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PRELIMINARY NOTE

A Method for the Study of the Peripheral Circulation in Man[1]

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Evaluation of the peripheral circulation in man is usually based upon observations of skin color and texture, temperature and sweating activity; or if one wishes more quantitative data, upon measurements of the clearance of radioactive tracers from depot injection sites, venous occlusion plethysmography, indicator dilution techniques or thermal conductivity (1). The method described in this report is based upon delineation and quantification of the distribution of radioactivity throughout the leg following intraarterial injection of macroaggregates of human serum albumin labeled with ^{131}I (MMA ^{131}I). Because of their size (10 to 100 micra), these aggregates become lodged in the first capillary bed they encounter. Because they are injected in exceedingly small quantities (0.01 to 0.03 mg/kg) and are subsequently metabolized, they cause neither hemodynamic effects nor toxicity.

A similar principle has been used successfully to measure regional pulmonary blood flow in man (2). In the latter case, one injects the aggregates into a peripheral vein from which they are carried to the lungs. When one wishes to measure regional circulation of an extremity, the injection is made into a peripheral artery. A major assumption of the method is that complete mixing of the aggregates takes place in the injected artery. A second assumption is that of uniform efficiency of the various regional capillary beds in extracting the aggregates from the blood. Arteriovenous shunts whose minimum diameter is greater than the size of the macroaggregates permit the latter to flow through the vascular bed and into the venous circulation.

By comparing the concentration of radioactivity from one region to another, one determines the relative distribution of blood flow through vessels whose diameter is less than that of the injected aggregates. In man, the distribution is determined by means of scintillation scanning. Quantification of the radioactivity in the delineated areas is based upon densitometric measurements of the photographic scanning image or by integrating the counting rates as the detector is moved over various regions during the procedure.

The techniques of scintillation scanning have been described elsewhere (3). The preparation of the macroaggregates of human serum albumin consists of

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preparing a 0.1 to 1.0 per cent solution of ^{131}I labeled human serum albumin in 0.9 per cent sodium chloride solution and carefully adjusting the pH to 5.5, the isoelectric point of human serum albumin. One heats the solution at 100° C for from 5 to 15 minutes in a water bath while continually agitating the container.

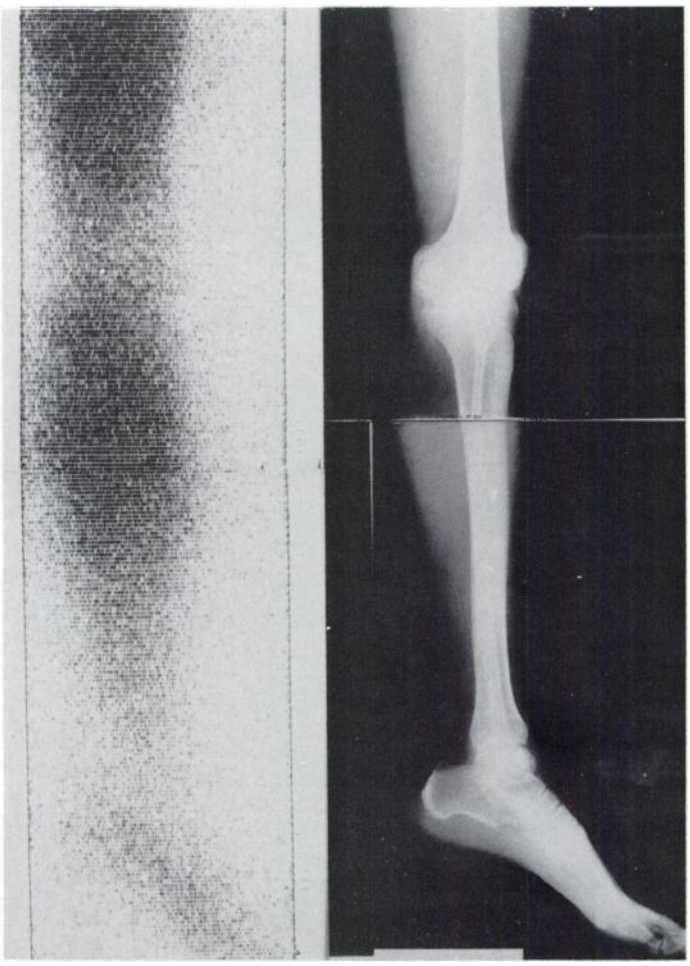

Fig. 1. Radioisotope scan of the leg following the injection of 300 μc of ^{131}I labeled macroaggregated albumin into the femoral artery. The dark areas correspond to the areas of increased concentration of radioactivity. The relatively avascular areas correspond with the knee and ankle.

