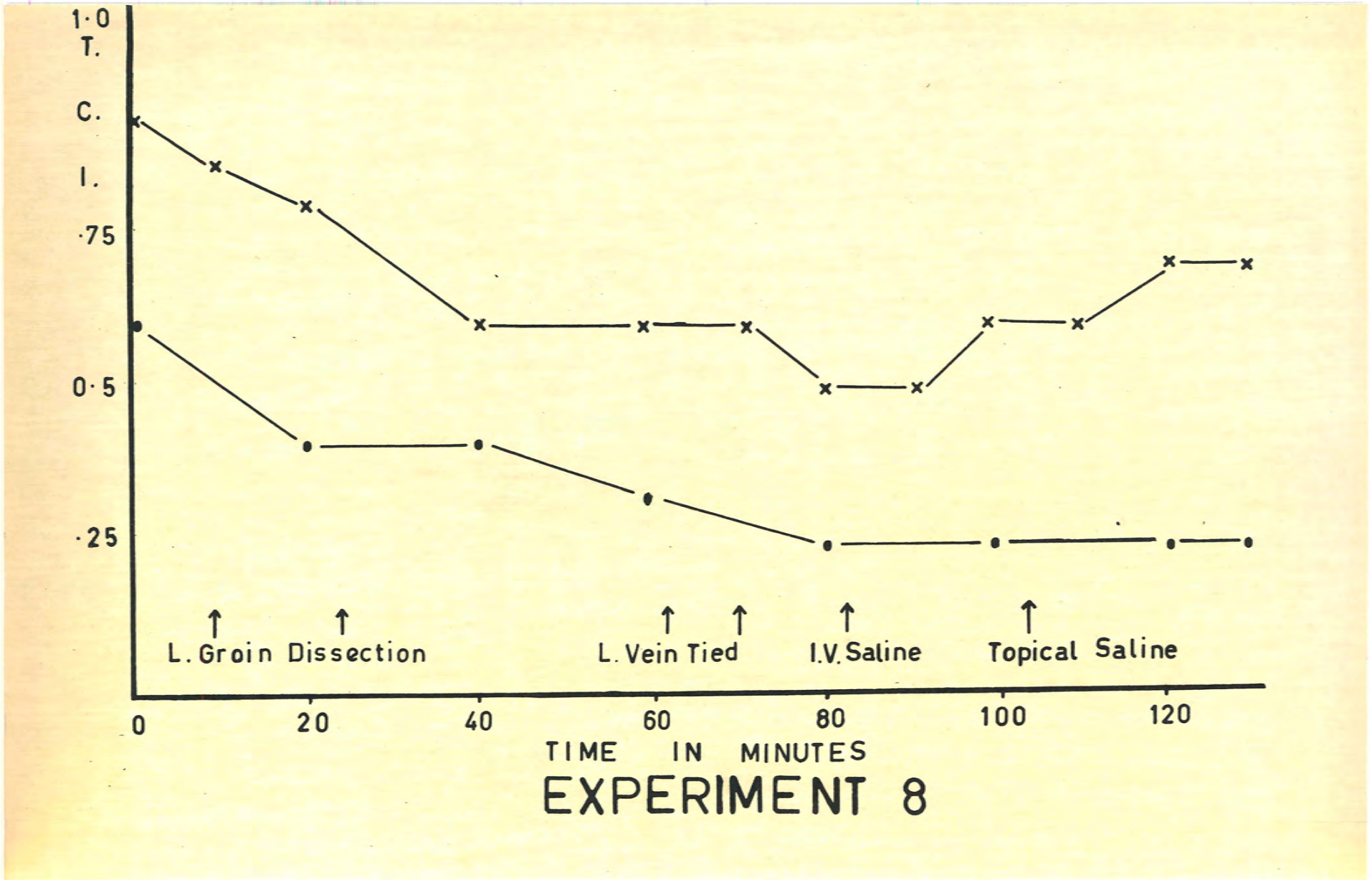
EXP. 5



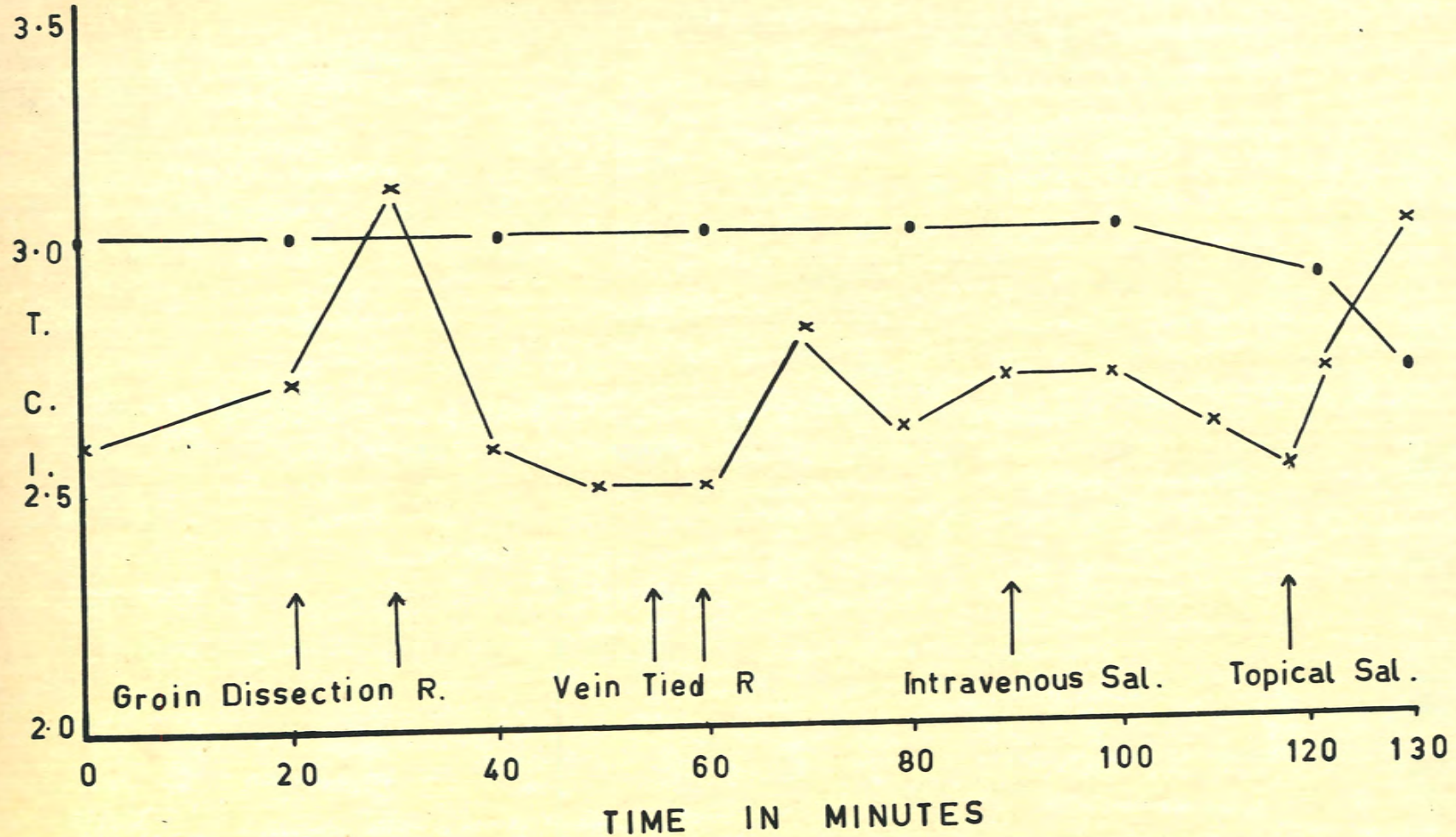
EXPERIMENT 6



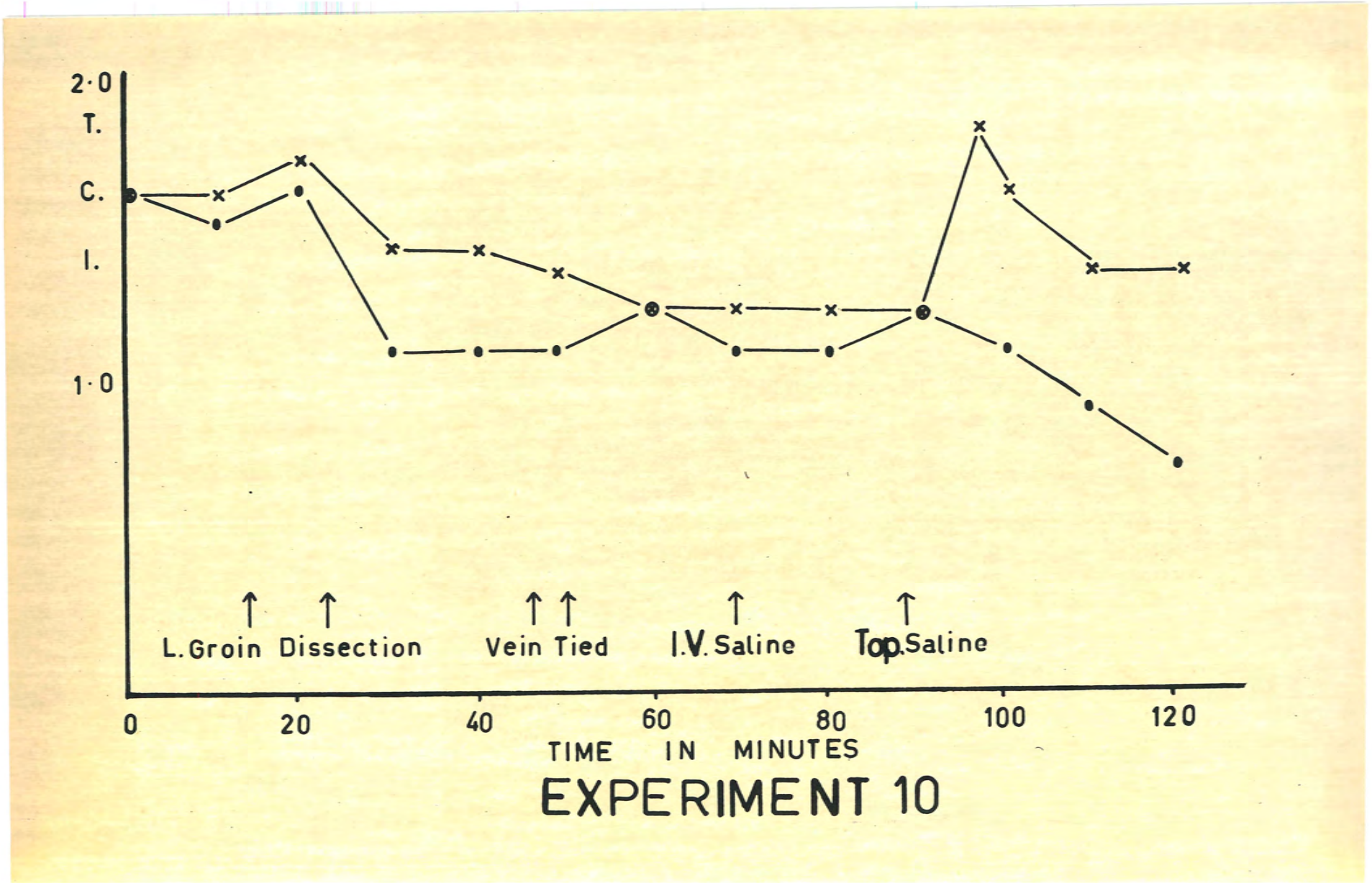
EXPERIMENT 7



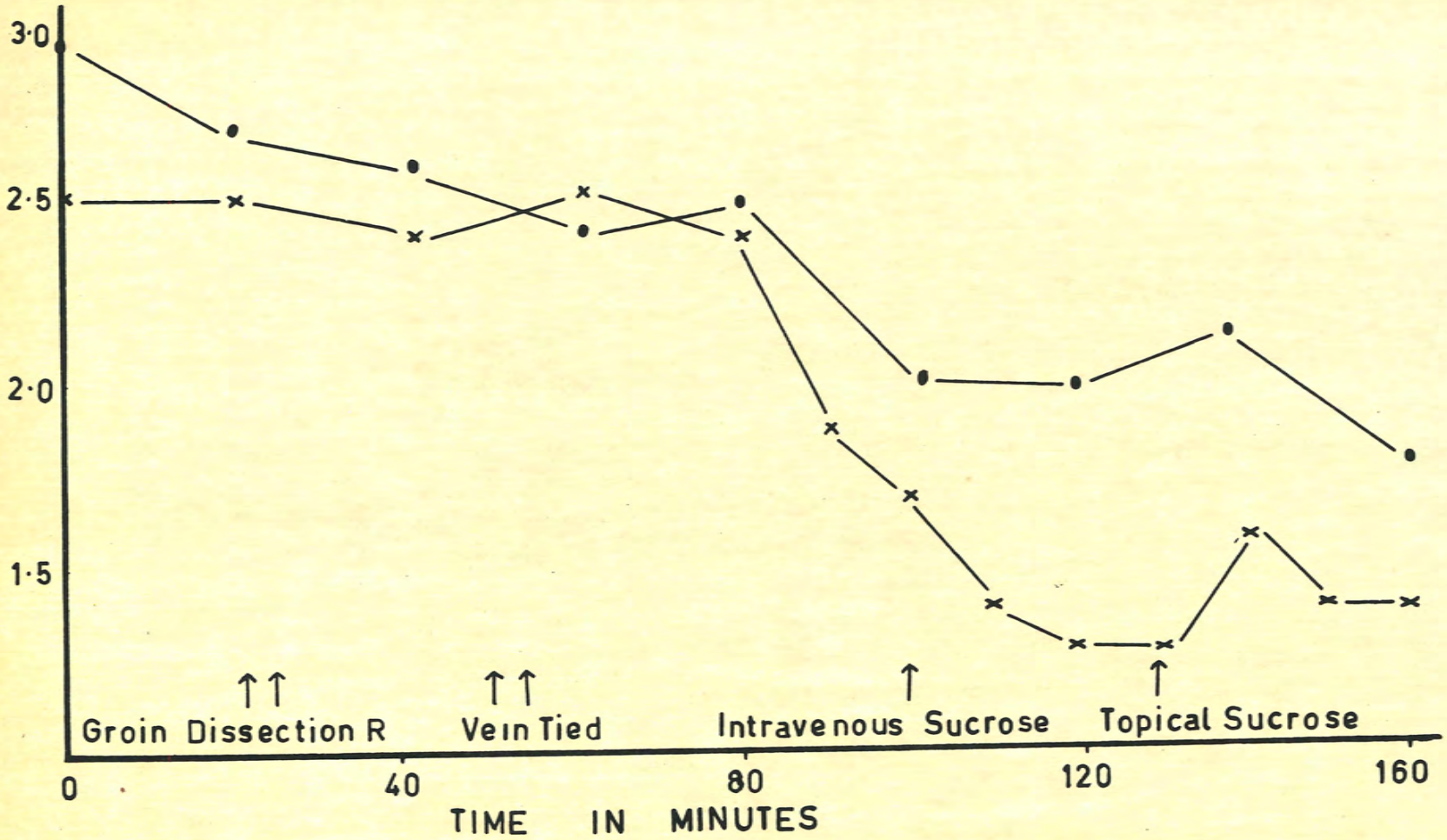
EXPERIMENT 8



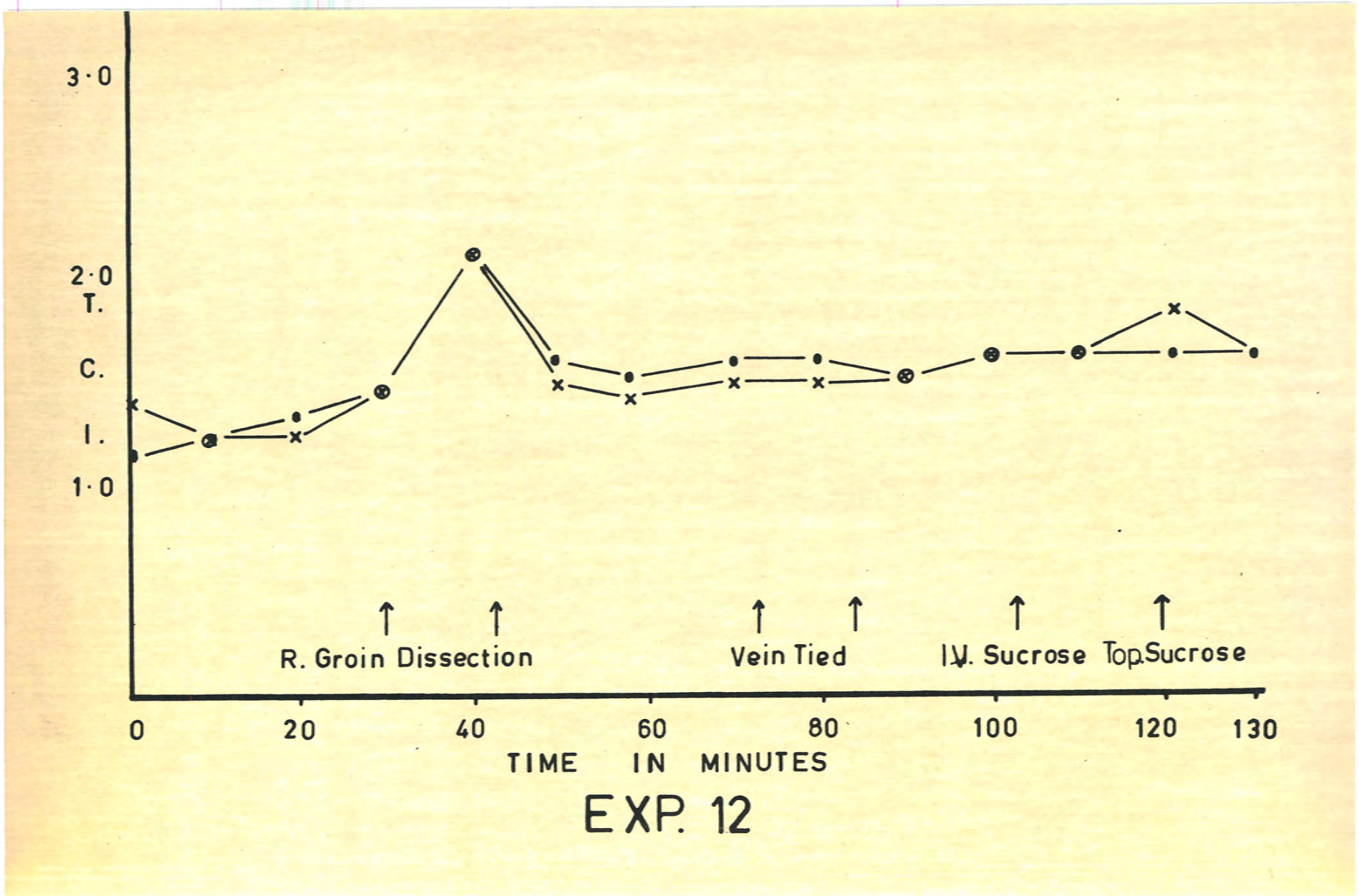
EXPERIMENT 9



EXPERIMENT 10


3·0
2·5
2·0
1·5
Groin Dissection R
Vein Tied
