2. "Premature Birth" as a Subject for Research

The issues so far discussed are related to administrative procedure, and have their main application in countries where many deliveries occur at home. Of even wider significance is the identification of birth weight with maturity for the purposes of investigation, which has resulted in an extensive literature ostensibly devoted to the subject of "prematurity."

From the point of view of effective research any convention is unfortunate which obscures differences by dealing collectively with problems which are different in origin. No doubt at an earlier stage in our knowledge it was worth recording certain observations on all stillbirths, or on all congenital malformations; but the day is past when anything useful can be added by investigations which fail to distinguish the separate issues which these terms embrace. The same considerations apply, *mutatis mutandis*, to the subject of "premature birth."

As an administrative device the use of weight as an index of maturity has the advantages and disadvantages to which we have referred; as a means of identifying an entity suitable for inquiry it could hardly be less satisfactory. From the point of view of the investigator interested in the aetiology of stillbirths and infant deaths, it is hard to see that any useful purpose is served by a convention which brings together such completely different subjects as congenital malformations, multiple births, toxaemia of pregnancy, trauma, induction of labour, and early onset of labour of unexplained origin. For it is deceiving oneself to suppose that progress can be made in prevention of "premature birth" due to congenital malformations, except through prevention of congenital malformations. This possibility is not yet in sight, but it can be delayed only by a practice which groups malformations with other causes of death. Similarly the early onset of labour in multiple pregnancies is an observation of considerable biological interest which will not be advanced without separate study of multiple births. Moreover, the confusion of these problems has diverted attention from cases in which the early onset of labour is unexplained, and is hence still the matter of primary interest.

What has been explored in the literature as "premature birth" is the subject of low birth weight; it is hardly surprising that investigation has not been particularly fruitful. If the administrative proposals made above, or some modification of them, commend themselves to clinicians, the research worker need have no regrets if the present conception of "premature birth" were abandoned. He could then return to the study of late foetal development and its relation to the duration of gestation. On this important issue we have as yet very little worth-while evidence.

Summary

Birth weight, duration of gestation, and the history of survival are recorded for 16,749 single births in Birmingham during 1947. The data are used to give: (1) The distribution of "premature births" by duration of gestation. More than half were delivered later than the end of the 37th week and about one-third later than the end of the 39th week. (2) The proportion of births "premature" in different weeks of gestation. (3) The percentage of births stillborn or dead within one month of birth related (*a*) to birth weight, and (*b*) to duration of gestation. It is shown that mortality is so closely associated with both birth weight and duration of gestation that there is little to choose between them as indices of the probability of survival.

The conception of "premature birth" is discussed in the light of these observations, which are used to suggest for consideration a possible modification of administrative procedure as follows. (1) Mothers in whom the onset of labour occurs more than four weeks before the expected date should be admitted to hospital. (2) Live-born infants born at home should be admitted to hospital if they weigh less than 4 lb. (1.8 kg.) at birth.

The effect of these proposals is exhibited on the Birmingham data. The first would have resulted in the admission of an additional 200 mothers (just over 1% of 16,749), whose confinements were in weeks in which the risk of stillbirth or foetal death is about one in three. It is suggested that these vulnerable births should have a high priority for institutional delivery, as nearly half of all deliveries in the city were in hospital, and the incidence of death (stillbirth or neonatal) in all hospital births was only one in twenty.

The operation of the first proposal would have reduced the number of births under 4 lb. (1.8 kg.) delivered at home by about three-quarters.

We are greatly indebted to Dr. Jean Mackintosh and her colleagues in the City of Birmingham Maternity and Child Welfare Department for the facilities which they have placed at our disposal.

REFERENCES

Hosemann, H. A. (1948). *Arch. Gynäk.*, **176**, 109.
McKeown, T., and Gibson, J. R. (1951). *Brit. J. soc. Med.*, **5**, 98.
Ministry of Health (1949). Report for the year ended March 31, 1949. London.
Ylppö, A. (1920). *Z. Kinderheilk.*, **24**, 1.

