under physical conditions simulating those found clinically have verified the feasibility of the technique and will be reported upon later.

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Similarity to Heparin of the Clotting Inhibitor in Acute Leucemia and the Significance of Hyperheparinemia in Estrapenic Cholinergic States

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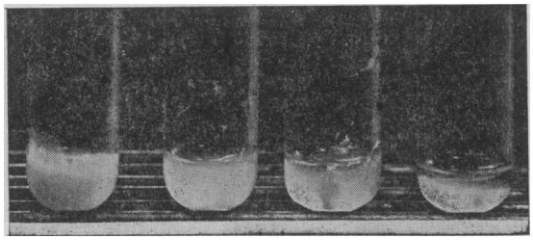
Heparin, the antithrombin of normal blood (*6*), is reported to be increased in instances of human pernicious anemia and leucoses (*2, 9*), in anaphylactic and peptone shock (*7*), and, more recently, in radiation morbidity in dogs (*1*). The basis for its identification in these conditions has been neutralization of thrombin (*2, 9*) or neutralization by globin (*2*) or by toluidine blue (*1*).



A B C D

FIG. 1. Human plasma clots formed by addition of Russell viper venom and calcium chloride to normal citrated plasma: A, normal clot; B, clot formed in presence of 1 mg% of heparin; C, 2 mg% of heparin; D, after dilution with an equal volume of plasma from a patient with terminal hemorrhagic acute leucemia.

Additional evidence for the heparin identity of the antithrombin in 5 patients with acute leucosis and 2 with thrombotic cardiogenic shock has been secured. Addition of the plasmas of these patients to citrated normal human plasma caused a dissociation in the precipitation rates of filiar and gelatinous fibrin when the plasma was clotted by calcium chloride-viper venom. In untreated citrated human plasma, the opaque filiar fibrin component (which appears to be precipitated through direct thromboplastin-fibrinogen interaction and is responsible for clot retraction, *4*) precipitates immediately prior to the formation of gelatinous fibrin (resulting from thrombin-fibrinogen interaction, the nonretractile, fibrinolyzable component), so that both components are disseminated uniformly throughout the body of the resulting opaque clot (Fig. 1A). In the presence of 1 mg% of heparin, gelatinization is delayed until retraction of the filiar fibrin has begun, so that both components of the clot can be separately distinguished (Fig. 1B). Dissociation is usually completed by the presence of 2 mg% of heparin (Fig. 1C). Fig. 1D shows the degree of dissociation produced by an added equal volume of the incoagulant plasma from a patient in the hemorrhagic phase of acute myeloblastosis, which indicates for this plasma a heparin content of between 2 and 3 mg%. Confirmation of this approximate figure for the heparin content of this patient's blood was secured by thrombin titration.

Hyperheparinemia of this extent, while explaining incoagulability, cannot, in itself, condition the hemorrhagic diathesis. Equal or greater heparin concentrations are frequently attained, temporarily at least, in human blood, since it is now common clinical practice in the treatment of thrombophlebitis to administer 100 mg of heparin by single intravenous injections. During dicumerol therapy, occasional patients who exhibit a spontaneous autochthonous hyperheparinemia have been encountered without relationship to any tendency to capillary bleeding.

Attention has been directed to the apparent limitation of hyperheparinemic extravasation to the estrapenic conditions, those characterized or attended by a diminution in the blood cholinesterase concentration (*5*). Estrapenia, per se, might explain hyperheparinemic extravasation on the basis of cholinergic capillary paresis, but the possible interrelationships of estrapenia and hyperheparinemia have not hitherto been clarified. By the citation of some additional facts, their corollaries and elaborations, it may now be justifiable to attempt an explanation of the mechanism of hyperheparinemia arising during the estrapenic dyscrasias.

(1) The administration of heparin to a subject with normal hemopoietic function is followed, after the usual period of diminished blood coagulability, by a hypercoagulability state. This is familiar to clinicians as the "heparin rebound," which may occur if too long an interval is allowed between successive heparin administrations in the treatment of thrombophlebitis and by which the condition may actually be aggravated. Heparin hypercoagulability may also be demonstrated in the rabbit and the dog; in the latter animal the writer has seen coagulation times of 20–30 *sec*, 4 hrs after administration of coagulation-abolishing doses of heparin.

(2) During heparin rebound, the thromboplastin concentration of the blood is markedly increased, while in the hemorrhagic phase of estrapenic hyperheparinemia it is considerably diminished (*3*). In the thrombopenic forms of the acute malignant hematologic dyscrasias, even where coagulation time is apparently normal, the filiar fibrin component of the clot and clot retraction may both be absent. Since thromboplastin enters directly into the formation of the retractile filiar fibrin (*3*), thromboplastin deficiency in these states is further indicated.

