THE VESSELS INVOLVED IN HYDROSTATIC TRANSUDATION

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PLATE 22

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The permeability of the walls of the cutaneous venules markedly exceeds that of the capillaries (1). Can it be that under circumstances of pathologically increased venous pressure, as in heart disease or when a limb is constricted, edema develops by a transudation which is localized, primarily at least, to the venules? We have sought to answer this question by testing the influence of slight increases of the venous pressure upon the region and rate of escape of materials from the cutaneous vessels, as indicated by the passage outwards of vital dyes devoid of complicating affinities.

Chicago blue 6B and pontamine sky blue were selected for the tests because the gradient of vascular permeability which importantly conditions the spread from the blood is readily demonstrable with them (2). They pass out of the vessels slowly, but their color is so intense that local differences in the rate of escape are plainly to be discerned. The ear of the mouse was used because the course of events can be followed directly in it; and its veins were obstructed to the desired degree by means of an apparatus developed for the purpose.

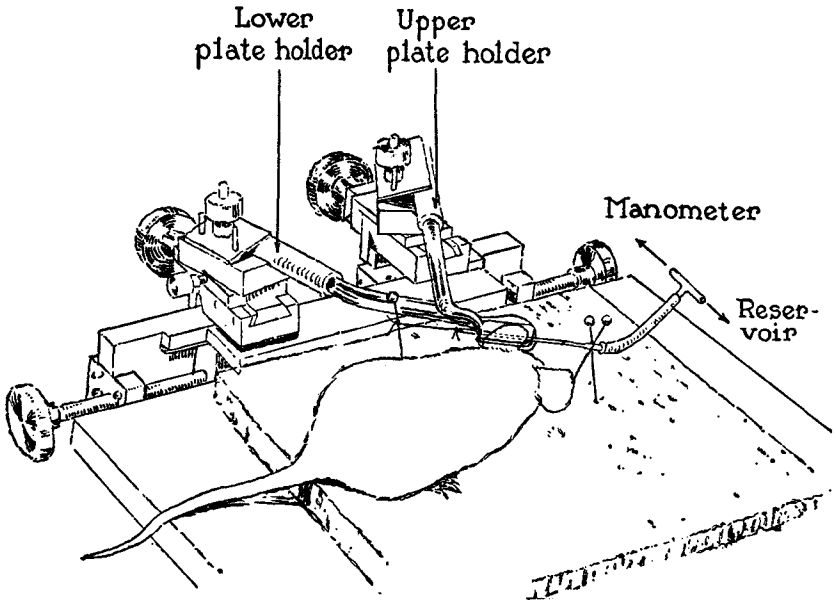
Method

The ear was viewed in paraffin oil between parallel glass plates; and before or after the injection of dye into the blood stream the vessels were obstructed near the middle of the organ by means of pressure exerted through a collodion bag.

A rhomboidal platform of white porcelain (1.5 x 2 cm.), fused to the end of a glass rod, is fixed horizontally in one clamp of a Chambers microdissection apparatus, over a cork animal board. On top of the platform, just inside its narrow free edge, is placed a slender, sausage-shaped, collodion bag, about 3 cm. long and 2 mm. in diameter when full of water. The bag connects by a water filled glass

cannula and rubber tubing with a manometer in which the water has been stained to make the readings easier. A side arm leads to a reservoir and a pump wherewith the manometer column can be raised or lowered very rapidly to any desired level. A looped thread is tied to the free end of the collodion bag and the latter is held in place with pins thrust into the animal board through this loop, and with others set to either side of the cannula (Text-fig. 1).

The mouse, under sodium luminal,—0.2 to 0.23 cc. of a 2 per cent solution for a



TEXT-FIG. 1. A diagrammatic sketch of the apparatus used for obstructing veins or arteries in the ear of the mouse.