Intravenous Sucrose
Topical Sucrose
0
40
80
120
160
TIME IN MINUTES

Exp. 11.


3·0
2·0
T.
C.
I.
1·0
R. Groin Dissection
Vein Tied
I.V. Sucrose
Top. Sucrose
0
20
40
60
80
100
120
130
TIME IN MINUTES

EXP. 12

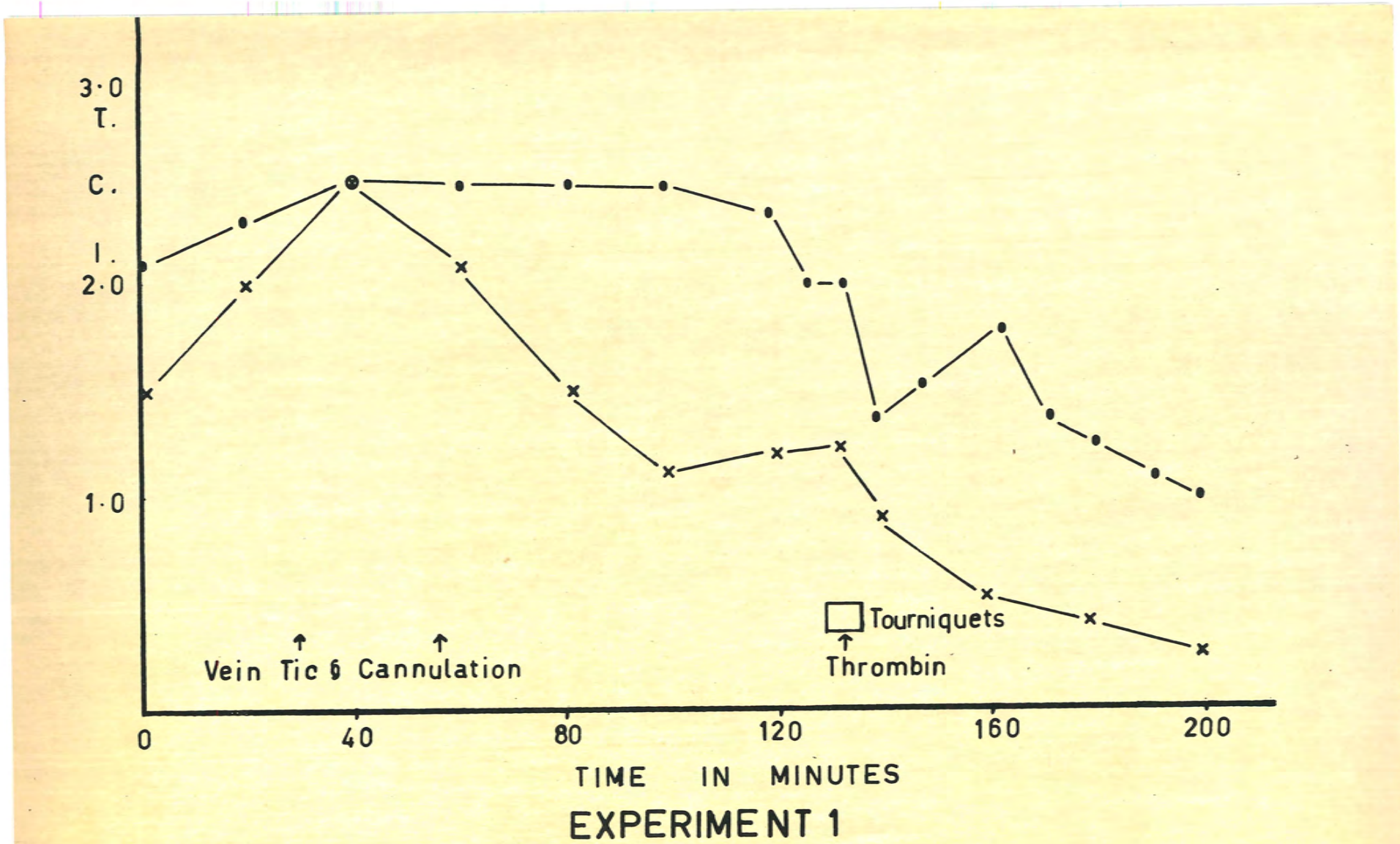
APPENDIX 3.

Graphic representation of results from the experiments constituting Series 3.

