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The Pathological Basis and Microanatomy of Occlusive Thrombus Formation in Human Coronary Arteries [and Discussion]

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The pathological basis and microanatomy of occlusive thrombus formation in human coronary arteries

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[Plate 1]

Myocardial necrosis, usually called infarction, occurs in different patterns. A common form is necrosis of one segment of the left ventricle, i.e., anterior, septal, lateral or posterior. This regional infarction is consistently associated with an acute occlusive thrombosis of the artery supplying that region. Diffuse necrosis involving the whole circumference, usually the subendocardial zone, of the ventricle is not consistently associated with thrombi. Occlusive thrombi identified in post-mortem coronary arteriograms have been reconstructed in their entirety from serial sections at 150 μm intervals. Most occlusive thrombi were found to be associated with a dissection track into the intima at an atheromatous plaque. The break into the plaque usually extended over several millimetres, often in spirals, so that a mass of thrombus within the plaque compressed the original lumen. Previous accounts of plaque rupture or cracking greatly underestimated the magnitude of the dissection of blood into the intima.

The exact role of coronary thrombosis in producing the clinical features of ischaemic heart disease has been uncertain. The incorporation of microthrombi into the surface cap of atherosclerotic plaques almost certainly contributes to their slow growth towards the horizon for clinical expression of disease. Much larger thrombi form on plaques and occlude the arterial lumen as a sudden event to precipitate myocardial necrosis. This paper is concerned with the latter type of occlusive thrombus.

A historical review of pathological observations linking the finding of an occlusive thrombus to an area of myocardial necrosis reveals such variation that two opposing interpretations have emerged (Davies *et al.* 1979). One proposes that an occlusive thrombus is the cause of myocardial necrosis in the region supplied by the artery (Chapman 1974; Chandler 1974; Davies *et al.* 1976). The other is that myocardial necrosis is not related consistently to occlusive thrombi and that thrombosis is a secondary process in arteries in which flow is reduced (Silver *et al.* 1980; Roberts 1972, 1974). The observations are so discordant and their interpretations so opposed that explanations have been found in differences of definition and case selection. Many publications define the terms myocardial necrosis and infarction differently. Definitions of infarction range from a macroscopic area of necrosis several centimetres across and confined to one region of ventricular muscle, to microscopic foci of necrosis scattered throughout the myocardium. Another type of infarction consists of macroscopic areas of necrosis involving the whole subendocardial zone of the ventricle.

A recent investigation of ours on the relation of patterns of necrosis to occlusive thrombosis has gone some way towards resolving the differences (Davies *et al.* 1979). Myocardial necrosis

was demonstrated in slices of heart by enzyme histochemistry. The technique increased the precision with which the margins of necrotic areas could be defined above that of simple visual inspection. Patterns of necrosis were classified into three groups; entirely regional, anterior, lateral or posterior; entirely diffuse, i.e. the whole circumference of the ventricle involved in a subendocardial necrotic zone; and complex mixtures of the other two patterns. There was a consistent association, namely in 70 of 71 cases, of regional infarction with occlusive thrombi. In contrast, diffuse necrosis was associated with widespread narrowing of the coronary arteries and not with occlusive thrombi.

Another major reason for the discrepancies has been a failure to distinguish between the terms sudden death and myocardial infarction. For myocardial necrosis to be demonstrable at autopsy the patient must survive at least 12 h after the onset of symptoms. When the patient survives only 6 h or less, infarction cannot be demonstrated. But it has been commonly assumed that an infarct would have been demonstrable after a longer period of survival. Clinical studies have now conclusively shown that patients who 'drop dead' and are resuscitated with instant defibrillation by emergency teams in an ambulance or on the street fall into two groups (Liberthson *et al.* 1974). Patients in the larger group do not develop any evidence, electrocardiographic or other, of myocardial infarction. Patients in the smaller group, about 25 %, develop myocardial infarction. Patients in the former, larger, group are now considered to have suffered from spontaneous ventricular fibrillation in an electrically unstable heart resulting from chronic ischaemia. Evidently the inclusion of such cases of sudden death without demonstrable necrosis will produce significantly lower figures of frequency of thrombi.

With the establishment of a constant association of regional infarction with occlusive thrombosis in the subtending artery, the microanatomy of the occlusive thrombi becomes of interest because it may throw light on the mechanisms of their formation.