THE NATURAL HISTORY OF VENOUS THROMBOSIS

BY

C. RAEBURN, M.R.C.S., L.R.C.P.
Assistant Pathologist, Central Histological Laboratory, Whittington Hospital

[WITH SPECIAL PLATE]

In 1856 Virchow described the mechanical effects of embolism; in 1889 Cohnheim showed that injury to vascular endothelium was favourable, if not essential, to thrombosis; and in 1909 Aschoff discussed the possible influence of eddies in the blood stream. Belt, in 1934, ruled out inflammation as a frequent cause of thrombosis and put pulmonary embolus into its correct category as a medical rather than a surgical complication. These are the milestones of a century in which the accumulated knowledge on the subject might be summarized as: if the venous endothelium is damaged then thrombosis and embolism may occur. It is a philosophical aphorism that when a problem is accurately stated the solution is near to hand. The purpose of this paper is to analyse the natural history of thrombosis so far as is possible by the histological method—a most neglected field—and so to endeavour to close, if only in a minute degree, the vast chasm between our knowledge and our control of a complication which so often kills those who might otherwise recover.

When a student I was taught that thrombosis and embolism were usually surgical complications, but very little observation was required to show that this conception was false and that they were in most cases associated with medical conditions such as congestive heart failure.

As a pathologist I very much doubted whether the concept of acute massive thrombosis was as simple as it seemed. A survey of the literature showed that all workers had neglected the histology of the venous system, apparently because signs of inflammation were unusual. They completely overlooked the obvious fact that the appearances of a thrombus at any given time are determined by its historical evolution. However ordinary may be the aspect, every thrombosed vein must bear the evidence of past history and, within limits, the future progress may be deduced. Accordingly in 130 consecutive unselected necropsies the venous system was carefully examined, with special reference to the main leg veins and their intramuscular tributaries. The necropsies were those of a general hospital with a preponderance of elderly patients; consequently only three were aged 40 or under, and the youngest was aged 12.

Technique

A brief account of the technique adopted is required. In addition to the routine complete necropsy the axillary, pelvic, and femoral veins were carefully examined and the calf muscles and posterior tibial vessels were excised and sectioned after a preliminary overnight fixation in formol–saline to secure cohesion of the muscle fibres. Blocks of muscle for histological examination were taken in all cases and when gross thrombi were present the firm adherent portions were sectioned and also any apparently thickened areas of vein. Cross-sections of the soleus muscle were taken for examination of the small intramuscular veins. In a few instances the deep veins of the foot were examined and thrombi were found, but as they presented no special features the main investigation was confined to the veins of the leg. Control blocks were also taken from the pectoralis major, deltoid, and triceps muscles. Sections were stained by haematoxylin and eosin, iron haematoxylin, and van Gieson, and in some instances by phosphotungstic-acid/haematoxylin and by Wilder's silver impregnation method. When necessary, serials were examined to exclude the possibility of misinterpretation of tissue included in the angle of confluence of venous tributaries.

The macroscopic findings and percentages are close to those of other workers. In 130 necropsies thrombosis of the veins of one or both legs was present in 35 (26.9%), massive pulmonary emboli were found in 13 (10%), and lesser emboli in 7 (5.5%). Any embolus (or emboli) estimated to occlude one-third of the total pulmonary circulation was considered massive.

The histological appearances were much more significant, and, so far as I know, have not previously been recorded. Of the 35 examples of venous thrombosis 19 (54.2%) showed evidence of recurrent thrombosis, and 12 of these had given rise to embolism. In the remaining 16 instances there was no evidence of previous thrombotic attacks, and in this group 8 had shed emboli. Of the 13 massive emboli 8 came from sites of recurrent thrombosis.

Histological Criteria

The concept of acute thrombosis in the generally accepted form was obviously erroneous, since in most instances it described only the final event in a series which occupied a period of anything from weeks to years. This is of the greatest importance in our approach to treatment, but before the thesis can be accepted the histological criteria must be discussed in detail and the relationships and potentialities of endothelium and connective tissue considered.