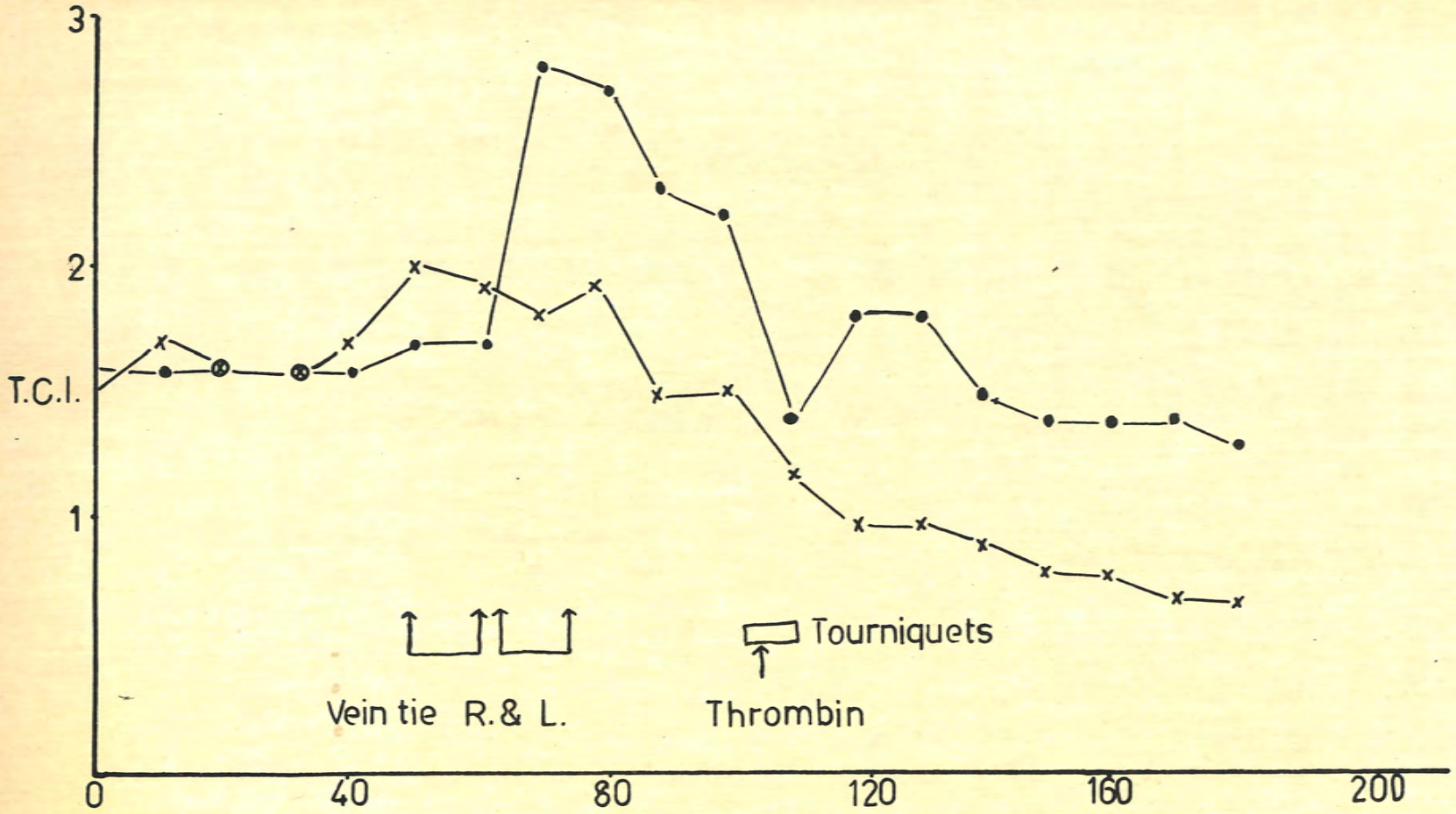
In Experiments 1, 2, 3, and 7 the treated leg was "Blue". Experiment 6 is included as representative of those experiments in which the treated leg was "white", and in which there is no alteration in blood flow, as compared with the control leg.

Abbreviations :

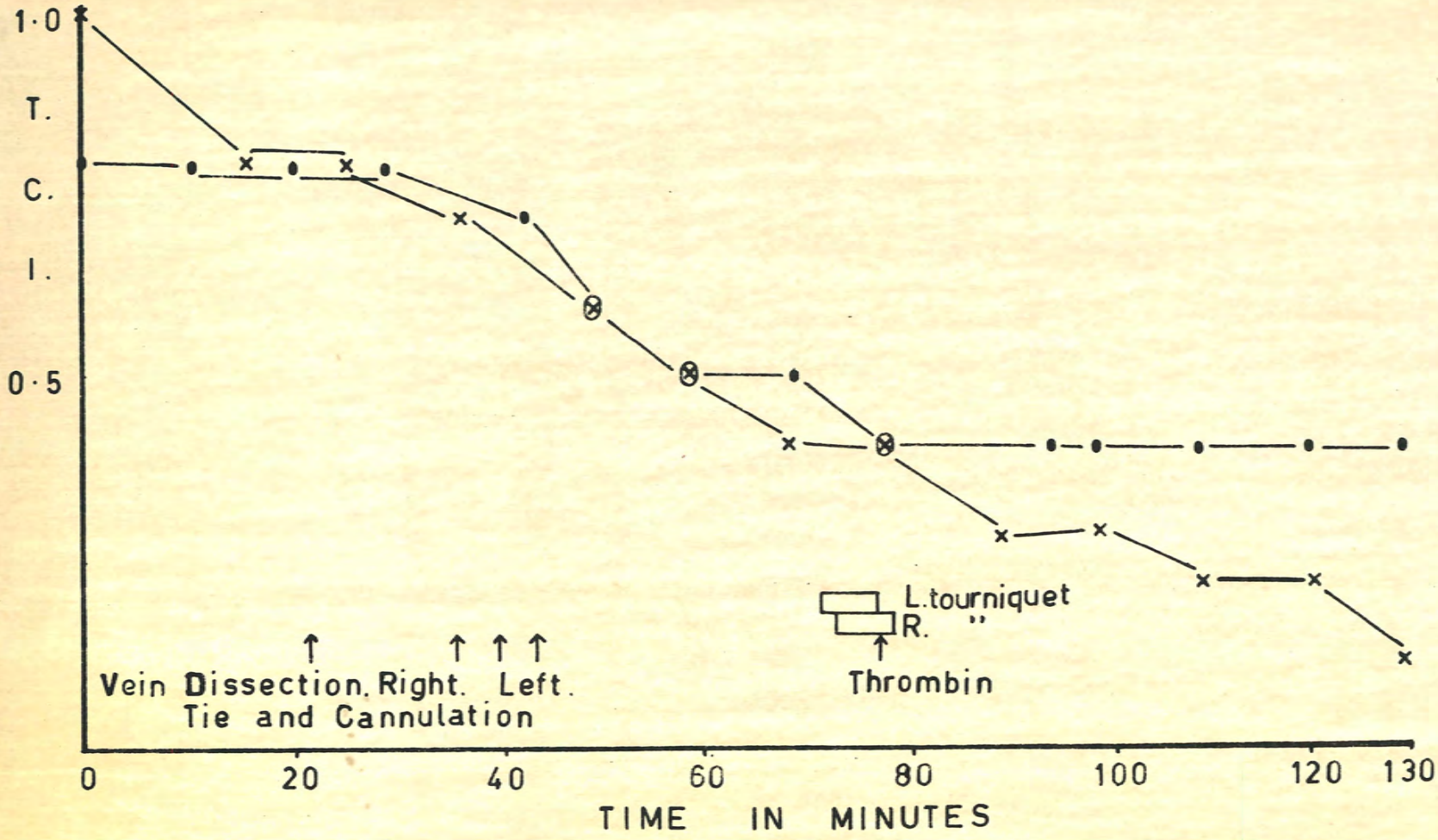
T.C.I. Thermal circulation index.



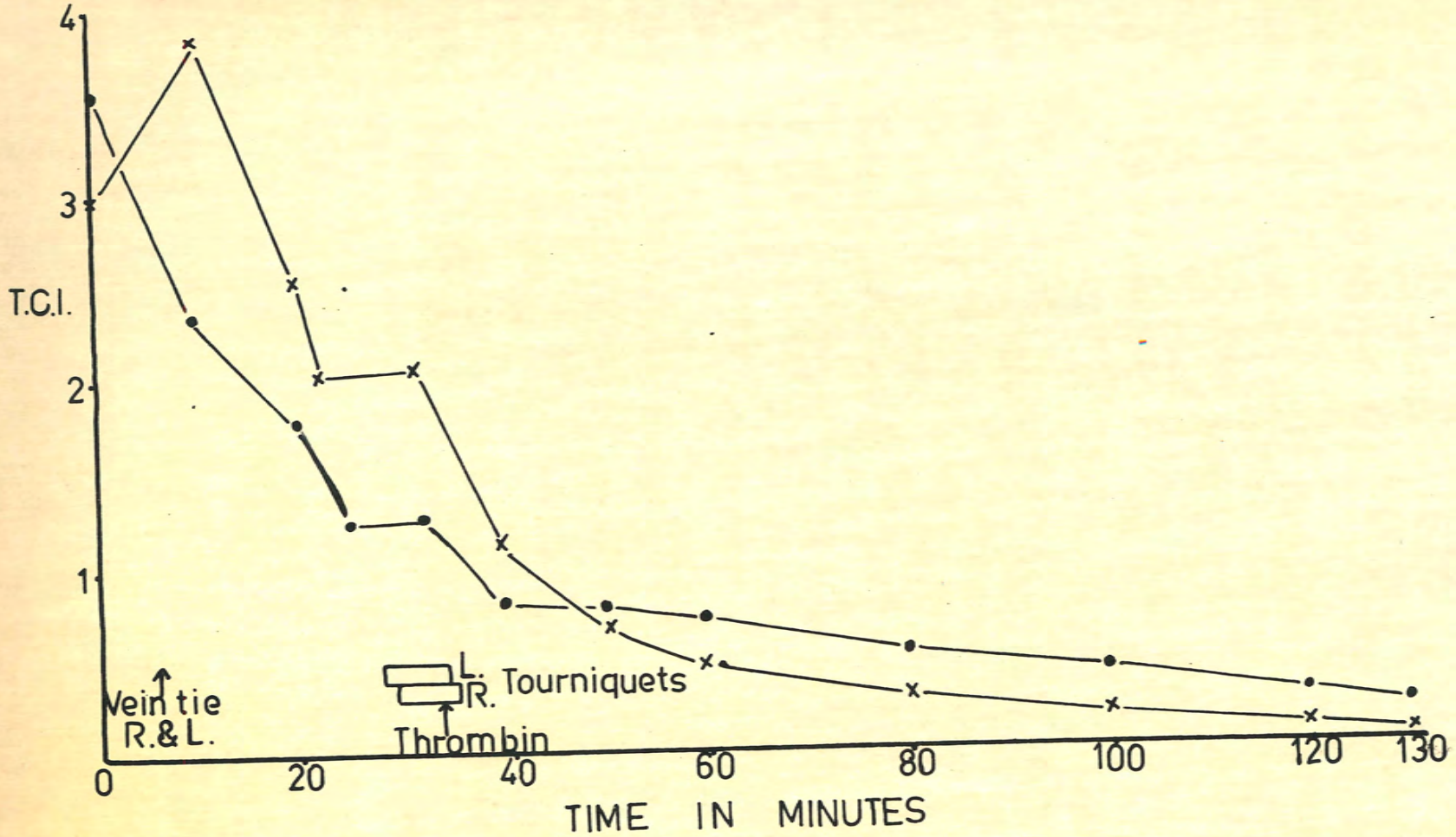
EXPERIMENT 1


3
2
1
T.C.I.
Tourniquets
Vein tie R.& L.
Thrombin
0
40
80
120
160
200
TIME IN MINUTES