The rhomboidal platform of white porcelain, fused to the end of a glass rod, is placed in the lower plate holder of a Chambers microdissection apparatus. The slender collodion bag stretches across the lower plate and is connected by glass and rubber tubing with the manometer, reservoir, and pump wherewith the manometer column can be raised to any desired level. The ear of the mouse lies on the rhomboidal platform and above the bag. A glass platform similar to the porcelain one is fixed in the upper plate holder of the Chambers apparatus and brought down over the ear.

20 gm. animal, given subcutaneously an hour or two beforehand,—is placed on its belly with the head next the platform, and the latter is so adjusted that the ear rests upon the bag with nearly half projecting beyond. Ear, platform, and bag are now flooded with neutral paraffin oil of low viscosity, and any skin folds are

smoothed out with a camel's hair brush before another platform, smaller than the first and of transparent glass, is brought down upon the preparation with the aid of the Chambers apparatus. The platforms should be parallel and as far apart as is compatible with compression on filling the bag. The oil renders the hairs invisible when the cooled light from an arc is properly directed by a plane mirror with a universal joint. The blood vessels immediately over the bag, as well as those beyond it, stand out so clearly that both the direct and indirect effects of the pressure changes can be followed with the binocular dissecting microscope. The direct effects are localized to a strip of tissue not more than 1 mm. wide. Only 0.3 cm. of water pressure is necessary to distend the bag, and 1 to 2 cm. causes a visible denting of the walls of the large veins of the ear where pressed upon.

The bags are made out of a 4 to 5 per cent collodion solution in ether and alcohol. Small glass rods coated with caramelized sugar serve as forms; and the sugar is dissolved in 95 per cent alcohol after the bags have dried sufficiently for use. They can be stored in alcohol. When properly made they are flexible, and leak only a negligible amount of water at pressures of 70 to 100 cm.

The bore of the manometer employed is only 0.5 mm.; but since all pressure determinations are relative to a base line determined to some extent by capillarity, this latter factor can be ruled from account. The pressure lag in the bag and the elastic rebound of the rubber connecting tubes can be minimized by avoiding jerky pressure changes.

Comparisons with the free ear of the animal have shown that when the obstructing bag is empty and the platforms at the optimum distance apart for pressure determinations the distribution of dyes is identical in the two. If the bag is close to the head, pressure from it may cause angulation of the cartilage and vessels with untrustworthy results. If it overlies the ear, it sinks irregularly into the soft tissue on distention, stretching and distorting the vessels and often closing some without affecting others of like sort. But when it is on the under side of the organ about half-way to the tip, its pressure is exerted evenly on the cartilage through a thin skin layer, and the ear vessels of the upper side, being pressed between the cartilage and the overlying glass plate, are closed off without evident traction upon them or distortion of the structures to either side. The pressure conditions under such circumstances resemble those with the distensible arm band used clinically. By direct inspection of the vessels one can tell within 1 to 2 cm. how great a column of water is required to shut off veins or arteries.

One worker manipulated the pressure apparatus, a second watched the vascular changes, and a third made notes. Only 2 to 3 seconds were required to bring the column in the manometer to the maximum height required for arterial occlusion, 70 cm., and a much shorter time when lower pressures were worked with.

The Arterial and Venous Pressures in the Mouse Ear

In a preceding paper the vascularization of the mouse ear has been described in detail (1). Its main vessels course upon the outerside

in a radiating fan. When the apparatus was properly adjusted, all the large veins (or arteries),—which one may liken to the sticks of this fan,—were equally affected by the pressure exerted through the bag. Repeated readings of the amount required to close off veins and arteries respectively, made at intervals of several minutes yielded identical results of pressure, and so too with determinations upon both ears of the same animal; but when such determinations on the same ear were made one after the other without intermission, they caused a local vasodilatation as shown by the fact that more and more pressure was required to close the veins despite the absence of any arterial pressure rise. With ether as anesthetic the arterial blood pressure varied almost from moment to moment, being on the average somewhat higher than after luminal. Pressures sufficient to close off the veins had no effect upon the arterial lumen unless the force of the heart had greatly failed.