Materials and methods

Twelve human hearts were studied in which acute regional infarction had been demonstrated by electrocardiography and the patient came to autopsy within a period of 2–5 days from the onset of chest pain. In all cases, strictly regional areas of myocardial necrosis were demonstrated by histochemistry of fresh slices of heart. The coronary artery orifices were cannulated and injected with a barium–gelatin suspension at pressures of less than 80 mmHg. The heart was X-rayed at 45 kV for 3.5 min, with the use of Industrex film. Then the coronary arteries were dissected free, decalcified in 10 % (by volume) acetic acid for 24 h, and X-rayed again. From these arteriograms the occluded segment was identified and removed intact. This arterial segment was cut serially at intervals of 150 μm into transverse sections 6 μm in thickness. The sections started proximal to the occlusion at a point where the barium outlined a normal luminal diameter and continued through the occlusion until the lumen was again patent. Each section was stained by a modified picro–Mallory trichrome method (Carstairs 1965), which differentiates red cells (stained yellow), fibrin (stained red), platelets (stained as purple punctate material) and collagen (stained light blue). The sections were projected and outline drawings made with a colour code for each type of tissue. Material was considered to be thrombus when it contained predominantly fibrin and/or platelets. From the series of transverse sections, the whole occluded segment of artery was reconstructed in longitudinal section.

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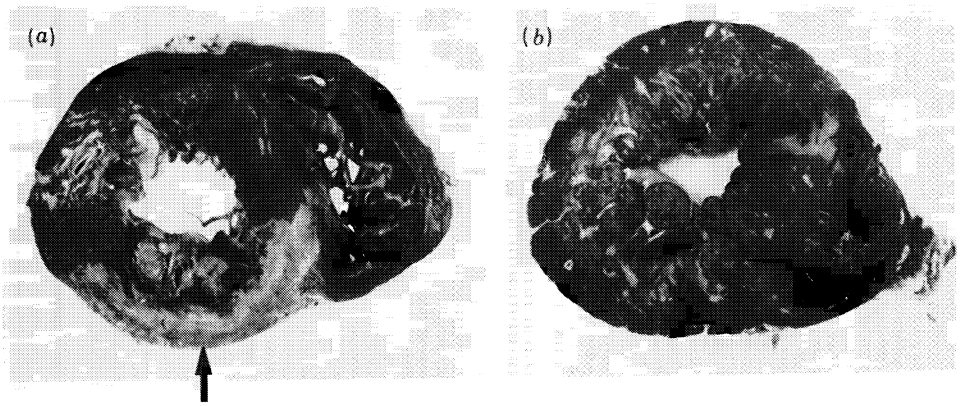

FIGURE 1. Transverse slice of human ventricular muscle stained to show succinic dehydrogenase activity (dark). In (*a*) an area of enzyme loss (pale) is confined to one region on the posterior wall (arrows) of the left ventricle. In (*b*) there are small focal pale areas throughout the whole circumference of the left ventricle.

