Capillary Circulation with Changes in Sympathetic Activity.* I. Blood Sludge from Sympathetic Stimulation. (17509)

EDMUND P. FOWLER, JR. (Introduced by W. S. Root)

From the Department of Otolaryngology, College of Physicians and Surgeons, Columbia University, New York City.

A study of the effects of sympathetic stimulation on the blood vessels of the conjunctiva of cats was undertaken incidental to some work on the physiological response of the nasal mucous membrane, but the findings seem of such general interest that it has been decided to report them separately. Suffice it to say here, that changes similar to those found in the blood vessels of the conjunctiva have been observed in the frontal sinuses and in the bullae of the middle ear as well as in the blood vessels of the fascia of the scalp. These latter regions are much more difficult to observe than are conjunctivae and there is, of course, much more tissue trauma in the preparation of these areas. This trauma can in itself produce blood sludging.(1)

Methods. Normal adult cats were anesthetized with veterinary nembutal, 30 mg per kilo intraperitoneally. The cervical sympathetic trunks were isolated for stimulation with a 60 cycle transformer resistance stimulator using 110 v. A.C. After tracheotomy, the cat's head was held firmly with a Grünfest head holder. The conjunctivae were made more accessible by slitting the external canthi with scissors and retracting the upper lids with traction sutures. The vessels of the eye were observed through a dissecting microscope (Leitz ×60-×120 magnification) using direct illumination from a dissecting lamp with two heat absorbing glass filters. The result is a clear view of venule and capillary circulation (Fig. 1). The arterioles are deeper and harder to see and are therefore not included in the diagram. The intact cervical sympathetic trunk was lifted gently from its bed and was stimulated on the observed side with sufficient current (¼ to ½ volt) to produce widening of the pupil.

Observations. Within a few seconds after cervical sympathetic trunk stimulation the arterioles and many of the venules of the conjunctiva can be seen to decrease in caliber. The red cells in the finer capillaries disappear or become very sparse. Meanwhile the flow in the venules and in at least some of the arterioles is markedly retarded, but in addition there are changes in the blood itself (Fig. 2). The blood cells cluster into clumps which appear identical with those described by Knisely *et al.*(2) as "blood sludge," *i. e.*, adherent aggregates of cells rather than ordinary rouleaux. As mentioned above, in some vessels the blood flow stops, but in a few venules, precapillaries, and capillaries it may reverse. This must be due to the arteriovenous shunts as has been described by Zweifach(3) and others. In somewhat larger vessels the flow continues, as a rule, in the same direction, but at a reduced rate. During stimulation almost all the blood cells in these vessels appear "clumped." In a few fields the clumps of blood cells can be seen squeezing out of a small constricted vessel into a larger vessel like cylinders of tooth paste coming out of a tube. These cylinders of clumped cells do not, as a rule, disintegrate on entering the next larger vessel in which blood flow continues more rapidly. After 15 seconds of stimulation the "sludging" effect increases for several seconds and then slowly disappears after 2 to 3 minutes with a return to normal of the caliber of most of those vessels which had been constricted. Later there seems to be dilatation of some of the vessels. At first, return to normal flow is observed in the larger vessels, then extending to the smaller vessels until all elements of the "sludge" have disap-

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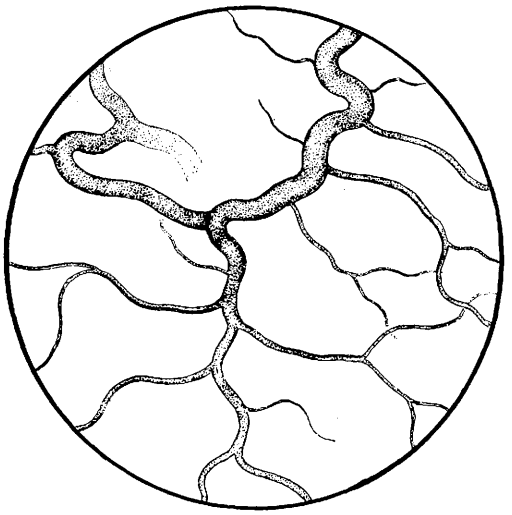
1. Knisely, Melvin H., Eliot, Theodore S., and Bloch, Edward, *Arch. Surg.*, 1945, v51, 220.

2. Knisely, Melvin H., Eliot, Theodore S., Bloch, Edward, and Warner, Louise, *Science*, 1947, v106, No. 2758.

3. Zweifach, Benjamin W., *Am. J. Anat.*, 1937, v60, 473.



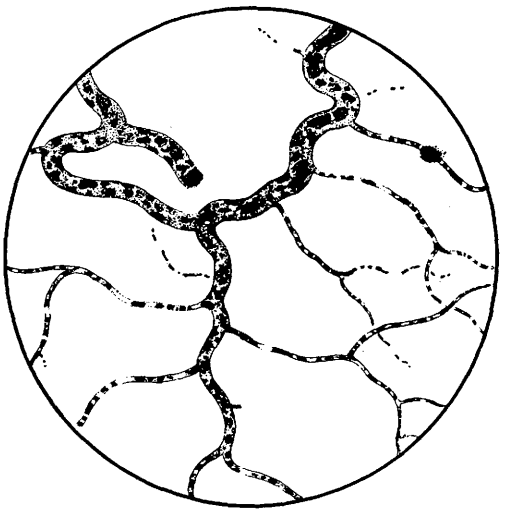


FIG. 1. (Left) Sketch of a normal conjunctival field × 100 approx.
FIG. 2 (Right) Sketch of the same conjunctival field after cervical sympathetic trunk stimulation or injection of intravenous epinephrin. The smudge, upper right, is a small hemorrhage.

peared. The changes can be repeated several times if one is careful to avoid a hot illuminating light and the conjunctiva is prevented from drying with occasional drops of Ringer's solution. If the stimulation is continued for 60 seconds the sludging effect lasts five to six minutes and some clumping may be seen in the opposite eye.