Depending on the duration of heating, progressively larger aggregates will be formed. The particles are sized by direct observation in a hemocytometer. The solution is tested for sterility and pyrogenicity prior to use in man. Direct injection is made into the femoral artery through a No. 20 or No. 22-gauge needle. To date, 11 studies have been performed, 7 in normal young males. Figure 1 is the scintillation scan and radiograph of the leg following the percutaneous injec-

tion of 300 μc of ^{131}MMA into the femoral artery. Figure 2 is the average count rate obtained by means of a stationary detector (¾ inch crystal with a flat-field collimator) placed one inch above the skin at various positions, two inches apart, beginning at the anterior superior spine of the iliac crest. The injections were made into the femoral artery at the level of the inguinal ligament. To permit

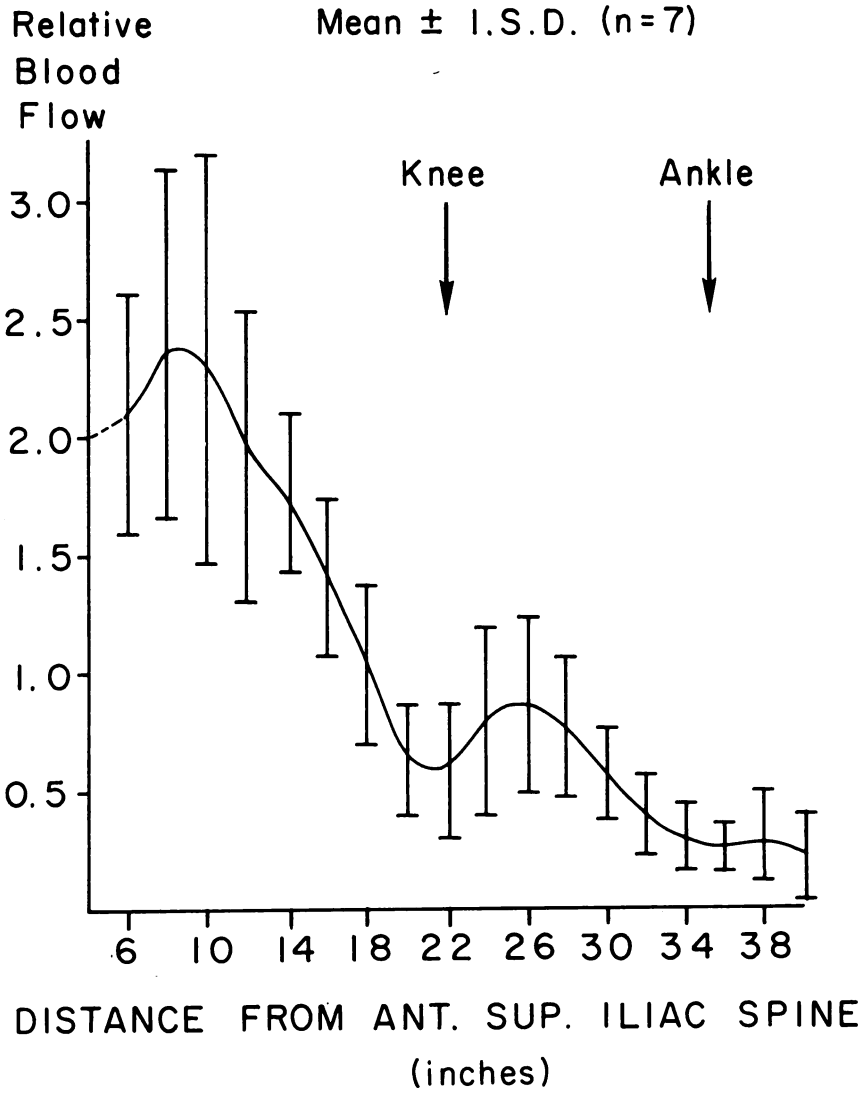

Fig. 2. Mean and standard deviation of the count rate obtained over various regions of the leg by means of a scintillation detector following the injection of 50μc of ^{131}I macro-aggregated albumin. The count rates were compared to that of the average count rate of the leg. A ratio of greater than 1.0 indicated a count rate greater than the average while one less than 1.0 indicated a blood flow less than the average for the entire leg. The decrease in blood flow to the knee and ankle can again be seen.