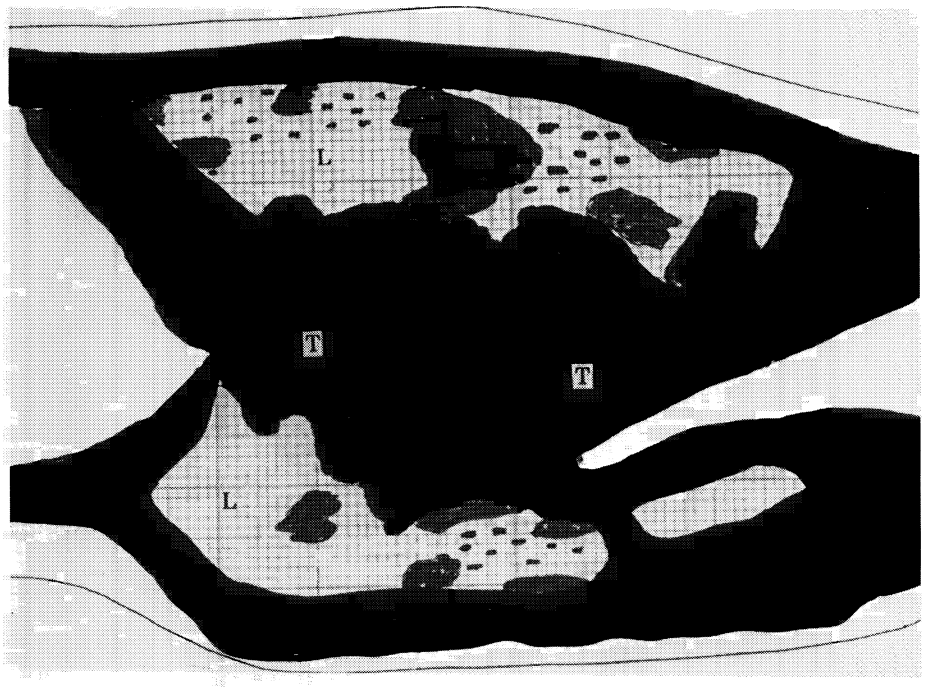

FIGURE 2. Reconstruction of a longitudinal section through an acute coronary occlusion. Thrombus (T) in the arterial lumen is in direct continuity with the lipid of the plaque (L) though numerous defects in the intima.

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Results

Twelve occlusive thrombi were reconstructed as described. Longitudinal sections of nine showed continuity between the thrombus occluding the lumen and thrombus deep within an atheromatous plaque. The breaks in the plaque cap allowing such continuity were often large, i.e. from 4 mm to about 15 mm long, and ran spirally along the artery. In three of the nine thrombi the barium proximal to the occlusion was continuous with that inside the plaque and could be identified in retrospect on the angiograms as a double lumen over several millimetres at the proximal end of the thrombus.

Thrombi deep within the atheromatous plaque extended proximally and distally from the tear into areas where on cross sections the plaque caps were intact. In two cases, lipid debris was extruded into the original lumen and admixed with thrombus distal to the tear. Thrombi in the vicinity of the tears and nearby in the plaques were rich in platelets. Thrombi extending proximally and distally in the arterial lumen were predominantly fibrin and red cells. Some thrombi had apparently increased the plaque volume, raising a flap of intima that narrowed the original lumen.

Three of the twelve occlusions had no demonstrable break in the intima underlying occlusive thrombi. These thrombi had apparently begun spontaneously at sites of gross stenosis and grown forward to the point of exit of a major branch.

Discussion

Cracking, fissuring or breakage of the cap of atheromatous plaques was proposed some time ago as an immediate cause of occlusive thrombosis (Friedman & Van Den Bovenkamp 1966; Constantinides 1966; Ridolfi & Hutchins 1977). Subsequent confirmation was hampered by random sectioning of occlusive thrombi, whereby the breaks were not found consistently. The present investigation establishes that sections proximal and distal to plaques can show thrombus in the lumen but no intimal break. Random sectioning will therefore greatly underestimate the frequency of such breaks and will, moreover, give no impression of the shape or size of the breaks when present. Our work shows that these breaks are larger than the microscopic fissures described previously. The associated thrombi extended deep into the plaques and occlusion was probably preceded by extensive passage of blood into and dissection of the intima. This process has been aptly likened to internal haemorrhage from the artery (G. V. R. Born, personal communication).

While the contribution of plaque rupture has been confirmed, there were cases in which it could not be demonstrated even by serial sections. This suggests an alternative initiation of coronary thrombosis, presumably through abnormalities in the blood flow through greatly narrowed arterial segments. The investigation reported here does not allow accurate assessment of the comparative frequency of the two causes, because the tedious technique restricted the number of reconstructions.

If plaque fissure and intimal dissection are frequent antecedents of occlusive thrombosis, it becomes important to determine what factors are responsible for the fissuring. The destruction that takes place in fissured plaques effectively rules out any morphological interpretation of events, but all were large plaques containing extensive pools of lipid. If rupture of a plaque were a random event in patients with only isolated lipid-rich atheromatous lesions, thrombosis

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may not occur again or at long time intervals, in keeping with the good prognosis of some patients who survive an acute myocardial infarction. On this assumption, patients with numerous lipid-rich plaques would run the risk of repeated episodes. Thrombosis without plaque fissure may be a manifestation of more diffuse coronary artery disease with widespread stenosis.

The microanatomy of the thrombi suggests that occlusion occurs over several hours or even 1–2 days. The initial crack allows blood to dissect the plaque with the formation of a platelet-rich thrombus, which may ultimately extend through the crack into the original lumen. From this occlusive platelet-rich thrombus, predominantly fibrinous thrombus extends proximally and also distally to the next major branch. This interpretation has been supported by evidence obtained from patients who were injected with radioactively labelled fibrinogen immediately after admission to hospital with chest pain (Erhardt 1976; Fulton & Sumner 1976). In those who came to autopsy, occlusive thrombi had no radioactivity in the centre, presumably where they originated in fissures, whereas the extensions in both directions were radioactive, presumably representing subsequent propagations.