Leonard Hill has sought to measure the pressure in the capillaries and venules of the ear of the mouse, applying for the purpose a transparent tambour (3). The least pressure that sufficed to slow the flow momentarily he took to equal the blood pressure, and using this criterion he concluded that the capillary pressure is only 1 to 3 cm. of water and the venous pressure even less in the bat's wing (4). But as Krogh has pointed out, what the method really measured was the pressure necessary to disturb the balance between the forces keeping the vessels open as opposed to those which would tend to close them (5).

We have ascertained the amount of pressure necessary to close the veins and arteries momentarily, as shown by the fact that they are emptied of blood in the region directly affected, and have taken this as representative of the maximum pressure within these vessels. Some small part of the force exerted by the bag was doubtless expended in deforming the intervening tissues; but this part is negligible since, as already mentioned, a pressure of 1 to 2 cm. H_2O suffices to dent the veins. The errors inherent in the indirect method of blood pressure measurement have been often debated. Fortunately a knowledge of absolute pressures has been unessential to the main purpose of our work, relative ones sufficing. Nevertheless, the figures obtained provide enlightening information.

In 34 mice of approximately 20 gm. under luminal anesthesia, the pressure required to flatten the fan veins, thus preventing flow, ranged

from 12 to 23 cm. of water. The systolic arterial pressure varied between 33 and 65 cm. Low arterial pressures were associated, in general though not always, with low venous ones, a systolic pressure of 33 cm. with a venous pressure of 12 cm., for example. Mention has already been made of the fact that on stimulation of the ear by rapidly repeated distension of the bag, the venous pressure rose while the arterial did not.

When a pressure was maintained which just sufficed to shut off the veins, flow was resumed within 10 or 15 seconds. And if now the pressure was raised still further, again just producing occlusion, the obstacle was once more overcome. Each successive slight increment was but transiently effective, and the pressure which closed the veins permanently was only a few centimeters less than that which shut off the arteries. For example, in one case the veins were not permanently occluded until 54 cm. H_2O had been reached, while at 56.5 cm. flow in the arteries was intermittent and jerky, ceasing entirely at 59 cm.

To explain the rapid rise of pressure back of a venous obstruction one thinks first of arteriovenous anastomoses such as exist in the extremities of various species (dog, cat, rabbit) (6). Grant has recently provided an excellent study of those of the rabbit ear (7). They are short cross-connections, often contorted, between vessels lying side by side; and normally they are closed. In the mouse ear injected with India ink gelatin mass none has been found (1); and the rapid injection of vital dyes into living mice, while the upper or lower side of the ear is watched, does not disclose any, although the course taken through the vessels by the advancing columns of stained blood can be plainly seen. Long, straight capillaries exist at the very edge of the ear, paralleling its outline, and flow in these is rapid and continuous, but it is no more rapid than in many capillaries toward the middle of the organ. Grant was frequently enabled to discover anastomoses in actively hyperemic rabbit ears by pulsations where the arterial blood directly entered a vein. We have rapidly injected dyes into mice with ear vessels that had become distended as result of almost complete venous occlusion by the pressure bag and have sought to perceive an entrance of stained blood by way of by-passes before the main flow entered the veins. It never occurred.

Always the stained blood took the way of the capillary web. It seems safe to conclude that effective arteriovenous anastomoses do not exist in the ear of the mouse.

When suddenly blocked the veins do not at once widen. The rapid mounting of pressure behind the obstacle presented by the collodion bag might conceivably be due to a fixation of the capillaries in tissue which does not give. But when the ear is touched on its upper surface with a rounded glass point the tissue is seen under a magnifying glass to dimple and to be loose, while furthermore there is room in it for the rapid accumulation of much edema fluid. This happens when a pressure is exerted upon the veins that is sufficiently high to shut them off while the arteries still pump blood in. Only when the obstacle to outflow is so considerable does capillary dilatation become well marked. A pressure which suffices merely to narrow the veins and to interfere to some extent with flow through them, as shown by a more rapid current where the bag indents the vessel, causes, it is true, some capillary widening as can be seen when the vessels distal and proximal to the bag are compared after the blood has been darkened with dye. But this widening is very slight. Krogh has stressed the fact that some of the contracted capillaries, of muscle especially, are not opened by great pressure (5), and Tannenberg and Fischer-Wasels state that after veins have been tied off the capillaries do not at once dilate (8). The present work shows that the patent capillaries of the mouse ear do not immediately give way when subjected to arterial pressure but transmit this with but little loss to the venous blood.