comparisons between one individual and another, the count rate at all positions was averaged and the count rate at any region was expressed as a ratio to the average count rate. Thus a count ratio greater than 1.0 corresponded to an area with a higher amount of radioactivity than the average for the entire leg, while count rate ratio less than 1.0 indicated an area with less blood flow than the average of the entire leg.

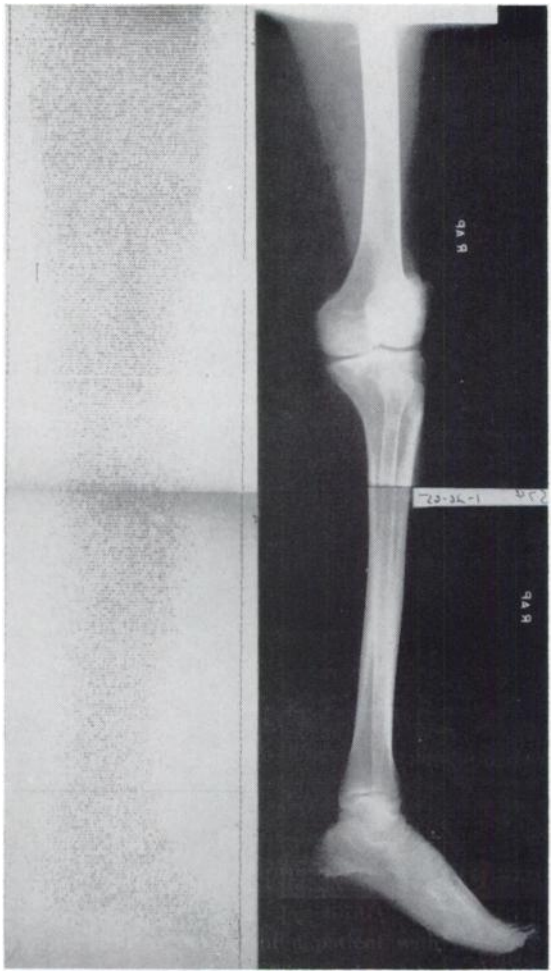

Fig. 3. Radioisotope scan of the leg of a patient with ischemic disease. The injection was made while the patient was at rest.

The most apparent information from the scan is that the distribution of radioactivity, and presumably blood flow, corresponds exactly with the distribution of the muscle masses. Although the regional concentrations of radioactivity in the thigh and calf were approximately equal (Fig. 1), the larger mass of the thigh resulted in a higher total count rate (Fig. 2). The regions of the knee and

ankle were relatively avascular as seen by the areas of decreased concentration of radioactivity. Similar results can be seen in Fig. 2 which summarizes the results of the point counting with a stationary detector. Again the regions of the knee and ankle had less radioactivity than the muscle masses.

Figure 3 is the scan of a patient with arteriosclerotic peripheral vascular disease who had striking symptoms of intermittent claudication and necrotic skin on the dorsum of the foot. In this patient, no area of the calf had a regional concentration of activity that was as great as the thigh. Whether the difference from the normal would have been accentuated by examination of blood flow after performance of exercise or ischemic exercise is not yet known although such studies are in progress. Using radioactive gases to measure muscle blood flow, Lassen and his associates have found that exercise is required for the clinical separation of patients from normals (4). Particularly valuable in their studies was observation of the time of onset of reactive hypermia following ischemic work. In the present studies, the radioactivity disappeared from the leg within a period of 48 hours. To prevent uptake of radioactive iodine by the thyroid, following metabolism of the macroaggregates, the thyroid was blocked by the administration of Lugol's solution.

Advantages of the technique that we have described are technical simplicity, safety, ready availability and the provision of information that has been lacking with previous techniques, namely, *regional* muscle blood flow that can be determined in the extremities under a variety of physiological and pathological conditions. One need only carry out the injection during the physiological circumstance that one wishes to investigate and then can more leisurely determine the distribution of radioactivity during the subsequent hours prior to metabolism of the particles.

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