The first problem is the age of the thrombus. That can be investigated by the study of tissue related to surgical incisions and by serial biopsy of the organizing clot in traumatized and ligated veins, but this bears no relation to the conditions usually prevailing inside a vessel. Authoritative opinions confine themselves to such statements as "white thrombus is older than red" and "white thrombus is formed in a rapid stream, red thrombus in a sluggish flow." There is some truth in both statements, but as generalizations they are untrue. In the arterial stream the mechanical conditions are such that thrombi can be built up only by slow continuous deposition in the form of a thin lamina which rapidly loses its cellular content, and so white is the prevailing colour. Organization is slow and endothelization of the surface is rarely demonstrable, though Duguid (1948) believes that atheromatous plaques may be formed in this way. In the heart, where the different mechanics of a large cavity and muscular contraction operate, organization is often extremely slow and the approximate duration may be known if it dates from clinical infarction. In veins the coagulum may remain macroscopically red until organization is widespread though irregular; isolated parts whiten probably from exposure to the remaining venous current. Organization certainly proceeds rapidly where the thrombus is adherent to the vein wall, and fibroblastic invasion occurs within four days, while endothelium spreads from the vein over the contiguous surface of the clot. If unchecked, this process continues to eventual organization and recanalization; but initially there is an unstable equilibrium, and a breakdown may result in spread of the thrombus and possibly embolism. There is then no means of accurately dating a thrombus, but extensive organization is evidence of a duration of at least weeks, and, more important, if successive and superimposed layers of organization can be demonstrated then the history is carried much further into the past.

The main histological findings in the intramuscular leg veins, in so far as time is a factor in their production, may be considered under three headings: (1) Early thrombotic lesions (Plate, Figs. 1–3); (2) intermediate organizing lesions (Figs. 4–6); and (3) residual fibrotic lesions (Figs. 7 and 8).

Early Lesions

Figure 1 (Special Plate) is a particularly fine example of the earliest demonstrable thrombus arising as a polyp, about 1.3 mm. in size, from a fibrous and vascularized area in the wall of an intramuscular vein. It is completely covered by endothelium, and organization is mainly peripheral and not confined to the base. The central portion consists of red cells and fibrin. Such lesions may be roughly spherical nodules or may extend as "candle gutterings" along the vein wall. As might be expected, agonal thrombus is often present in these situations.

Fig. 2 shows a lesion based on a fibrotic area in the vein and partially covered by endothelium. The thrombus extended into the main leg veins.

Fig. 3 represents an unendothelized mass of thrombus based on a fibrotic area of vein and extending into the main veins. There is slight basal organization, and pigment-laden macrophages are numerous.

C. RAEBURN: NATURAL HISTORY OF VENOUS THROMBOSIS

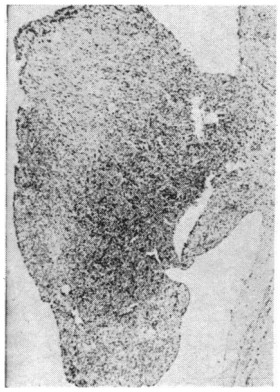


FIG. 1.—Thrombus on scar in wall of intramuscular vein. Covered by endothelium; basal and peripheral organization. Central mass of red cells. (H. and E. ×40.)

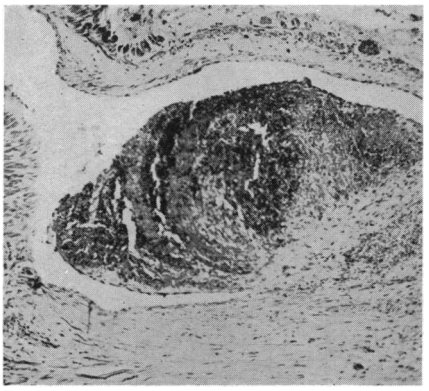


FIG. 2.—Partially endothelized thrombus from a fibrotic area in vein wall. Slight peripheral organization overlying main mass of red cells and fibrin. (H. and E. ×50.)

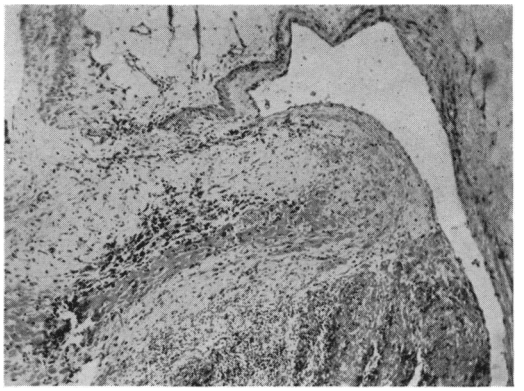


FIG. 3.—Thrombus arising from a scar in the vein wall. Note the breach in the media and basal organization. Endothelium has spread a short distance on to the thrombus. (H. and E. ×60.)