(3) The elaboration of the major fraction, at least, of the blood (erythrocytic) cholinesterase is a hemopoietic marrow function (*3*). This is likewise true of the elaboration of the major fraction, at least, of the

[1] The observations recorded were made at Halloran General Hospital, Staten Island, prior to its closing as an Army installation. The kind cooperation and sponsorship of Maj. Helmuth Sprinz, Chief of Laboratory Service, is gratefully acknowledged.

blood thromboplastin (the thrombocytic). Estrapenia connotes a depression of the hemopoietic marrow, which is usually inclusive; not only erythropoiesis but mature granulopoiesis and thrombopoiesis are concomitantly depressed. Thromboplastin deficiency may be related to the estrapenia only in the sense that the latter usually signifies panmyelophthisis, the marrow being unable to elaborate thromboplastin because it can elaborate few, if any, of its peripheropetal products.

If in light of the foregoing points the further assumption be permitted that heparin is the agent that evokes and regulates the rate and extent of thromboplastin production by the hemopoietic marrow (heparin having, in turn, its own antithrombic activity curtailed by the elaborate), there is forthcoming an explanation not only of the dynamic equilibrium maintaining normal intravascular fluidity but also one of the origin of hyperheparinemia in marrow failure. The blood heparin concentration will rise when blood thromboplastin is not available for its neutralization, a situation extant in the myelophthises. The teleologic possibility that heparinemia is augmented under these circumstances by cholinergic activation of mast cell function remains to be explored.

Addendum: The actuality of cholinergic mast cell proliferation has been indicated by the recent finding of coincident basophilic myelocytosis, absolute hyperheparinemia, and estrapenia in three patients with purpura (*3*).

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Use of a Plastic Material to Increase the Action of the Sodium Salt of 2,4-D[1]

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The effect of various compounds in increasing the action of the sodium salt of 2,4-D has been reported (*1, 2*). It was demonstrated that the herbicidal action of the sodium salt of 2,4-D can be greatly increased either by acidification of the solution or by the use of certain onion extracts in combination with 2,4-D.

Materials or methods which are able to modify the action of 2,4-D may provide additional clues to explain the mechanism of metabolic processes in plants. This paper reports some very striking effects produced on bean plants when the sodium salt of 2,4-D was combined with a plastic material formulated from polyvinyl chloride, which is nontoxic to plants and is called Geon 31X latex.[2]

Experiment I. Seeds of red kidney bean, selected for uniformity, were planted in 4″ pots in the greenhouse. Each pot contained two plants that were treated when the first trifoliate leaf was expanding. Ten pots were used for each treatment.

Application of 2,4-D was made by dipping one of the primary leaves of each treated plant into solutions containing the sodium salt of 2,4-D in varying concentrations of 0, 5, 50, 250, and 500 ppm. After the solutions had dried, the treated leaves of half of the plants were sprayed with a dispersion of 5% Geon 31X latex.

Within 48 hrs after treatment, marked differences were noted between the plastic- and nonplastic-treated lots. Curvature of the first internode and epinasty of the leaves were much more pronounced in the plants which had received a plastic coating in addition to the 2,4-D treatment. Nine days after treatment, all the plants that had been treated with 500 ppm of 2,4-D were dead. In the group treated with 250 ppm, death occurred in all the plants which had received, in addition to the 2,4-D, the 5% plastic coating. Those plants that received only 2,4-D were beginning to resume new growth. Although the stems were swollen and the leaves and petioles somewhat twisted, the plants were definitely recovering from the treatment (Fig. 1). In the group treated with 50 ppm of 2,4-D, only those plants that had received, in addition, a 5% spray of Geon 31X latex were severely affected; some of the plants were dead, and those not killed by the treatment showed no new growth and no sign of recovery. Where 5 ppm of 2,4-D was used, the addition of the plastic did not increase the response of the plants.

FIG. 1. Effect of Geon 31X in increasing the action of 2,4-D. Plants on the left were treated with 250 ppm of 2,4-D salt by dipping one of the primary leaves in the solution of 2,4-D. Plants on the right received the same concentration of 2,4-D, but, in addition, the treated leaves were sprayed with 5% of Geon 31X plastic.

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[2] The material was obtained through the courtesy of the B. F. Goodrich Chemical Company, Cleveland, Ohio.