Effect of Increased Venous Pressure on the Escape of Substances from the Blood Stream

The opportunity for vital dyes to escape from the blood into the corium of mouse skin, whether of the ear or of the body, increases along the further portion of the capillary web and is greatest in the region of the primary venules. This is not because of a more favorable ratio of wall surface to vascular content. It results from intrinsic local differences in vascular permeability. During the first minutes after an intravenous injection of Chicago blue 6B bright blue patches develop in the corium of the ear, owing to an escape of dye from the further part of the capillary web and the adjoining venules before

any gets out elsewhere. Eventually the staining becomes uniform owing to a redistribution within the tissues. With the more poorly diffusible pontamine sky blue the patches develop more slowly and are smaller, while with highly diffusible dyes (brom phenol blue, patent blue V) some general coloration develops at the same time as the patching, because the capillary web is everywhere permeable to these dyes, though unequally so. These findings have been illustrated in a preceding paper (1).

In the present experiments a known degree of obstruction to the venous outflow was produced, Chicago blue or pontamine blue was injected, and the ear compared with its fellow. The course of the staining was followed under the microscope in the organ that was pressed upon, differences in the distribution of stain to the tissue proximal and distal to the pressure bag being readily seen. At various times after the injection both ears were lopped off, the pressure was only then relaxed, and the specimens were compared while side by side in oil under a single cover slip with their proximal halves, wherein no difference could be expected, blocked from sight with squares of white paper.

When the systolic pressure was very low, the ear with partially obstructed veins did not stain as well as the control because the arteries were compromised by the pressure exerted, as could be directly observed, and the turnover of stained blood was cut down. All such instances were discarded. In mice with a vigorous circulation (and a venous pressure of 18 to 23 cm.) it was found that a water column 5 to 6 cm. high was required to narrow the veins sufficiently for recognizable interference with outflow. Slighter pressures caused some denting of the veins but the latter were still so broad that there was no visible change in the blood current; and the staining in such instances did not differ from that in the control organ. Pressures of 5 to 6 cm. had pronounced results on the staining. Pontamine blue and Chicago blue began to escape at once from the small venules of the ear and the further portion of the capillary web, with result that the characteristic, patchy staining was already marked at a time when no dye had emerged in the region proximal to the pressure bag and none in the control ear. The subsequent coloration was more intense than in the control tissue. Its distribution in relation to the vessels was not altered from the ordinary, however. With pressures of 12 and 13 cm., which did not prevent an abundant rapid flow through the veins though compressing them to half size or less, the ear again became patched with blue more quickly and intensely than its fellow, and the patches were larger than ordinary, because dye escaped into the tissues further back along the capillary web in the

direction of the arterioles. In addition a narrow zone of deep blue formed along the larger veins, in some cases even along the largest (fan veins), and there was some diffuse staining of the ear as a whole before any developed in the control. In animals having a very low arterial blood pressure, and excluded for such reason, some of these differences in distribution could be noted despite the fact that the staining was less intense than that in the control ear.

The findings show that a slight interference with venous outflow enhances the escape of dye through the walls of the venules and the adjoining portion of the capillary web. When the interference is more considerable these effects extend further back along the capillary web, and veins not ordinarily permeable let dye through. A typical result of such interference has been photographed in Fig. 1. Even when the changes are very marked the color pattern still indicates that the opportunity for escape from the blood is greatest in the region of the primary venules and least in the proximal part of the capillary web, that near the arterioles.