Local application of 3 to 4 drops of epinephrine (1:10,000-1:50,000) produces a similar effect for a short time. A dilution of 1:1,000 usually produces prolonged stasis and a heavy sludge in most of the superficial vessels. One is immediately led to believe that the temporary hemostatic effect of epinephrin, so often used by surgeons, is not only due to contraction of the vessels, but also due to the creation of the multiple small "sludges" and only in some cases by thrombi in the vessels affected by the drug. Thus we have two mechanisms rather than one in the creation of hemostasis with local epinephrin when applied topically. The release of the corklike masses of "sludge" with dilatation of the vessels as the effect of the drug wears off may be an additional factor in the rather temporary character of the hemostasis produced in this way. A generalized "sludging" effect is produced by intravenous injection of epinephrin. Depending upon the speed of injection and the strength of the solution (1:1,000,000-1:10,000) almost any degree of blood "sludging" can be produced in a few seconds. Minute doses produce the faintest demonstrable clumping of the red blood cells, but increasing the dosage produces more and larger aggregates of cells until there is complete arrest of blood flow in the peripheral and central circulation with death of the animal. Very occasionally there are changes in capillary wall permeability which permits a few red cells to escape into the tissues. (Fig. 2, upper right). The effect of Nor-adrenalin is similar to epinephrin, but the response is much more transient.

Intravenous injection of novocaine in small doses will often reverse the sludging process, at least for a time, but this varies with the concentration of novocaine and the speed of injection. Further elaboration of the above experiment in various parts of the body and the various diseases now being studied for "sludge" should be interesting and illuminating.

Since fright or anxiety can produce stimulation of the sympathetic system(4) and blood sludge can be produced by sympathetic stimulation and since "blood sludging" has already been observed in psychotic states(2) one can not help calling attention to the possible occurrence of "blood sludge" and its

4. Cannon, Walter B., *Bodily Changes in Fear, Hunger, and Rage*, D. Appleton, 1929.

consequences from emotional stimulation of the sympathetic pathways in the many diseases thought to be psychosomatic.

Summary. Stimulation of the cervical sympathetic trunk, application of local epinephrin, and injection of epinephrin intravenously has been found to produce, not only the classical picture of decreased circulation from narrowing of the vascular bed, but also what looks like blood "sludge" within the vessels. It is suggested that this may be of interest to those studying small vessel circulation and "sludge" and may have applications in general surgery, general medicine, and psychosomatics.

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Quantitative Measurement of Cutaneous Fluorescein Fluorescence as Indicator of the Capillary Circulation.* (17510)

ALFRED A. SCHILLER

From the Department of Physiology, University of Illinois College of Medicine, Chicago, Ill.

When sodium fluorescein is administered intravenously, it rapidly enters the interstitial fluid compartment. Due to its strong green fluorescence, its presence can be readily detected even in low concentrations when the skin, mucosa, or the surface of organs are viewed in suitably filtered long wave UV in a darkened room. Recently the passage of fluorescein into the interstitial fluid spaces was described as a function of capillary permeability.(1,2) However, no conclusive experiments designed to demonstrate this relationship have appeared in the literature. Although the specific factors regulating the passage of the dye through the capillary wall are not known with certainty, it can be clearly demonstrated that the patterns of cutaneous fluorescence, with respect to time and intensity, strongly mirror the capillary status of the region observed. Thus, intracutaneous epinephrine prevents fluorescein fluorescence at the site of injection, whereas histamine, acetylcholine, heat, etc. augment fluorescence.(1-4) Further, the intensity of fluorescence is quantitatively related to the concentration of the intracutaneously administered drugs as well as the amount of intravenously administered dye.(1,3) On the basis of this cursory relationship between fluorescein fluorescence and vascularity, it seemed worthwhile to refine methods of accurately measuring fluorescence *in vivo* with the intention of providing an objective tool for the quantitative study of the capillary circulation in physiologically intact preparations. Although Lange and Krewer(5) and Crismon and Fuhrman(6) have measured cutaneous fluorescein fluorescence by quantitative methods, experience with components of their apparatus have shown that they lack sufficient sensitivity and control to warrant usefulness as precision detectors of minute changes in fluorescence.

The instrumentation and methods reported herein are a modification of a procedure used for the determination of fluorescence in solids,(7) operating in principle similar to that of the dermofluorometer.(5)

Description of the Apparatus. The fluorescence measuring device designated as the

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1. Bukantz, S. C., and Dammin, G. J., *Science*, 1948, v107, 224.

2. Lange, K., and Boyd, L. J., *Arch. Int. Med.*, 1944, v74, 175.

3. Schiller, A. A., *Fed. Proc.*, 1949, v8, 139.

4. Schiller, A. A., to be published.

5. Lange, K., and Krewer, S. E., *J. Lab. and Clin. Med.*, 1943, v28, 1946.

6. Crismon, J. M., and Fuhrman, F. A., *J. Clin. Invest.*, 1947, v26, 259.

7. Schiller, A. A., and Cecchini, L. P., Project NM 001 008, Report No. 3, 21 July, 1948, Naval Medical Research Institute, Bethesda, Maryland.