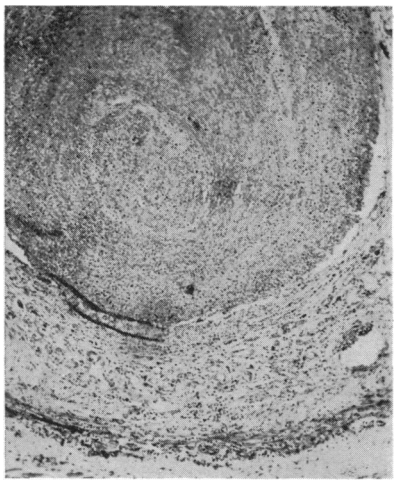


FIG. 4.—Vein lined by granulation tissue, product of fusion of intima with organizing thrombus. Recent thrombus in lumen. (H. and E. ×50.)

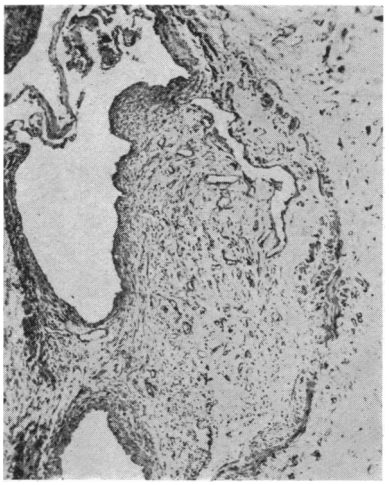


FIG. 5.—An advanced stage of re-establishment of venous channels. (H. and E. ×55.)

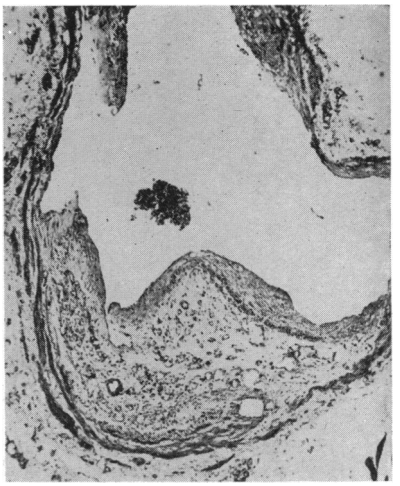


FIG. 6.—The final stage in organization of a small discrete thrombus: a vascular and fibrous nodule with a superimposed lamina of organizing thrombus—a second thrombotic sequence. (H. and E. ×55.)

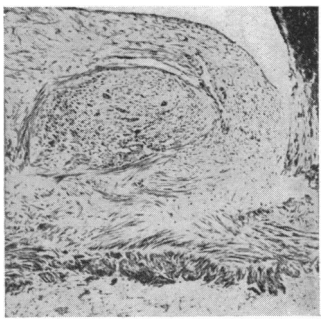


FIG. 7.—Successive zones of thrombosis and organization. (H. and E. ×45.)

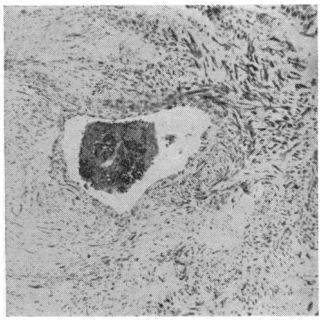
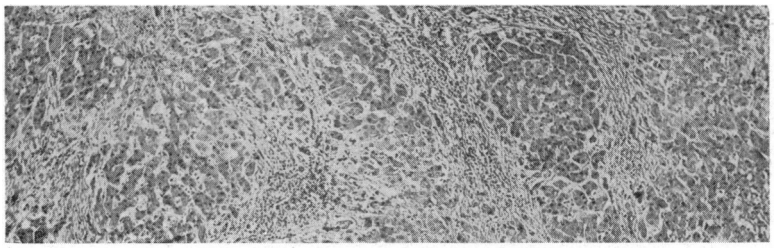
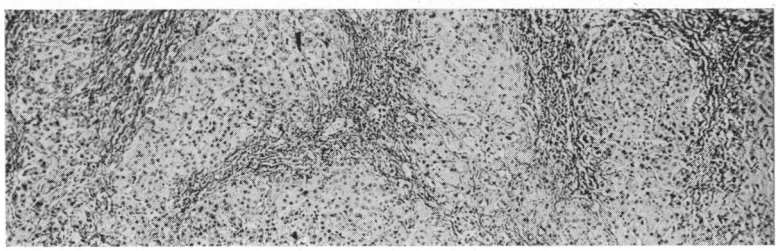