As already mentioned, the smallest pressure increase causing an evident obstruction to venous outflow gave rise also to a perceptible widening of the capillaries. This was unaccompanied by any pronounced increase in their general permeability, a fact sufficiently attested by the unaltered though accentuated staining pattern. With a sustained pressure obstacle of 12 to 13 cm. of water, distention of the capillaries was considerable and edema of the ear developed, as shown by thickening of it, pitting under pressure, and an almost complete emptying of the vessels when the organ was cut off. The ear colored rapidly but the existence of a gradient of distribution was plainly to be perceived.

In an accessory group of experiments the maximal venous obstruction compatible with flow was produced,—that is to say, the pressure in the bag was raised to within a few centimeters of the systolic arterial pressure and maintained for a few minutes. During this period the capillary web became greatly distended and solid columns of red cells formed in some of the meshes. Now dye was injected. It at once passed out everywhere along the capillary web, except from the blocked meshes, and a deep, generalized staining rapidly developed, without trace of the pattern indicative of the ordinary gradient of capillary and venular permeability. Staining of the same sort occurred when

the pressure obstacle had been done away with just prior to introducing the dye, as also when the local circulation was stopped by bag pressure just after the stained blood had been distributed through the vessels. Evidently the distention of the capillaries was accompanied by a great increase in the permeability of their walls, a change which was not immediately reversible.

When an anesthetized mouse is suspended head downwards, the arterial and venous pressures in the ear mount rapidly and the organ becomes engorged with bright blood. We have followed the phenomena with the anesthetized animal hanging by the hind legs over a platform on which the ear is spread as usual. Repeated rapid distension of the collodion bag causes the pressure to rise under ordinary conditions, but it is a far more effective stimulus when the animal hangs head downward. There is a prompt return to ordinary pressures, however, when the mouse is placed once again on its abdomen. These facts can be illustrated by the following protocol.

Mouse weighing 18 gm., given 0.21 cc. of a 2 per cent solution of sodium luminal into the subcutaneous tissue 1½ hours prior to the experiment.

The venous pressure in the ear with the animal on its abdomen was 21 cm. H_2O and the systolic arterial pressure 3 minutes later 40 cm. Now the mouse was hung head downwards for 12½ minutes. The venous pressure at the end of this time proved to be 27 cm. H_2O, with an arterial pressure of 65 cm. and jerky flow at 62 cm. A pressure of 30 cm. exerted 1½ minutes after this last reading failed to shut off the veins and so too did 35 cm. after 45 seconds more, but 40 cm. applied after another minute, occluded them. The ear was now engorged with bright blood.

The animal was replaced on its belly and 4 minutes later a pressure of 20 cm. sufficed to shut off the veins. Repeated readings at short intervals yielded the same result, and the arterial pressure, taken next, proved to be 54 cm. with pulsatile flow at 52 cm. A minute afterwards the venous pressure was between 23 and 25 cm.; and finally, after 2 minutes more, the arterial pressure was once again 54 cm. H_2O.

The distribution of dyes was followed in some of the suspended animals. Controls, of identical weight, anesthetized in the same way but lying on the abdomen, were injected simultaneously. When the animals had been suspended for a few minutes only, the character of the staining showed that the gradient of vascular permeability still existed; but the coloration developed sooner and was much more

intense than in the controls, dye escaping from all of the capillary meshes except those immediately next the arterioles. In addition a zone of stain formed just outside the larger veins. The rapidity with which the dye was carried through the vascular web showed, as had the color of the ear prior to staining, that an active hyperemia was present.

Some mice were suspended for 3 to 4 hours before receiving the dye. The position was well tolerated, but in some cases a slight edema of the ear had developed at the time of injection. At the end of the preliminary period the fan veins had widened markedly, and so too with the lesser veins and venules, the changes persisting for an hour or more after the animals were again prone, as did also the vascular engorgement and high venous pressure. Dye injection while the animal was still suspended caused a rapid, generalized staining, with a broad zone of deeper color along the large fan veins. The fact could still be discerned however, that the staining was progressively more intense along the capillary web and greatest in the tissue about the venules. It was plain that a gradient of permeability still existed along the capillaries, reaching its peak in the venules.