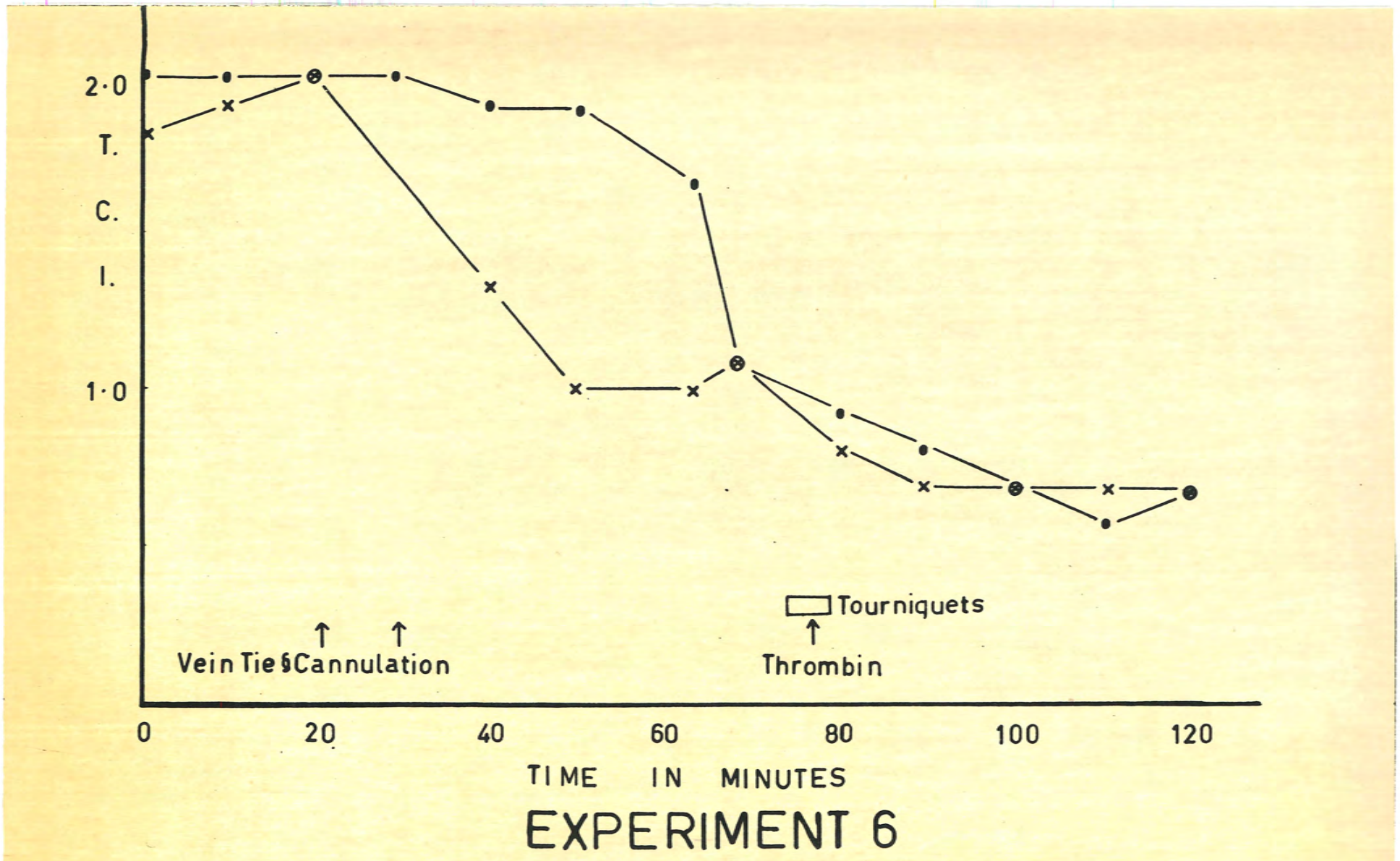
Exp. 2.



EXPERIMENT 3


4
3
T.C.I.
2
1
Vein tie
R.&L.
L.
R.
Tourniquets
Thrombin
0
20
40
60
80
100
120
130
TIME IN MINUTES

Exp. 7.



EXPERIMENT 6

APPENDIX 4.

Aortograms from the experiments constituting Series 4.

Eight aortograms are present in four series of two films each.

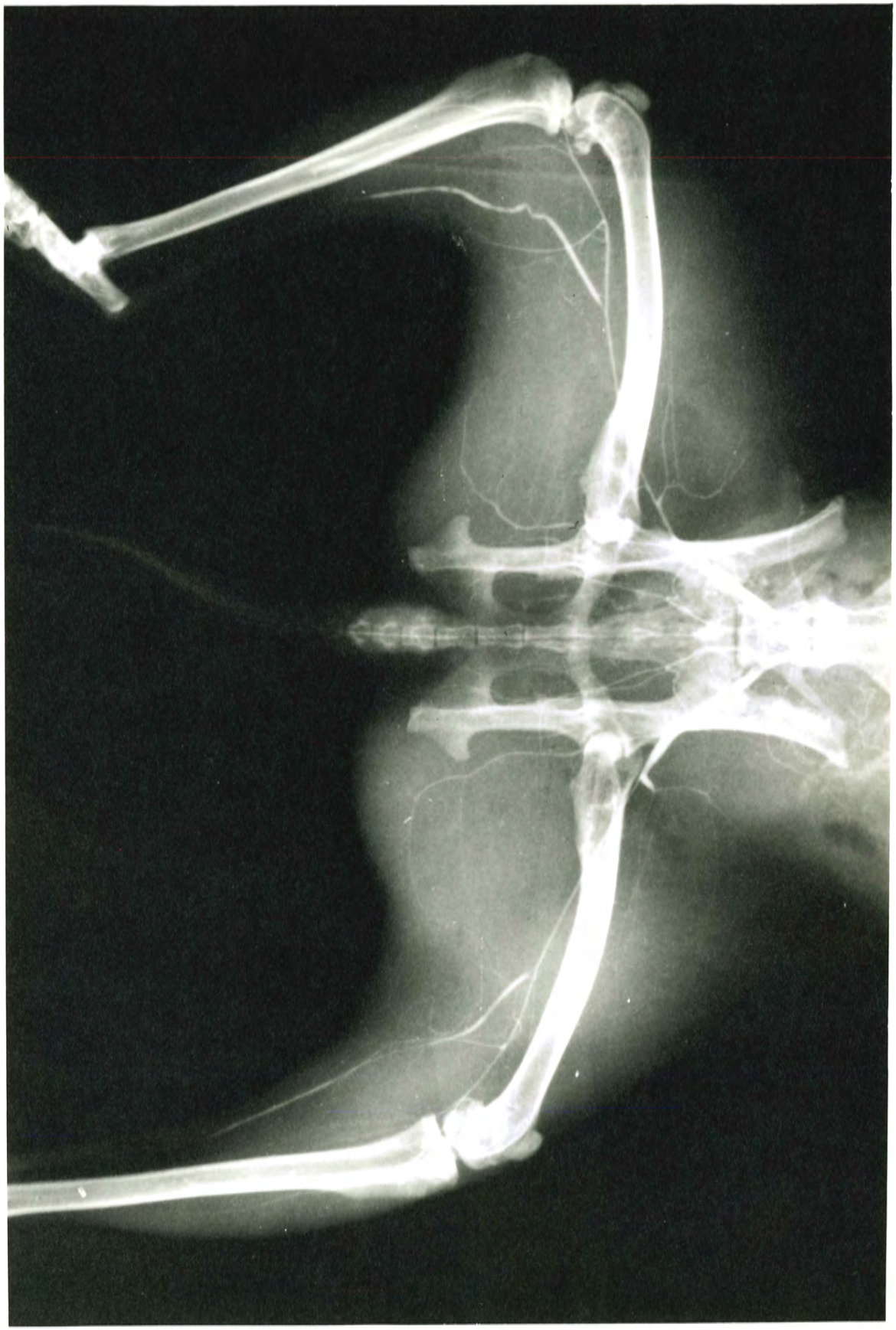
Each pair of films illustrates the same animal before and after lumbar sympathetic block.

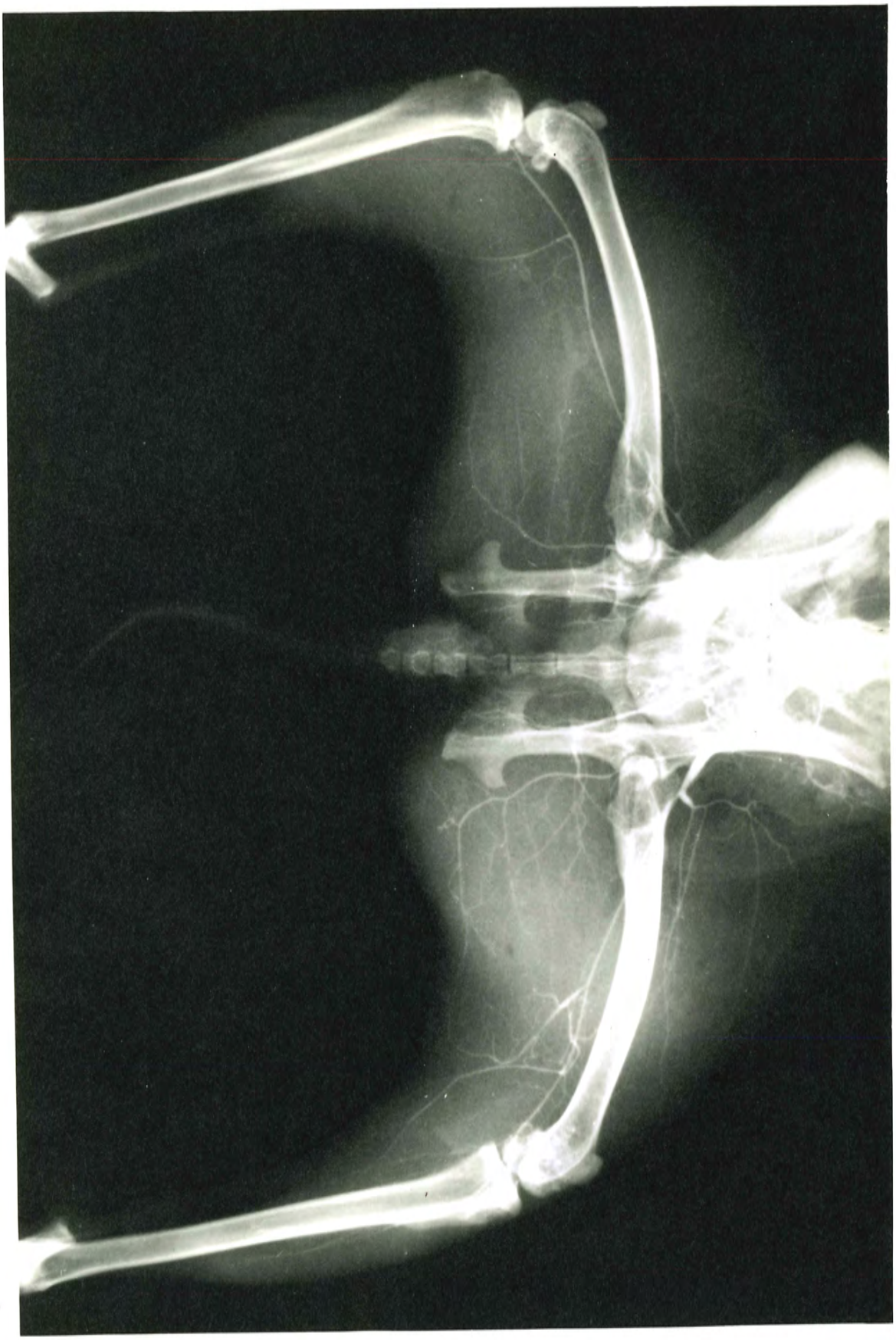
The right (treated limb) is on the observers' right side.

Angiograms 1 and 2 constitute a pair performed in an animal with a right sided "white" leg.

In the first film note slight diminution in the calibre of the major vessels and some loss of small vessel filling on the right.

In the second film the response to sympathetic interruption is marked. There is now much more small vessel filling on the right.

