

could be moved alternately, as well as could normal 4th and supernumerary 4th. Visual control or touching of the finger to be moved independently greatly facilitated the dissociability. Fatigue, on the other hand, seemed to reduce it. The girl, according to her own statement, had always to spend a certain amount of effort on keeping homologous fingers from working in association.

On the whole, the conclusion seems to be warranted that cortical activity, as expressed by conscious effort and focussed attention, can momentarily abolish the association between homologous muscles existing on lower levels of central activity. It is obvious that the primary condition is the association while the dissociability is the result of secondary acute intervention of the cortex. Animals lacking a cerebral cortex such as the amphibia may therefore not be expected to show phenomena of secondary dissociation, and as a matter of fact have never thus far displayed any.³

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Mechanism of Increased Capillary Permeability in Inflammation.*

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When various types of inflammatory exudates obtained from dogs or rabbits are introduced into the normal skin of either of these animals an immediate vasodilatation and increased capillary permeability follow. This is demonstrated by the diffuse accumulation of a dye (trypan blue) from the circulating blood into areas treated in this way.^{1, 2, 3} This finding suggests that an active substance increasing capillary permeability is present in exudates. The effective agent may be recovered by treating the exudates with saturated ammonium sulphate or 20% sodium sulphate. It is thermostable and is active at pH 7.4 to 6.5. Dialysis of the

³ Weiss, Paul, *Ergebn. d. Biol.*, 1928, **3**, 1; *Proc. Soc. Exp. Biol. and Med.*, 1935, **33**, 241.

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¹ Menkin, V., *J. Exp. Med.*, 1929, **50**, 171.

² Menkin, V., and Menkin, M. F., *J. Exp. Med.*, 1930, **51**, 285.

³ Menkin, V., *Am. J. Med. Sci.*, 1935, **190**, 583.

ammonium sulphate treated exudate yields a water soluble crystalline material in the evaporated dialysate which is fully potent, whereas the dialyzed material remaining in the cellophane bag is inactive. Direct dialysis of the untreated cell-free exudate likewise yields some of the active material in the evaporated dialysate. By this latter procedure, however, a small part of the active material remains in the cellophane bag apparently in a non-diffusible form. Since the active substance does not possess the properties of histamine, a definite objection is raised to the hypothesis of Sir Thomas Lewis which involves the action of histamine or an "H-like" substance.⁴ Histamine in the rabbit skin in varying concentrations dissolved in either water, saline, or serum causes central blanching and occasionally a peripheral accumulation of the dye from the blood stream in a "flare-like" formation. The active material found in exudates induces diffuse accumulation of dye throughout the treated skin area. Histamine contracts the guinea pig intestine. The active material from exudates, on the other hand, relaxes the isolated strip of intestine. These opposed effects would rule out the possibility that the active material in exudates is histamine or its closely related H-substance. Similar results as with the exudates of dogs and rabbits were obtained with a human exudate from a case of pleural effusion containing hemolytic streptococci. This exudate was obtained through the courtesy of Doctor H. L. Blumgart and Mrs. D. R. Gilligan of the Beth Israel Hospital, Boston.

The ashing of the exudate yields an aggregation of inorganic substances which when dissolved or suspended in water induce in the normal skin an almost immediate increase in capillary permeability. There is at present no available evidence that phosphates, iron, copper, aluminum, or silicon participate in this effect. The bulk of the ash consists of potassium, sodium, calcium, and magnesium. Potassium solutions, either as the chloride or the hydroxide, injected intracutaneously induce an accelerated passage of dye through the capillary wall in concentrations, however, that are higher than the amount of potassium recovered from an exudate. Chemical determinations show that the level of potassium is as a rule about twice as great in exudates than in blood serum. In this connection it may also be mentioned that either undiluted or ashed blood serum produces a weaker effect on the capillary wall than the corresponding inflammatory exudate. Potassium

⁴ Lewis, Th., *The Blood Vessels of the Human Skin and Their Responses*, Shaw and Son, Ltd., London, 1927.

salts, as in the case of exudates, depress the tonus of the guinea pig intestine. Magnesium, sodium, and calcium are found in no higher concentration in a non-purulent exudate than in the blood serum. Calcium, however, is found in higher concentrations in the later stage of inflammation when the exudate is frankly purulent. It is consequently merely suggestive that the greater effect obtained on the capillary wall by ashed exudate as compared with that elicited by similarly treated blood serum may in part be referable to the greater concentration of potassium in injured tissue as compared to that in serum. This increase in potassium concentration is found even in an exudate obtained during the first few hours of the inflammatory reaction. That other inorganic ions, besides potassium or perhaps in conjunction with it, may play a part either directly or indirectly in enhancing capillary permeability is as yet not precluded by the available data.

An attempt was also made to determine whether additional effective organic substances, other than histamine, are present in exudates. In view of the results with the previously described dialysis experiments, the end products of protein breakdown were studied. The level of amino acid concentration was usually found to be somewhat higher in exudates than in serum. This difference was invariably correlated by the more pronounced effect of the exudate in increasing capillary permeability. The total protein concentration in exudate and serum was shown to follow a trend opposite to that of amino acids. In other words there seems to be an inverse type of reciprocal relationship when one compares the concentration of total proteins and amino acids both in an inflammatory exudate and in the blood serum. This would suggest that proteolysis is very active in exudates yielding thus perhaps a number of intermediary products of protein catabolism. Proteose-peptone mixtures, peptone preparations, and certain of the alpha-amino acids have been found to increase capillary permeability when introduced into normal skin tissues.

The present observations indicate that in an inflammatory exudate certain of the inorganic ions, notably potassium found in increased concentrations, and various products of nitrogenous metabolism or intermediary protein catabolism, other than histamine, seem to play a rôle as substances connected with the mechanism of increased capillary permeability at the site of inflammation. These studies are being continued in an endeavor to purify and identify the active crystalline-like material isolated from an inflammatory exudate. The details of this investigation will be reported *in extenso* elsewhere.