DISCUSSION

Under normal circumstances a mounting gradient of permeability exists along the further portion of the capillaries supplying the corium; but the venules into which they empty are more permeable still (1). The present experiments prove that slight increases in venous pressure increase the opportunity for the passage outwards of dye substances from the venules and the further portion of the capillary web without essentially modifying the conditions elsewhere. Greater increases have the added effect of causing the capillary wall further back toward the arteriole to become unusually permeable. Since there is some attendant dilatation of the capillaries one cannot be certain whether the more abundant escape of dye is due to a graded increase in the amount of surface through which diffusion can occur, with some increase in local permeability due to thinning of the wall, or whether the heightened hydrostatic pressure has caused active filtration. Perhaps all these influences are at work. The wall of the larger veins is certainly rendered more permeable by the pressure, for it lets through materials which ordinarily do not pass. Nevertheless the venules remain the most permeable of all the small vessels. Only when the venous pressure is raised nearly to that in the arteries,

and the capillaries, as result, have been forcibly distended, does the characteristic gradient of vascular permeability disappear.

In mammalian skin, especially that of human beings, venules largely take the place of capillaries; and they are differentiated for special functions (9). In voluntary muscle on the other hand the arrangement of the venules, transverse to the muscle fibres, indicates, like their shape and size, that they are merely drainage channels. In muscle the vascular permeability is greatest toward the end of the capillaries, and it is here that a heightened venous pressure exerts its greatest effect, not in the region of the venules (10).

The dyes employed for the observations do not at once become fixed upon, or stored in, the skin but color it because contained in the intercellular fluid into which they pass from the plasma through the barrier of the vessel wall (10). The point is an important one in the present relation because venous pressures which suffice to extend and emphasize markedly the gradient of vascular permeability give rise to edema at the same time. There can be no doubt that the region of greatest escape, under such circumstances, of dyes dissolved in the plasma will also be that of greatest fluid escape.[1] One is justified in inferring from the color pattern that transudation through the small venules is more important for the rapid development of edema of the skin as result of increased venous pressure than is transudation through the capillaries. Edema occurring as the result of vascular injury by heat or cold, on the other hand, comes about mainly by loss of fluid from the capillaries as shown in an accompanying paper (11). Several explanations of the edema of heart disease have been offered in the past (12–15). Not only are the small vessels caught, so to speak, between the arterial pressure and an abnormally high venous one, but nutritive or toxic disturbances of the vascular endothelium may occur and affect permeability. The endothelium of the venules should suffer as much from these problematic disturbances as that of the capillaries, if not more. Most of the edema fluid accumulates in the subcutaneous tissue. Whether it finds its way there secondarily from

[1] This is not to say that wherever dyes escape from the blood under ordinary circumstances there must be a flow of water as well. They pass out by diffusion, in the absence of hydrostatic pressure, and yield the color pattern indicative of the ordinary gradient of vascular permeability (10).

the skin or is the result of fluid escape from the relatively infrequent subcutaneous vessels is a problem as yet unsolved.

The abnormal permeability of large veins widened by high pressure (as evidenced by the escape of dyes into the ears of mice suspended for long periods head down) needs no comment. One may recall in connection with it the seepage of fluid from the abnormally distended veins of human beings.

The capillaries in the soft tissue of the mouse ear transmit pressure with but little loss, as shown by the rapidity with which this mounts behind an obstacle to venous outflow. Our observations confirm those of Landis (16) who found by direct determinations on human capillaries that temporary decreases in the venous flow (as in Valsalva's experiment) cause a prompt intracapillary rise. As he points out, the capillaries that he punctured for the purpose of pressure readings were supported by the firm tissue of the nail-bed and their walls were relatively rigid. This was not the case in the mouse ear. In the mouse ear the least increase in venous pressure that enhances the permeability of the venules, as shown by the rate of escape of dyes, causes also a perceptible widening of the capillaries; but the gradient of permeability along these latter is almost unaffected. High pressures do away with the gradient completely. The uniformity of the staining that develops when the capillary barrier has been broken down by such pressures attests to the fact that the color pattern developing under ordinary circumstances is not due to structural differences in the tissue surrounding the capillaries. Previous work from this laboratory has ruled out the possibility that it is the result of a graded tonic contraction of these vessels or other functional conditions (10). There is good reason to refer it to a structural differentiation along the capillary.