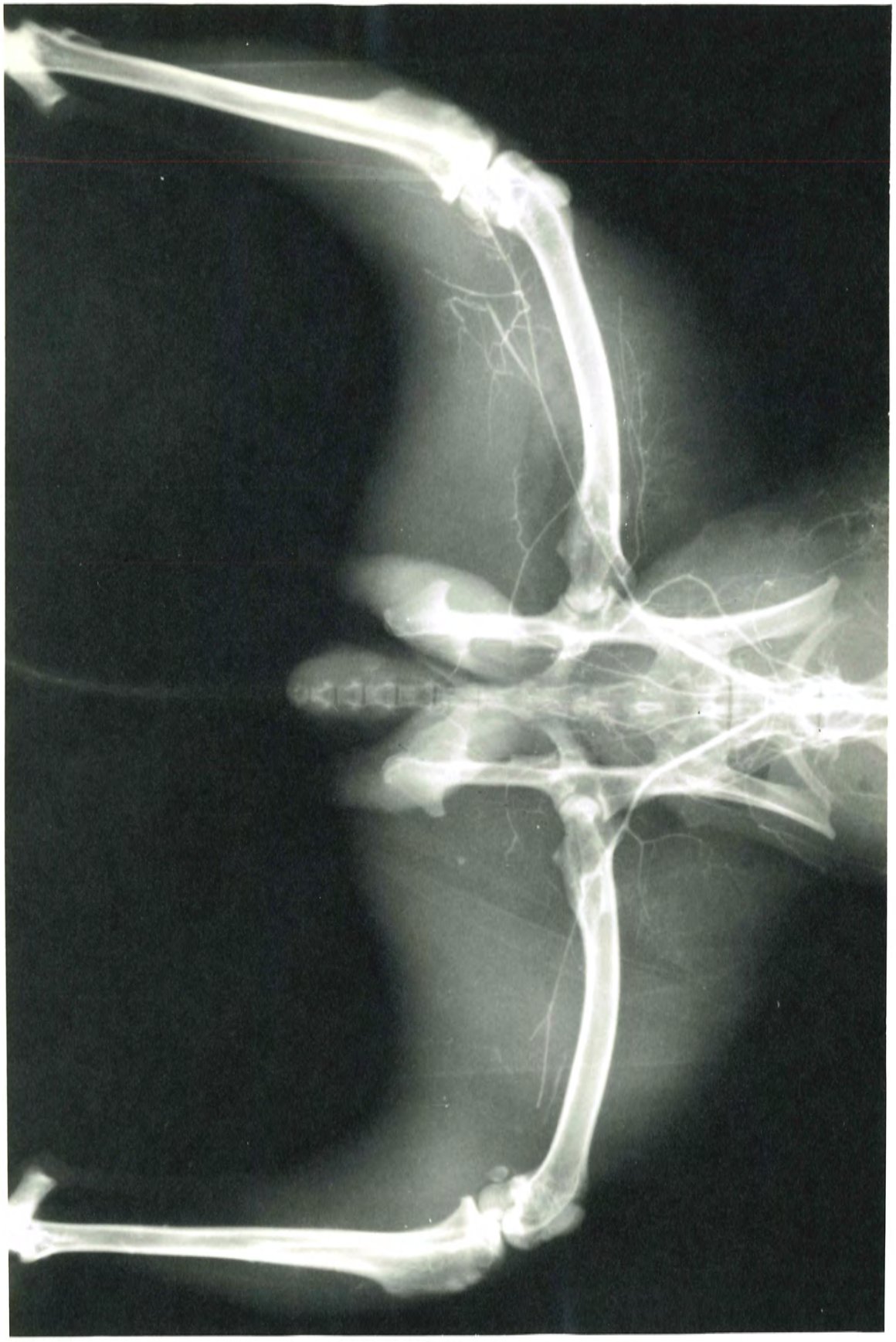


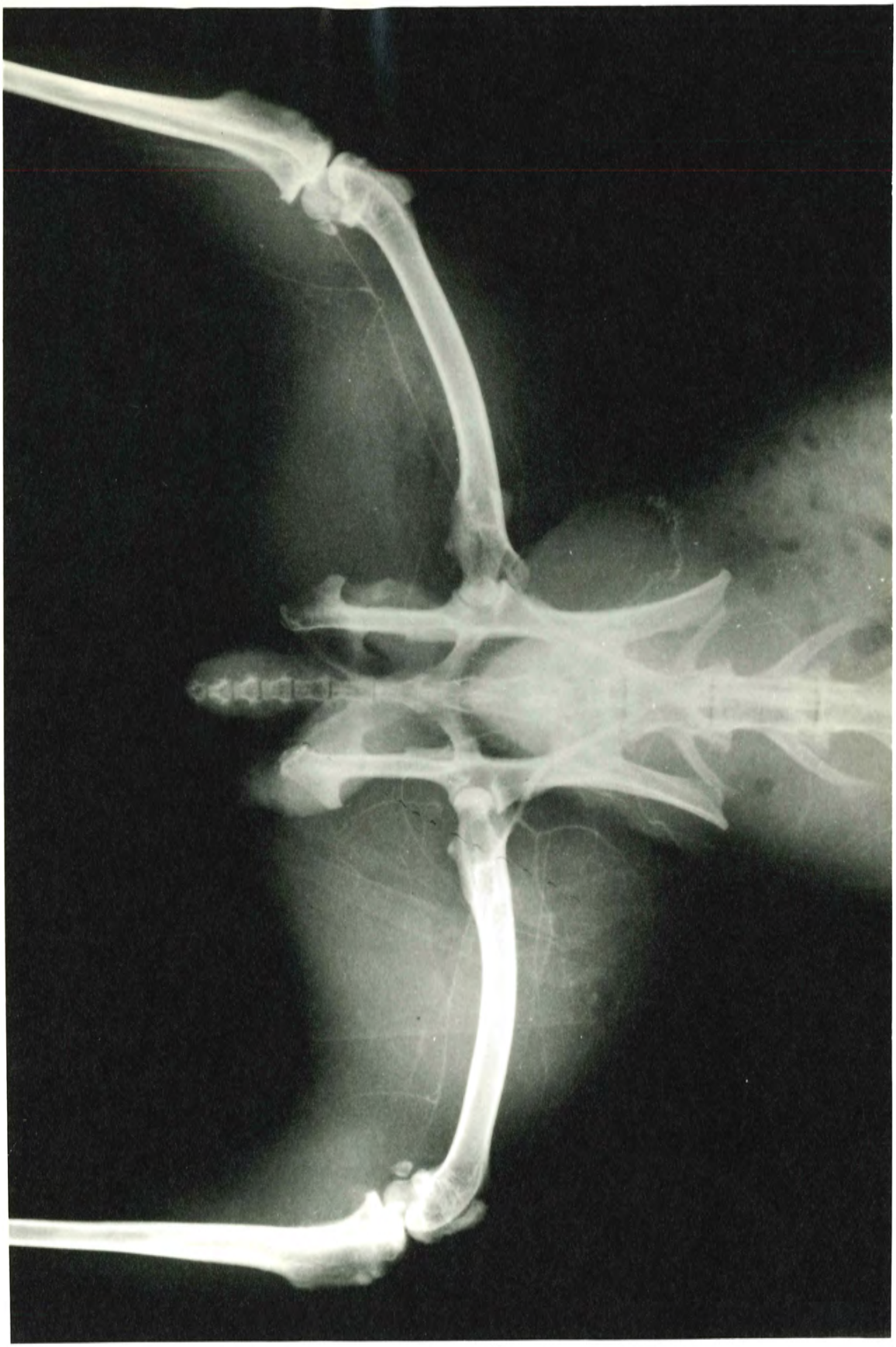


Angiograms 3 and 4 constitute a pair performed in an animal with a right sided White" leg.

In the first film, note marked slowing of arterial filling, and considerable loss of small vessel filling on the right.

In the second film, (After sympathetic interruption) note a marked increase in small vessel filling on the right.