FIG. 8.—Concentric zones of fibrosis indicating three throm-

T. S. L. BESWICK AND H. BUTLER: FATAL HAEMATEMESIS



A



B

FIG. 1.—Low-power views of sections of the liver showing the irregular sheets of regenerating liver tissue. (A) Stained with haematoxylin and eosin. (B) Stained

The important features of this group are: (*a*) The thrombi are more or less covered by endothelium and endothelization precedes organization, except, possibly, in the basal area. (*b*) The lesions are based on previously damaged areas of vein wall as shown by focal muscular atrophy and fibrosis and vascularization of the intima, which may become almost angiomatous in appearance. (*c*) A study of endothelial and fibroblastic proliferation and capillary formation in such a relatively simple histological field affords visual evidence of the identity of fibroblast and endothelial cell. (*d*) The cell pattern suggests that fibroblasts migrate from the basal area peripherally until the surface is reached. Under the impact of a new environment they undergo modification and become endothelial cells. If a new thrombosis occurred fibroblastic potentialities would be reassumed by the surviving cells. Succeeding fibroblasts orientate themselves deep to the endothelium and account for the early peripheral organization.

The simplifying concept of cellular pluripotentiality is widely recognized by histologists, but application to pathological histology has been neglected; hence the persistence of such mythical tumours as the "endothelioma."

Intermediate Lesions

When a layer of mural thrombus in a small vein is able to organize completely the appearances are those seen in Fig. 4. The intima has become vascularized and blended with the organized thrombus, and superimposed on this zone of granulation tissue is recent thrombus. The muscularis has atrophied. The last stage in this phase is a spongy and relatively acellular granulation tissue completely filling the vein. The changes from now on are atrophic and consist of further loss of cellularity, increasing collagenization, and necrosis of connective-tissue partitions so that larger vascular channels are formed (Fig. 5).

Fig. 6 illustrates the end-result in a small discrete thrombus: a raised vascular nodule incorporated in the vein wall upon which is superimposed a layer of more recent organizing thrombus, while agonal clot is present in the lumen. This would be the optimum end-result of the lesion illustrated by Figs. 1 and 2.

Residual Lesions

Fig. 7 is a slightly oblique section through a vein of about 2 mm. diameter. The fibrosed muscularis extends transversely at the lower part of the photomicrograph, and internally are successive zones of organization and recanalization, representing two thrombotic sequences, and, finally, early organization of the recent thrombus, seen on the right-hand side.

Fig. 8 is a similar lesion showing concentric rings of fibrosis in a vein of the same size. The remains of the muscularis are visible on the upper right-hand side. The most cellular and most recent zone of fibrosis is towards the lumen. Excluding the plug of recent thrombus, which is not adherent at this point, there is evidence of three sequences of thrombosis and organization.

Other Findings

The other histological components of muscle can be dealt with briefly.

Nerves.—These show no histological abnormality.

Arteries.—Occasionally intimal fibrosis and atheromatous lesions occur in the larger vessels.

Muscle Fibres.—Invariably oedema, and occasionally diffuse fibrosis and myodegeneration, are present. In one instance there were areas of myodegeneration progressing to necrosis but without cellular reaction, and therefore probably a terminal happening. In another instance there was a focal interstitial myositis of the soleus muscle. The cells are mainly lymphocytes with a few plasma cells, and are grouped round dilated capillaries. The included muscle fibres are basophil-staining and show multiplication of sarcolemma nuclei, suggesting that the cellular infiltration is primary and a stimulus to proliferation. There is no myodegeneration.