SUMMARY

The gradient of permeability which exists along the cutaneous capillaries and venules is accentuated and broadened in scope by increasing the venous pressure moderately. Under such circumstances transudation leading to edema takes place most abundantly from the venules. The permeability of the portion of the capillary web that is near the arterioles increases only when the venous pressure rises so

high as to approximate that in the arteries. Under such circumstances the gradient of permeability along the small vessels disappears, the capillaries and venules everywhere leaking fluid. The character of the vital staining developing under such circumstances indicates, like the evidence of previous work, that the cause for the gradient is to be sought in a structural differentiation.

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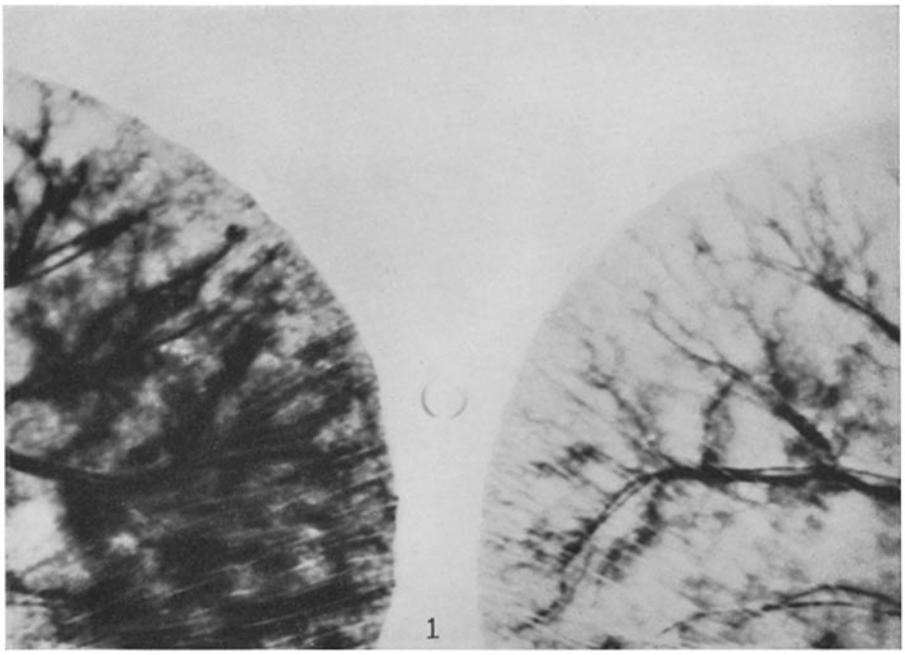
EXPLANATION OF PLATE 22

FIG. 1. Ears of a mouse after an intravenous injection of pontamine sky blue,—to illustrate some of the changes in permeability when the venous pressure has been raised to a moderate degree. A pressure of 9.4 cm. water was exerted upon the fan vessels of the left ear by means of the apparatus described in the text. The pressure was not great enough to occlude the large veins but compressed them to about half their original diameter and there was an abundant rapid flow past the obstruction. After exerting the pressure for 3 minutes the injection of dye into the circulation was begun, the total quantity being given in half a minute. $3\frac{3}{4}$ minutes after the end of the injection the pressure was relaxed and the ears were immediately severed and photographed during the next 2 minutes.

It will be seen that in both ears there was a patchy staining. In the control this was slight and it was restricted to the region supplied by the venules and the

furthest portion of the capillary web. In the ear subjected to venous hyperemia the coloration was intense. The dye had escaped in great abundance from the venules and back along the capillaries as well. Some had got out even from the large veins.



Photographed by Louis Schmidt