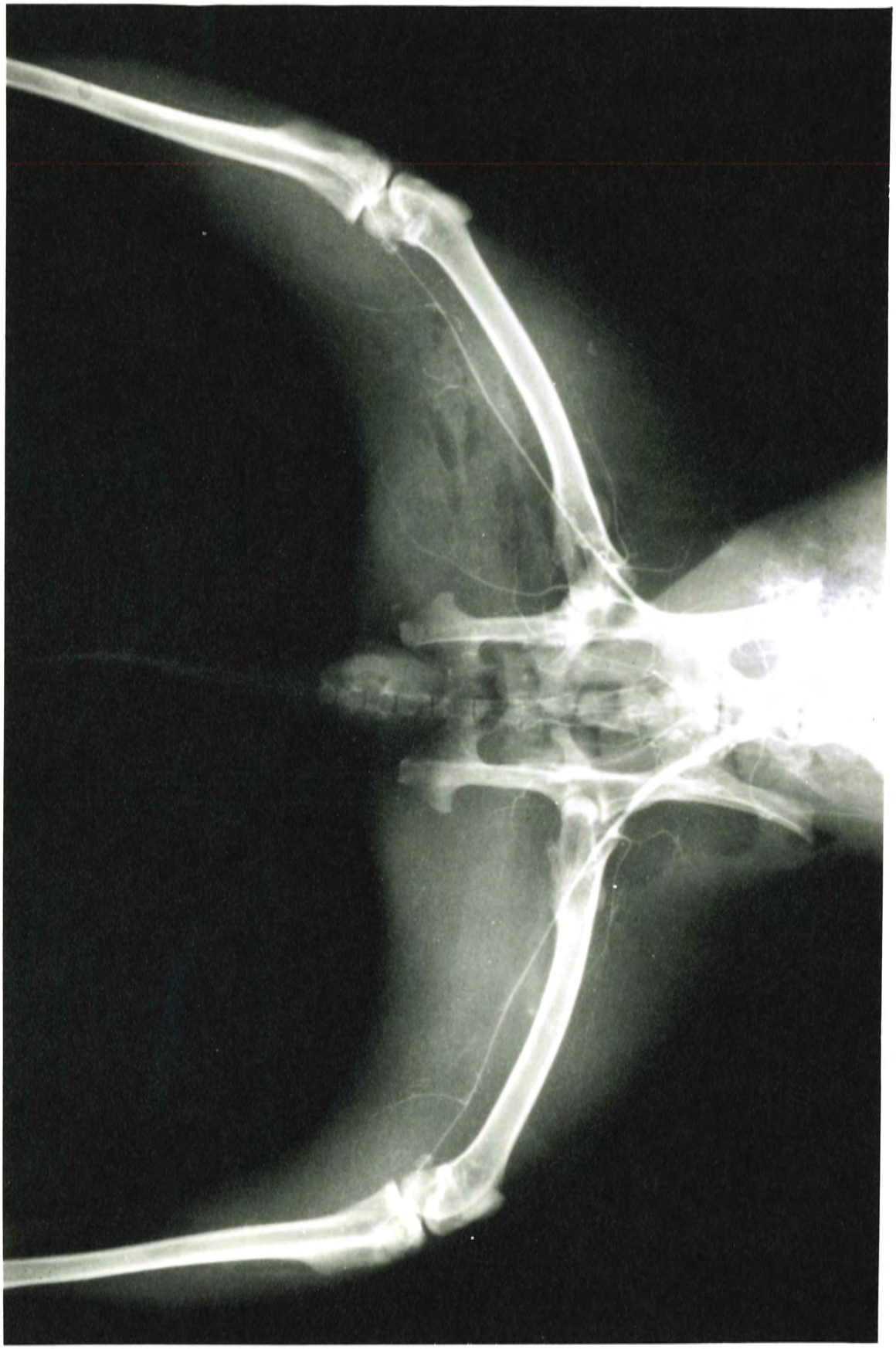


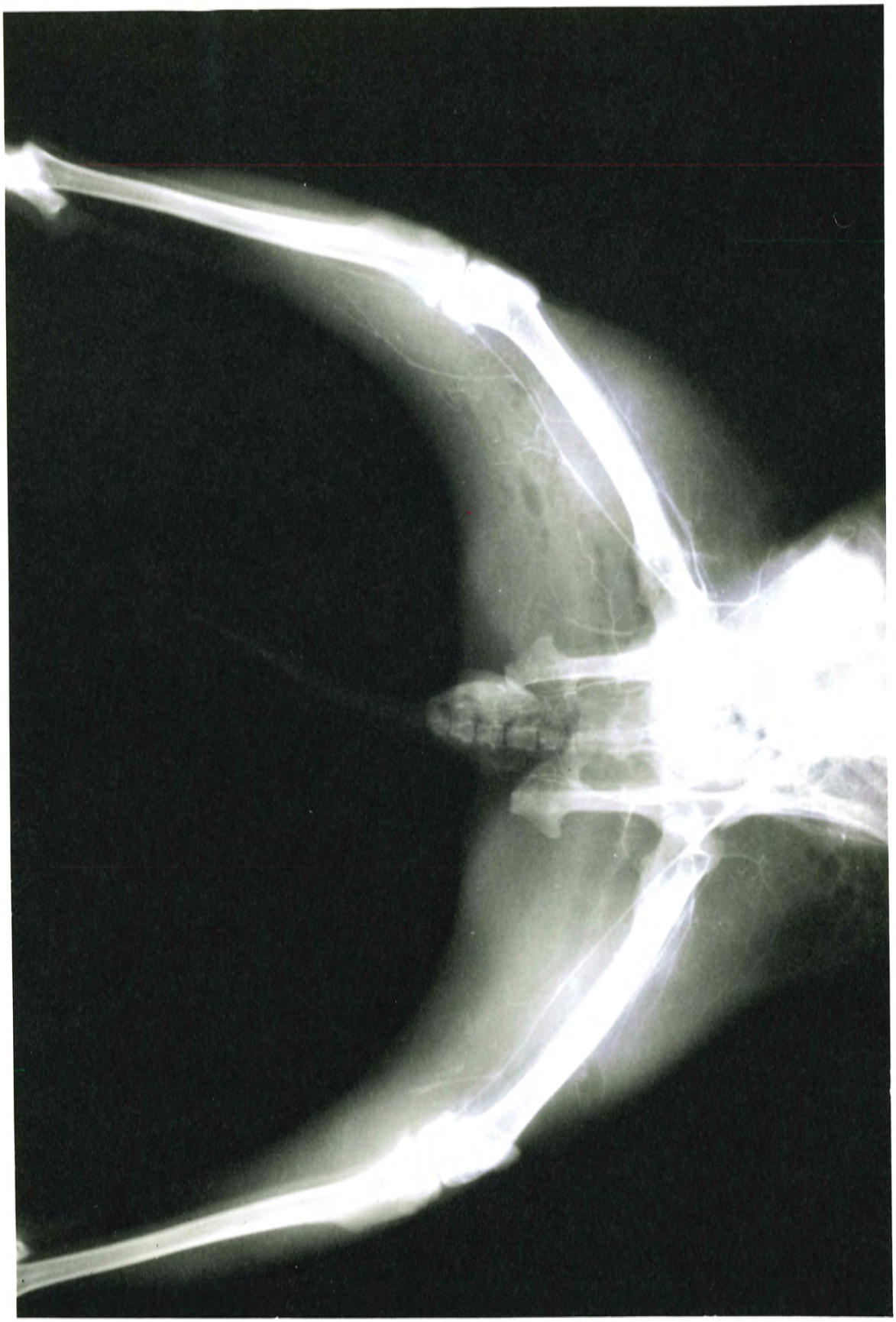


Angiograms 5 and 6 constitute a pair performed in an animal with a right sided "blue" leg.

In the first film, note some slowing of arterial filling with marked loss of small vessel filling. There is no appreciable difference in the calibre of the major vessels.

In the second film, after right sided lumbar sympathetic block, there is virtually no change.

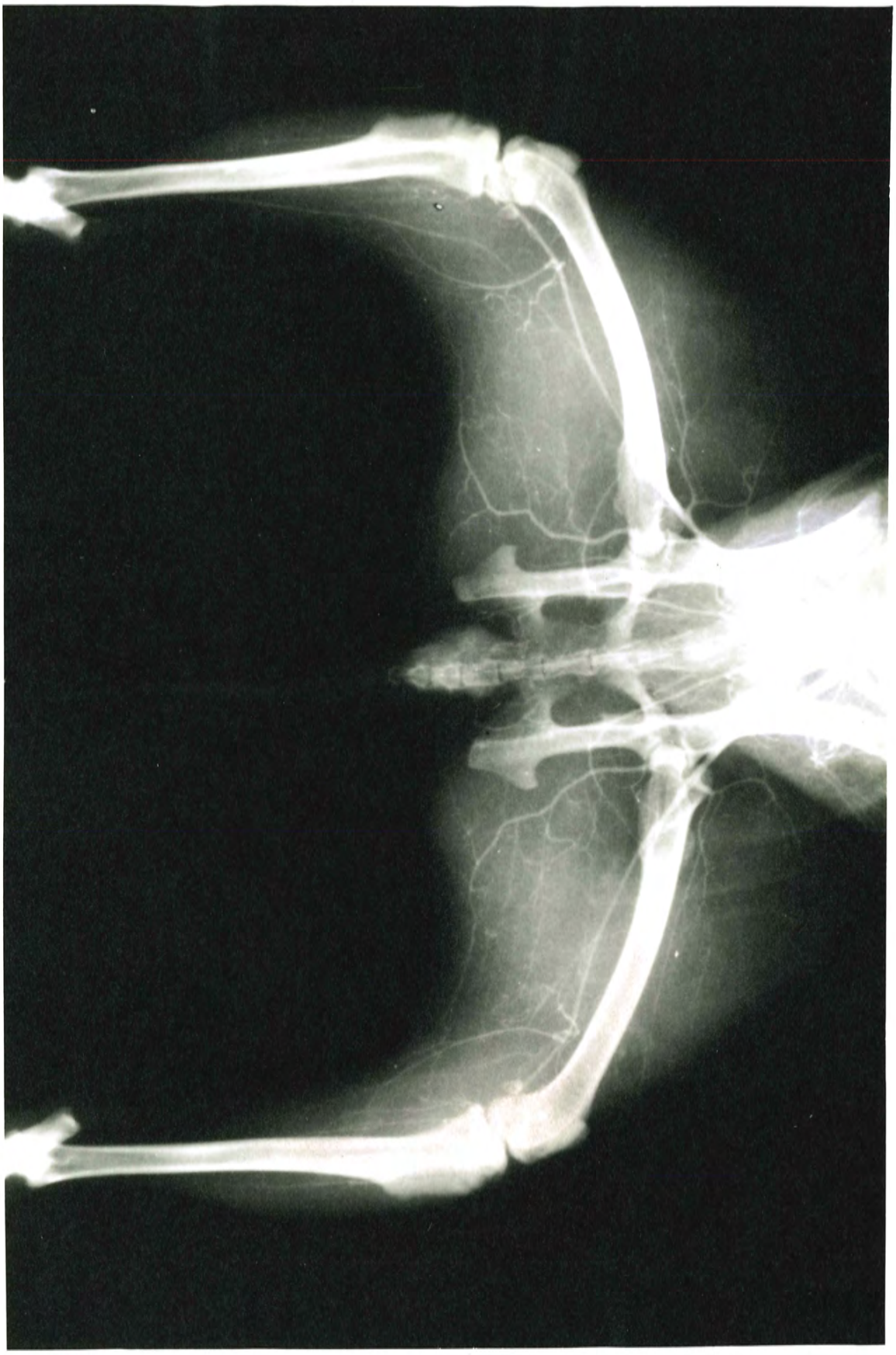


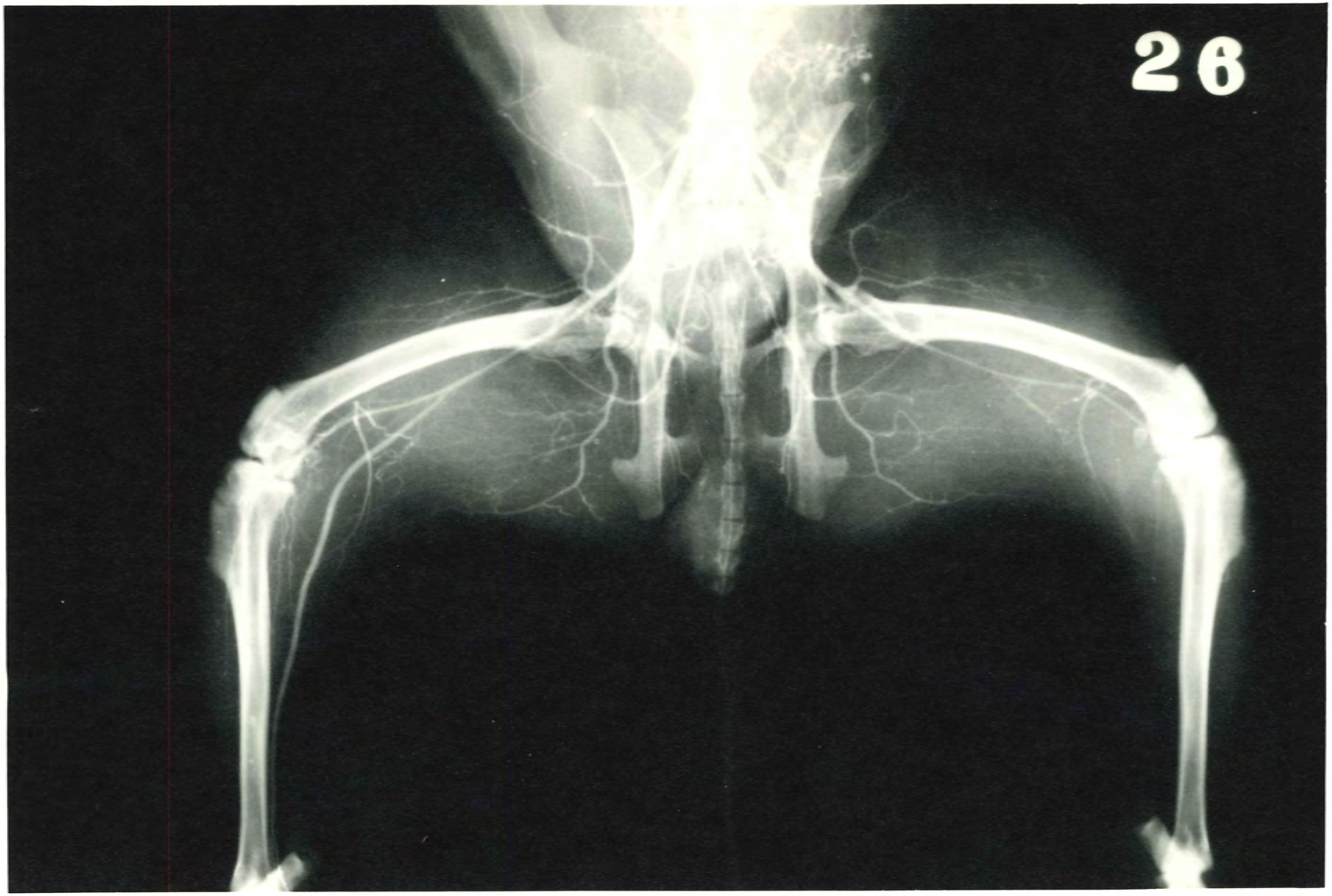


Angiograms 7 and 8 constitute a pair performed in an animal with a right sided "blue" leg

In the first film, there is good filling on both sides but progressing more slowly on the right.

In the second film after right sided lumbar sympathetic block the picture on the right is unchanged. Note the arterial filling down to the sole on the left, and the persisting smaller calibre of the major vessels on the right.




26

APPENDIX 5.