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Discussion

J. McMichael, F.R.S. (2 *North Square, London NW*11 7*AA, U.K.*). This is an important demonstration of the complex situation at the site of occlusion. The contribution of mechanical damage is obvious and brings to mind steering wheel injuries, which can cause thrombosis of the arteries in the anterior wall of the heart. In more than 800 young men on military service who developed coronary occlusion, about one-third followed extreme physical exertion (Yater *et al.*, *Am. Heart J.* **36**, 334, 481, 683 (1948)). Jogging also has its mortality.

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P. D. Richardson (*Brown University, Providence, R.I., U.S.A.*). The authors have provided an excellent description of plaque rupture and associated thrombus formation in coronary arteries. It would seem worth while to investigate mechanical factors associated with plaque rupture as this appears to be the immediate cause of thrombus formation. Relevant mechanical factors are, first, the mechanical strength of the cap which preserves the integrity of the plaque and, secondly, the fluid dynamic stresses induced on the plaque by the pulsatile flow of blood in the artery. The stresses are determined by the frequency of pulsation as well as by the pressure. Consequently it would be interesting to investigate the role of heart rate as well as blood pressure as a risk factor for myocardial infarction. It would also be useful to obtain information about the mechanical strength of plaque cap material.

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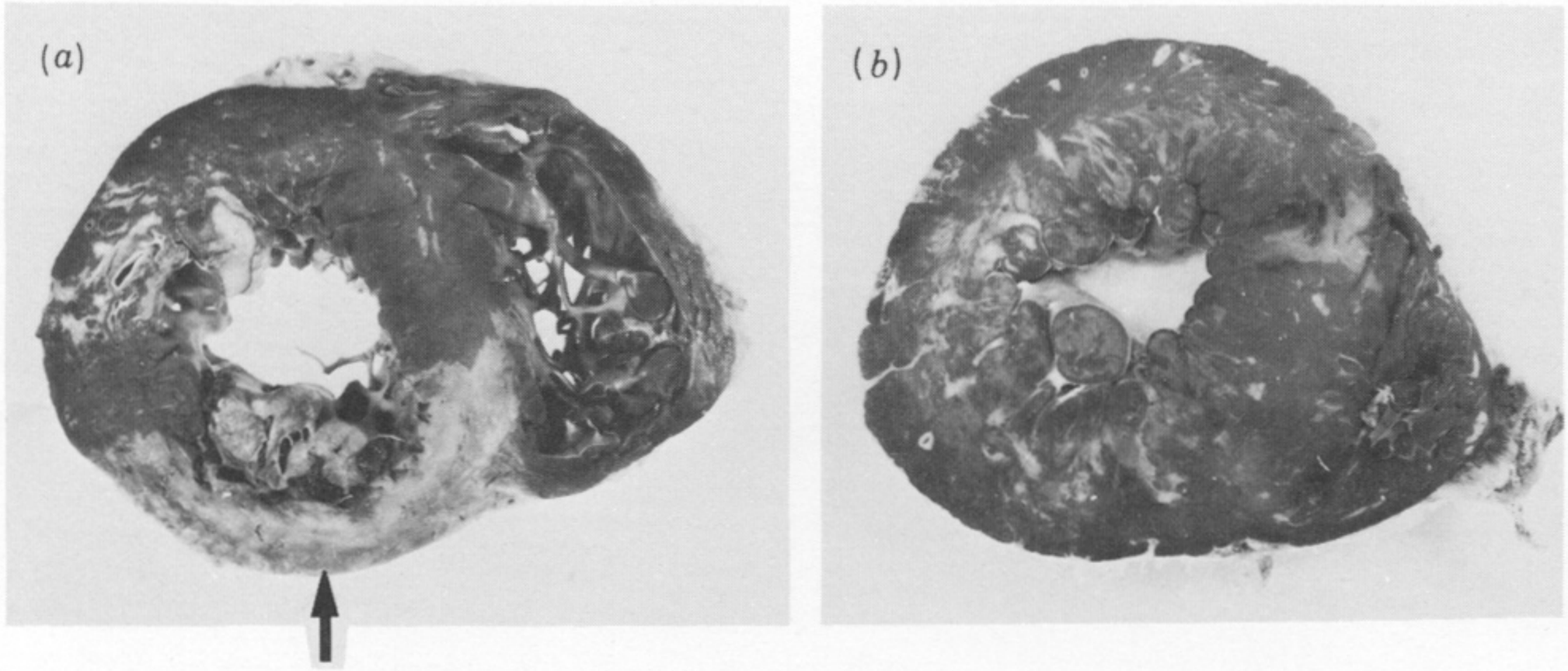