One negative finding is of aetiological importance. Thrombosis does *not* occur in veins of a diameter of less than 1 mm. approximately—that is, in veins which are freely anastomotic and without valves.

Lesions were not found in the control sections of muscle from the upper extremity.

Discussion

Certain undisputed facts concerning the initiation of thrombosis have been well known since the days of Virchow and Cohnheim, but the unfortunate pre-eminence ascribed to surgery has been allowed to dominate their critical assessment. The prime cause of thrombosis is simple confinement to bed, particularly in the case of elderly people, and the only way in which surgery contributes to the incidence is by fulfilling this condition and by adding to it other factors conducing to venous stasis, such as immobilization of the leg or restriction of abdominal respiration. In the series here considered many were aged and the clinical notes were not very detailed, so that reference to previous lengthy confinements to bed was not always possible, though obviously such periods are a probability in a long life; it is of interest, however, that of three of the youngest (aged 47, 32, and 12) two (those aged 47 and 32) had a history of duodenal ulcer and several spells of bed treatment, and two (those aged 47 and 12) had rheumatic cardiac lesions. Chronic right heart failure was present in 9 of the 35 examples of venous thrombosis.

Venous stasis, whether due to immobility and muscular atrophy or to right heart failure, or to a combination of these factors, is the most important of the local phenomena, and may, I believe, in itself initiate thrombosis, provided that the metabolism of the vascular endothelium is disordered. I deliberately reject the word "injury" because it suggests necrosis and loss of surface—a venous ulcer as the basis of thrombosis. This is a quite unnecessary postulate. Cohnheim's original statement in 1889 that "as long as the endothelium is intact and performs its function normally the blood will remain fluid in the vessels" has two gross inaccuracies in that it postulates loss of surface and, as he subsequently makes clear, it embodies a teleological concept—the specific dynamic, antithrombotic property of endothelial cells. His second dictum, that "stasis alone cannot induce thrombosis," has been tacitly accepted, and constitutes a bar to progress, as it is quite obvious that congestive heart failure is a great source of damage to all epithelial cells and there is no reason to suppose that endothelial cells are unscathed, though our histological technique may be inadequate to detect the cytoplasmic changes. As an example, albuminuria is not necessarily accompanied by any visible change in the renal epithelium.

Can we, then, explain the formation of thrombus on any particular place in the vascular lining? Trauma must be allowed as a minor cause. Needle puncture

must always cause a minute lesion, and this may in favourable, but fortunately rare, circumstances spread. Sepsis is an occasional and special cause, and need not be considered here. If the veins are engorged and the valves are still efficient strong muscular contraction could produce a great rise in intravenous pressure and cause a tear at the valve commissures. By forcible injection of gelatin containing brilliant green at arterial pressure I have sometimes produced such lesions in the cadaver. At the site of rupture the dye stained the intima. Drinker, Wislocki, and Field (1933) have recorded that the pressure in the afferent lymphatics of the popliteal area of a dog is *nil* at rest but up to 25 mm. of mercury with passive motion. There is at present no means of estimating intramuscular lymphatic or venous pressure during active movement. Certainly thrombosis seems to be confined to veins with valves, but again there is no need to postulate more than a point of biochemical weakness. In the smaller valveless veins the blood is capable of movement by anastomotic channels, and the tissue oxygenation is therefore better.

Platelet adhesiveness has somehow been assigned a causative function, but it is merely a part of the mechanism of the thrombotic reaction and not the prime cause. If, however, we can show that the intimal surface becomes adhesive when biochemically abnormal then the process is readily explained, as two sticky objects will be in contact.

It is well known that collagen is markedly adhesive, as may be shown by spreading and drying areolar tissue on a slide. Day (1947) has demonstrated that this adhesiveness is a property of the cement substance binding the collagen fibres, and it is this substance which undergoes a partially reversible sol–gel reaction if it is treated first with weak acid and then with saline. Vascular endothelium is in direct contact with underlying collagen fibres and, moreover, is derived from the fibroblast. In any granulation tissue fibroblasts can be seen arranging themselves to form vascular channels. The endothelial cell is merely a fibroblast which has assumed new properties in virtue of its position on a surface.