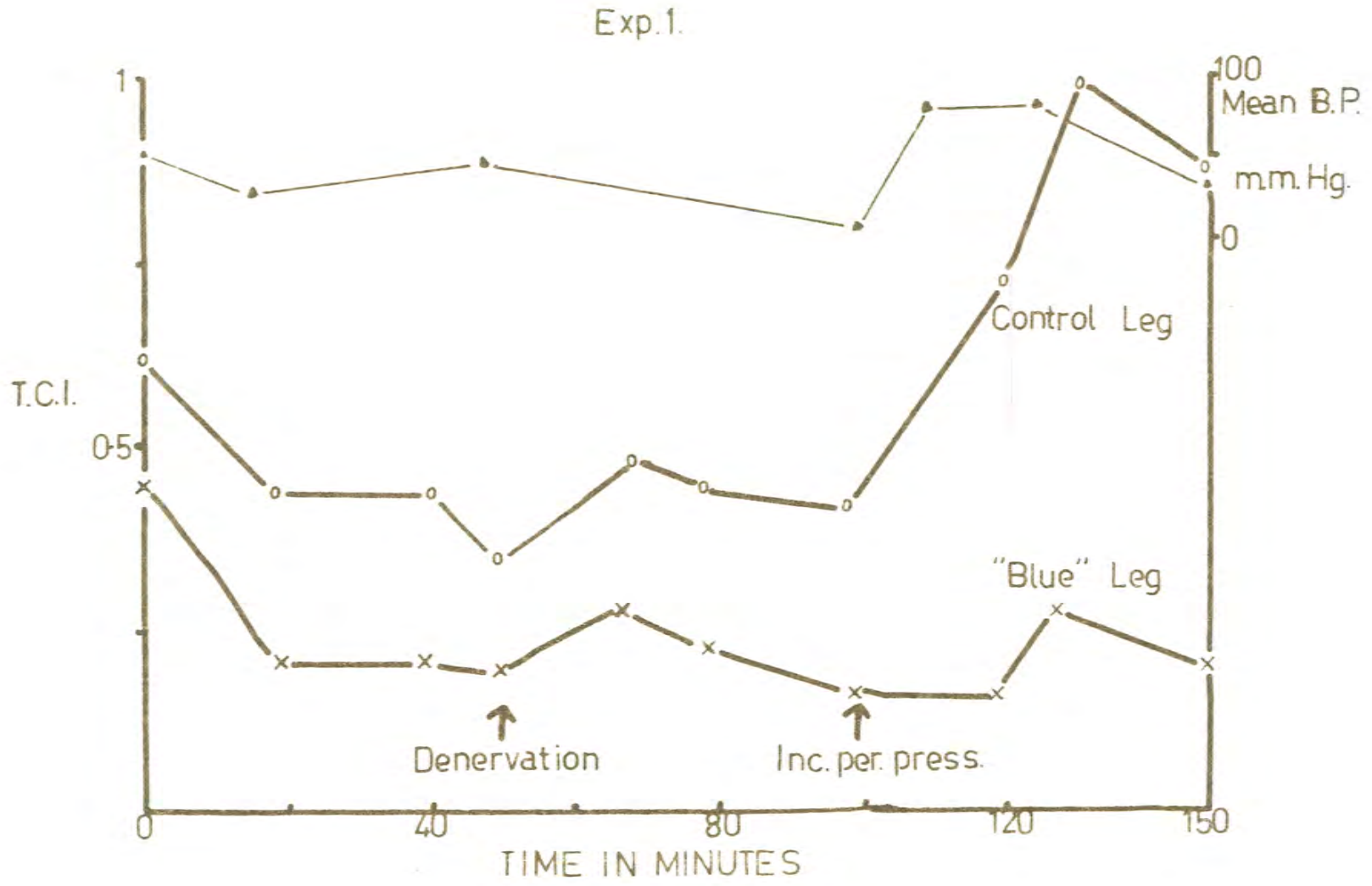
Graphic representation of results from the experiments constituting Series 5.

Experiments 6 and 8 are in the text as Figures 19 and 20.

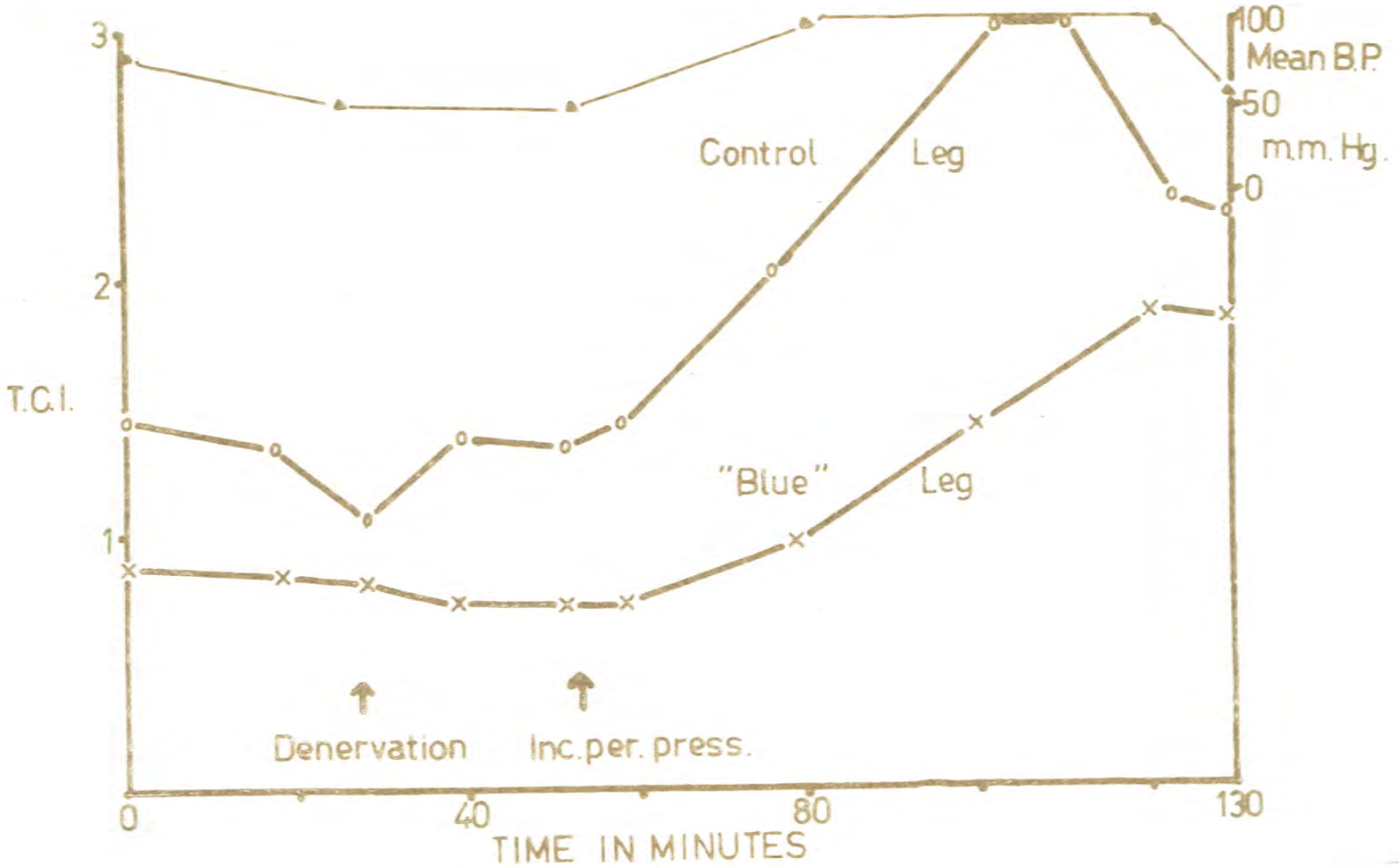
Abbreviations :

T.C.I. "Thermal circulation index".

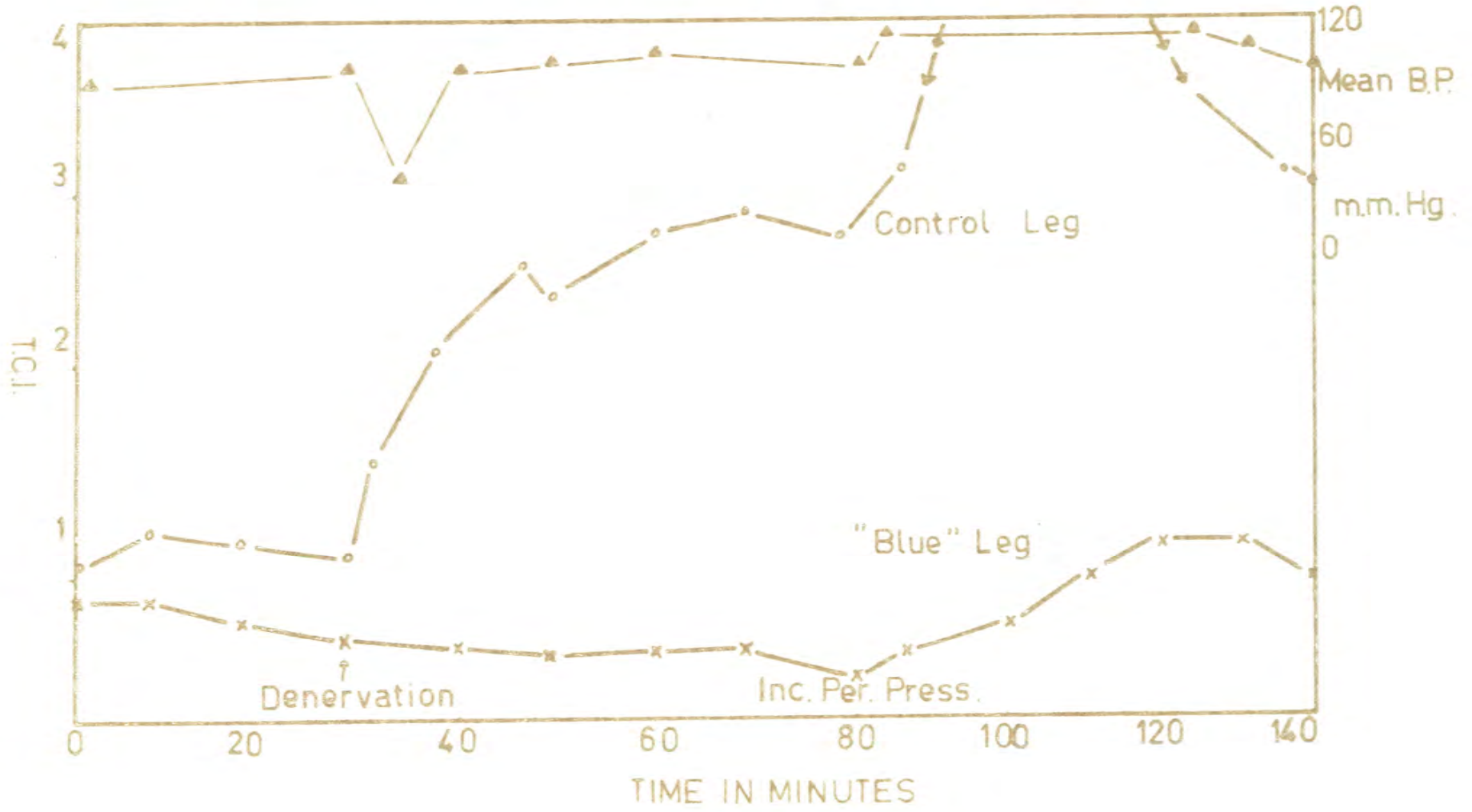
Inc. per. pres. - increase of perfusion pressure of 30 mm. Hg.


Exp. 1.
1
100
Mean B.P.
m.m. Hg.
0
Control Leg
T.C.I.
0·5
"Blue" Leg
Denervation
Inc. per. press.
0
40
80
120
150
TIME IN MINUTES