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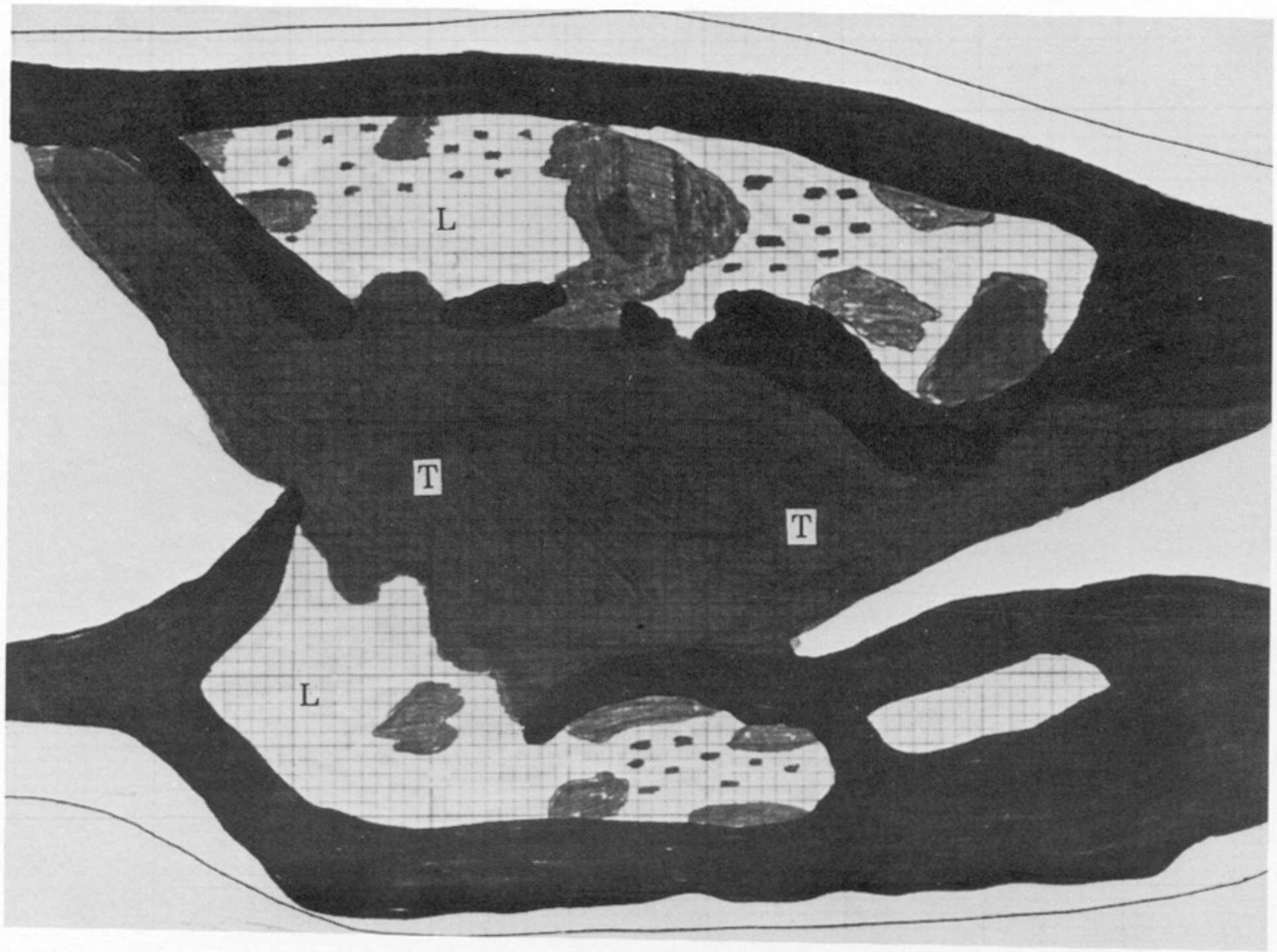

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