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Non-Antigenic Property of the Leukocytosis-Promoting Factor of Inflammatory Exudates.*

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Earlier studies have demonstrated the presence in inflammatory exudates of dogs, rabbits, and man of a factor responsible for the associated leukocytosis frequently encountered with inflammation.[1-3] These studies on rabbit exudates have been confirmed by Reifenstein and his collaborators.[4] Purification of exudative material has revealed that the active principle is either a pseudoglobulin or that it is at least associated with that particular fraction of exudates.[5-7] More recent studies have indicated that the leukocytosis-promoting factor (termed also LPF) not only causes a discharge of immature granulocytes from the bone marrow into the circulating blood stream; but that it likewise induces a hyperplasia of granulocytic elements as well as megakaryocytes in the marrow.[8] In view of the fact that the prognosis of many infectious processes is to a large extent referable to the number of circulating leukocytes,[9] it has been pointed out by the writer that this substance may prove to be of clinical significance in connection with a variety of inflammatory conditions as well as perhaps in certain hypoplastic states of the bone marrow.[8]

Before clinical usage of this active material is attempted, it is important to determine whether it is antigenic *per se*. The fact that it is protein-like in property, at least at its present stage of purification, does not necessarily indicate an antigenic capacity. As pointed out previously,[10] inflammation is a manifestation of severe cellular injury, and as such, the chemistry of the cell is profoundly altered. As a result of the basic cellular disturbance, various substances, wholly different in nature from ordinary known biochemical substances, are liberated in the exudate. These, in turn, are responsible for the fundamentally stereotyped reaction discerned in inflammation. Thus leukotaxine,[2] the leukocytosis-promoting factor, and necrosin[11] represent such active biological substances liberated by injured cells. As indicated in an accompanying communication,[11] necrosin, which seems to be linked to the euglobulin fraction of exudates, is antigenic in character. Is this state of affairs true also of the leukocytosis-promoting factor associated with the pseudoglobulin fraction of inflammatory exudates?

Several rabbits were repeatedly injected subcutaneously with samples of the leukocytosis-promoting factor. The injections were performed at intervals of about 6 days apart, for a period of about 4 to 5 weeks. In contrast to the effect of necrosin,[11] such injections induced no appreciable local cutaneous reaction as the period of immunization progressed; or at most an occasional rapidly transient acute inflammation developed which essentially disappeared in a day or two. There was no sustained skin manifestation

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which could truly be termed a classical Arthus Phenomenon or local anaphylaxis. Precipitin antibodies were also measured in the blood serum in an endeavor to determine whether the material, as in the case of necrosin, proved to be antigenic. In no instance was there any appreciable level of antibody found in the serum. The readings in the serological tubes were completely negative, or at most with high concentration of the antigen (*i.e.* the LPF) a mere trace of cloudiness could at times be discerned. The facts indicated that the leukocytosis-promoting factor obtained from canine exudates was essentially non-antigenic to the rabbit.

Subsequently, observations were made on guinea pigs with the leukocytosis-promoting factor of dog exudates in an attempt to determine whether the active material is capable of inducing a state of anaphylaxis. The leukocytosis-promoting factor contained in 1 cc of aqueous fluid was injected subcutaneously in several guinea pigs. About a month later a similar dose of the active material was reinjected intraperitoneally. In no case was there any evidence of the least sign of discomfort to respiration or any other anaphylactic manifestations. These observations corroborated further the evidence obtained in rabbits that the factor from exudates of another species is essentially non-antigenic. Furthermore, when the leukocytosis-promoting factor of human exudates was injected into a dog at varying intervals of about a month apart or thereabouts, there was no appreciable evidence found of any anaphylactic reaction following such injections.

Conclusions. The indications are that the leukocytosis-promoting factor of inflammatory exudates is essentially non-antigenic, *i.e.* when the active material derived from one animal form is introduced into an animal of a completely different species. The present observations should serve to dispel, in large part, any apprehension that may arise in regard to the possible clinical application of the leukocytosis-promoting factor.

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Upper Auriculo-Ventricular Rhythm (Coronary Sinus Rhythm) Experimentally Produced.*

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If an a-v rhythm presents inverted P-waves preceding the QRS-complex at a normal or slightly shortened distance, the focus of origin is supposed to be situated in that part of the a-v node which extends to the coronary sinus. This assumption is based on experiments of Zahn[1] who warmed this area by means of a thermode, and studies by Meek and Eyster[2] who used direct leads in order to locate the area of primary activity. Zahn did not record electrocardiograms, and some doubt was expressed to the effect that it is not possible to warm such a small focus (Meek and Eyster)[1] and that the determination of the precise site of stimulus formation in such small structures with the methods employed is "precarious" (Lewis).[3]

Therefore, it seemed desirable to obtain further evidence that stimulus formation takes place in the coronary sinus if the electrocardiogram described above is registered.

In a previous study it was demonstrated[4] that in hearts of dogs, perfused by the Langendorff method, warming of the coronary

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