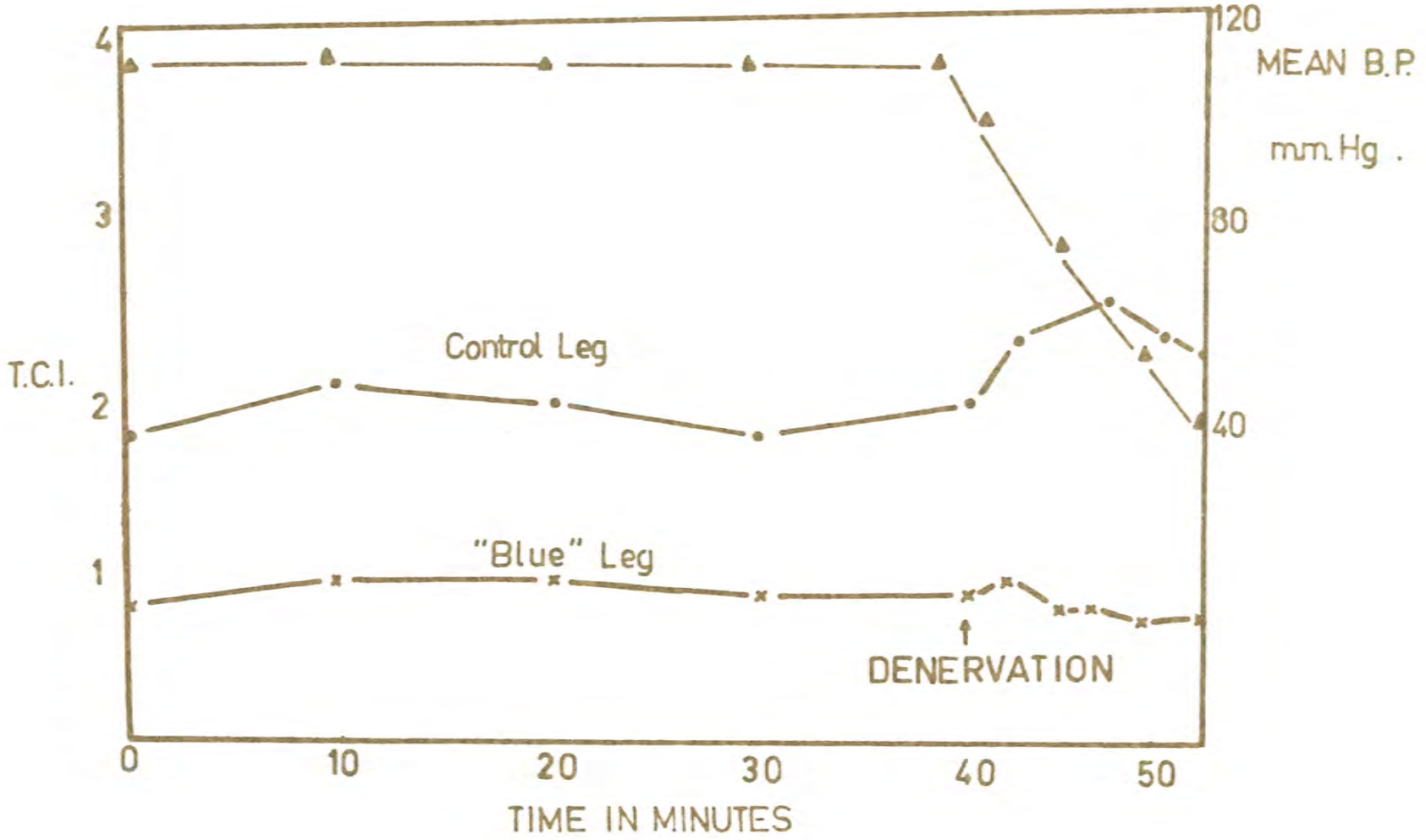
Exp. 2.


3
2
1
T.C.I.
100
Mean B.P.
50
m.m. Hg.
0
Control Leg
"Blue" Leg
Denervation
Inc. per. press.
0
40
80
130
TIME IN MINUTES

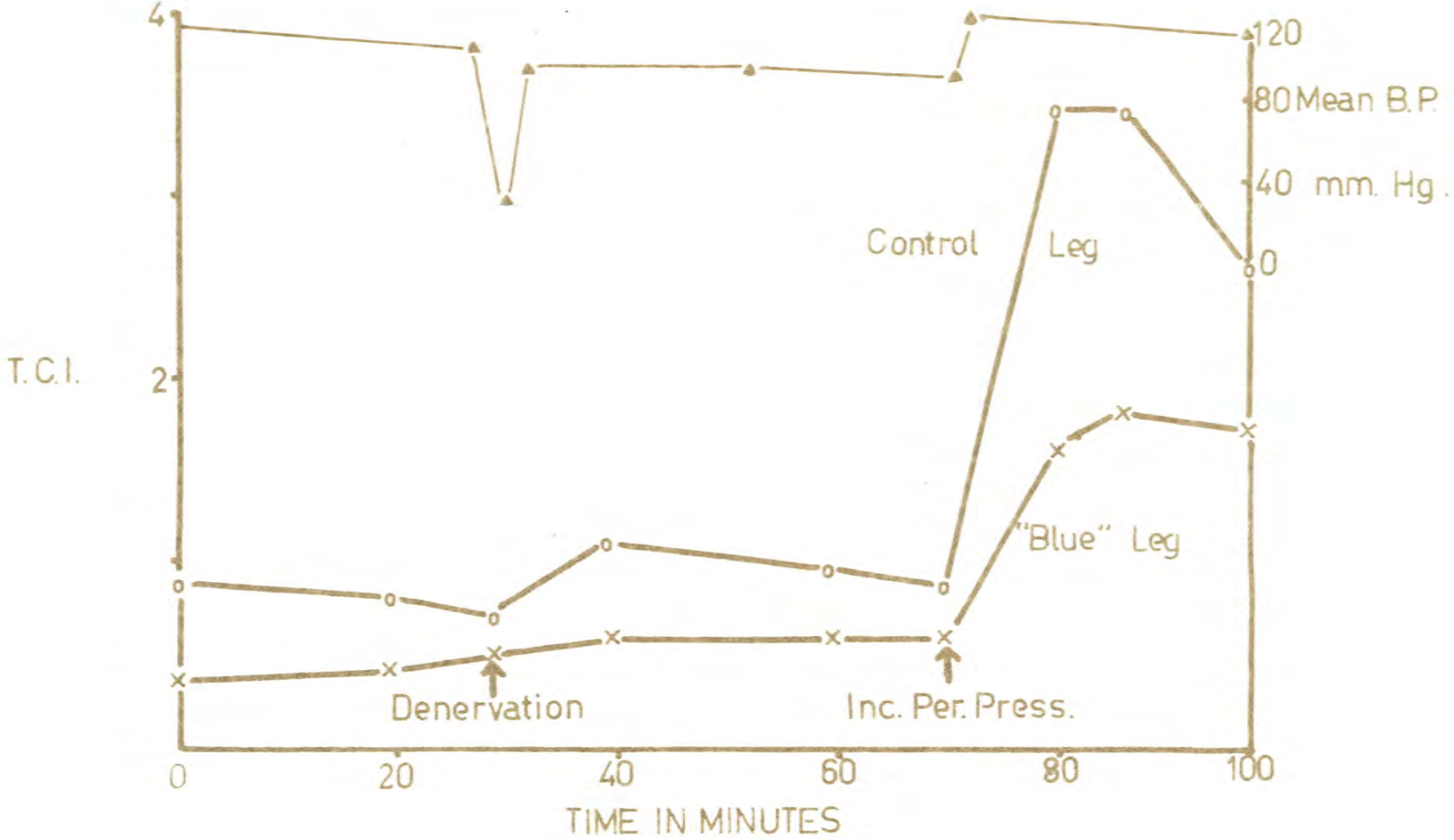
Exp. 3.


4
3
2
1
T.C.I.
120
Mean B.P.
60
m.m. Hg.
0
Control Leg
"Blue" Leg
Denervation
Inc. Per. Press.
0
20
40
60
80
100
120
140
TIME IN MINUTES

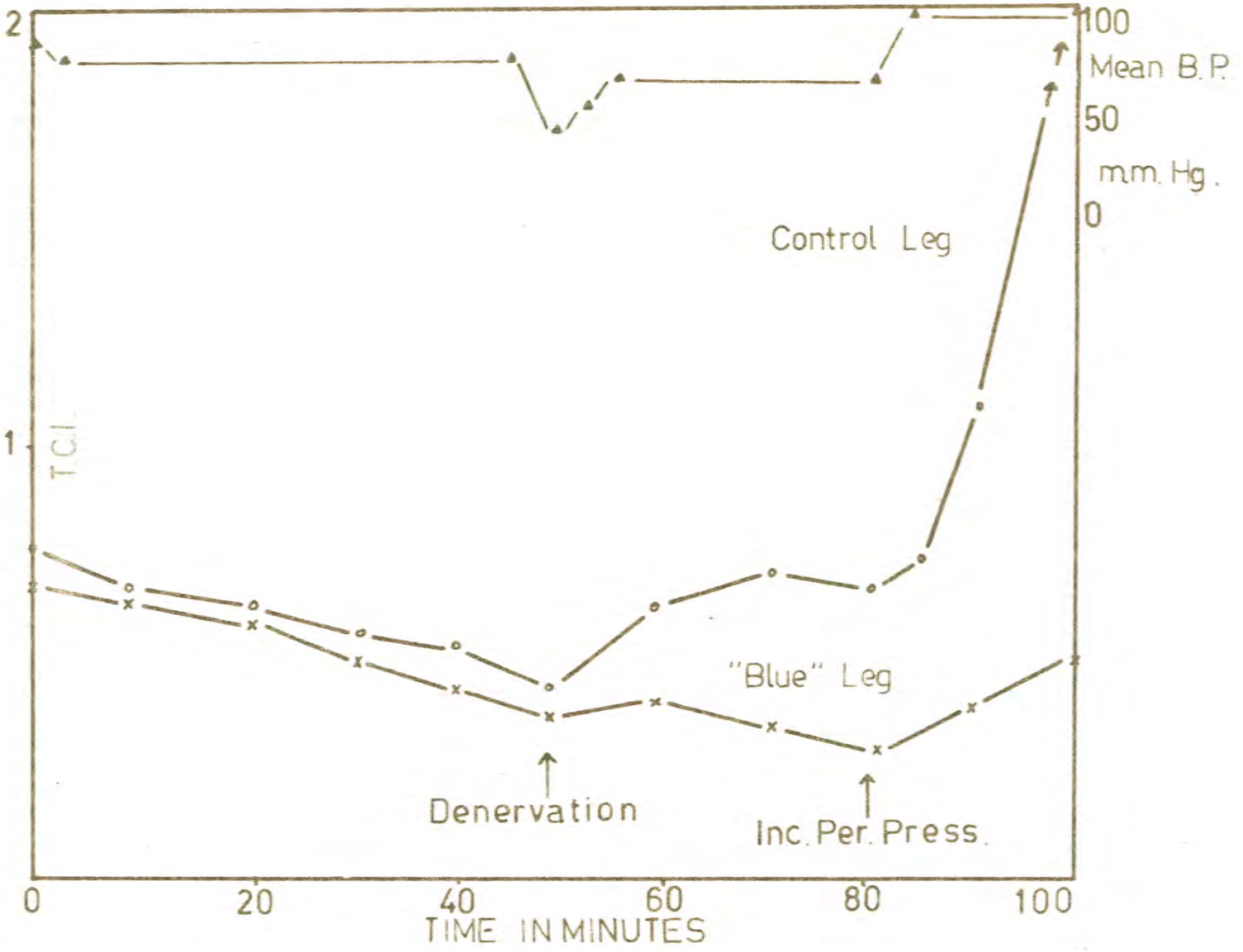
Exp. 4.


4
3
2
1
T.C.I.
120
MEAN B.P.
mm. Hg .
80
40
Control Leg
"Blue" Leg
DENERVATION
0
10
20
30
40
50
TIME IN MINUTES

Exp. 5.


4
2
T.C.I.
120
80 Mean B.P.
40 mm. Hg.
0
Control Leg
"Blue" Leg
Denervation
Inc. Per. Press.
0
20
40
60
80
100
TIME IN MINUTES

Exp. 7


2
1
T.C.I.
100
Mean B.P.
50
m.m. Hg.
0
Control Leg
"Blue" Leg
Denervation
Inc. Per. Press.
0
20
40
60
80
100
TIME IN MINUTES

APPENDIX 6.

STATISTICAL METHODS.

(a) Whether a mean result differed significantly from the zero or resting level was decided as follows :-

The variance of the sample $S^2 = \frac{\Sigma(x - \bar{x})}{N-1}$ is calculated.

The variance of the mean $S^2_{\bar{x}} = \frac{S^2}{N}$

The S.D. of the mean $S_{\bar{x}} = \sqrt{\frac{S^2}{N}}$

$$t = \frac{\bar{x}}{S_{\bar{x}}}$$

Probability (p) corresponding to the calculated value of t was taken from "Statistical Tables for Agricultural, Biological, and Medical Research" (1953) R.A. Fisher and F. Yates (Oliver and Boyd : Edinburgh).

(b) The significance of the difference of two means was calculated as follows :

The common variance of the samples is calculated

$$S^2_{x^1} = (\Sigma x^2 - \bar{x}\Sigma x) + (\Sigma x1^2 - \bar{x}1\Sigma x^1)$$

The S.D. of the difference of the means S.D. =

$$\sqrt{\frac{S^2_{xx}1}{N} + \frac{S^2_{xx}1}{N1}}$$

$$t = \frac{\bar{x} - \bar{x}^1}{S.D.}$$

Probability (p) is derived from the tables as before.