A crude experiment demonstrates the adhesiveness of the underlying collagen. Take two segments of vein or artery—and artery is better because of the added rigidity and thickness—and open them carefully so as not to damage the endothelium. Wash with saline, scratch the centre of one piece with a needle, then press both, intimal surface downwards, on a smooth clean glass surface. Dry off in the incubator overnight and then test the attachment of both portions. The unscarified portion will have detached itself, or will at most be lightly adherent, while the scarified piece will be firmly adherent at the point of damage. This is due to exposure of collagen and local release of the intercollagenous cement substance.

I suggest that biochemical changes in the endothelium allow permeation of this cement substance or that the endothelial cell itself, in virtue of inherent fibroblastic potentials, becomes adhesive, and that this is the primary vascular defect upon which platelet thrombus forms. (If the endothelium be removed from an atheromatous nodule in an artery the exposed necrotic material is intensely adhesive.)

It remains to explain why thrombosis rarely occurs in sites such as the arm. The pelvic and gluteal veins are fairly often thrombosed, but these may be regarded as part of the lower extremity. Thrombosis of the arm veins, when it occurs, is always associated with trauma, sepsis, neoplastic compression, or rigid immobilization. The additional factor required to induce and propagate thrombus is immobility and associated muscular atrophy, which encourages the local oedema and tissue circulatory failure. This factor is present in some degree during any lengthy period of rest in bed, but the arms, throughout the most severe illness, are kept moving almost to the time of death. As a corollary to this, any limb thrombosis is a great rarity in infants, for at that age all four limbs are kept in motion. The only thromboses that I have encountered in the legs of infants were associated with surgical procedures and immobilization of the limb.

The entire process can now be presented in chronological order. The physico-chemical state of the endothelial cell is affected by general or, in some instances, local modification of the blood and tissue fluids and responds by an alteration of surface tension in the direction of adhesiveness. Platelet and red-cell thrombus forms, usually at a great number of points, in the intramuscular and main leg veins. If conditions are unfavourable to the propagation of thrombus these lesions endothelize and organize, and are finally represented by a fibrotic nodule containing large capillaries and a few pigment-laden phagocytes—a common finding in sections of leg veins. If conditions are favourable the thrombus spreads and coalesces with similarly formed thrombi. The third possibility is alternating quiescence and spread as endothelization waxes and wanes in response to the necessary chemical stimuli. From the histological evidence it is probable that a scar in the vein wall is commonly the starting-point of a later thrombotic event.

Embolism becomes an increasing probability as the thrombus increases in size and tends to lie free in the large veins. When this stage is reached the only possible mode of healing is by the establishment of adhesions and by subsequent peripheral organization.

Summary

Histological evidence shows that of thromboses discovered at necropsy 54.2% are built up by successive thrombotic sequences. If the histological criteria of recurrent thrombosis are accepted it will be recognized that error must be in the direction of omission, as it is impossible to examine in detail the entire microvenous system of the leg muscles.

The thesis is therefore advanced that in most instances venous thrombosis in the leg is a chronic additive process and not, as is generally accepted, an acute disorder. The essential lesion is considered to be a modification of the colloid properties of groups of endothelial cells which encourages platelet adhesion.

My acknowledgments are due to Dr. H. Loewenthal, Director of the Pathological Laboratories at Chase Farm Hospital, where the major part of the work was carried out; to Dr. A. B. Bratton, of the Central Histological Laboratory, for enabling me to complete the work; and to Mr. G. W. Moore for the photomicrographs.

REFERENCES

Aschoff, L. (1909). *Med. Klinik.*, **5**, 1702.
Belt, T. H. (1934). *Amer. J. Path.*, **10**, 129.
Cohnheim, J. (1889). *Lectures on General Pathology*, **1**, 172. Translated by A. B. McKee. New Sydenham Society, London.
Day, T. D. (1947). *J. Path. Bact.*, **59**, 567.
Drinker, C. K., Wislocki, G. B., and Field, M. E. (1933). *Anat. Rec.*, **56**, 261.
Duguid, J. B. (1948). *J. Path. Bact.*, **60**, 57.
Virchow, R. (1856). *Virchows Arch.*, **10**, 225.