TECHNICAL PAPERS

A Coagulation Defect Produced by Nitrogen Mustard[1]

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The observations of Allen, *et al.* (*1, 2*) have indicated that exposure to ionizing radiations, especially in the lethal or semilethal range, produces a prolongation in the whole-blood coagulation time of humans and animals. This effect was found to be due to the appearance of an anticoagulant in the blood biologically indistinguishable from heparin.

Recent observations in our laboratories on 5 human subjects with neoplastic disease and on normal rabbits (*3*) indicate that one of the nitrogen mustards (methyl-bis(β-chloroethyl)amine hydrochloride) produces a coagulation defect identical to that induced by radiations. Previous reports (*4, 5*) dealt with the serious toxic reactions involving the blood and blood-forming tissue of patients with neoplastic disease treated with this agent. A standard course of treatment[3] was found which was relatively safe in the sense that spontaneous recovery always followed in spite of the occasional severe destructive effects on the hemopoietic system. In no instance was the whole-blood clotting time considered to be significantly prolonged.

Of the 5 patients considered in this report, two were given 0.1 mg/kg of body weight on four consecutive days; the third received four injections of 0.1 mg/kg at intervals of 12 hrs; the fourth was given four injections of 0.1 mg/kg at intervals of 7 hrs; and the fifth patient was given only two injections of 0.3 mg/kg, 6 hrs apart. The total dose in each of the 5 cases was 25.4, 26.8, 22.4, 20.0, and 38.0, respectively. Within two weeks after administration of the drug, all 5 patients developed a moderate anemia, severe leucopenia, thrombocytopenia, prolonged bleeding time, cutaneous petechiae, and ecchymoses. The whole-blood coagulation time (Lee White) in each instance was definitely prolonged or was incoagulable in 24 hrs. Gastrointestinal and cerebral hemorrhages were serious complications, and death occurred in two patients. The intravenous administration of toluidine blue or protamine at a dose of approximately 2 mg/kg was usually sufficient to reverse the clotting time to normal for a 24-hr period. The initial or a higher dose of the antiheparin substance was repeated each 24 hrs, as indicated, in an attempt to maintain a normal clotting time. In the test tube also, prolonged whole-blood clotting time could be returned to normal limits by the addition of protamine or toluidine blue. The prothrombin time of all 5 of the individuals was normal.

This report is intended to emphasize the fact that in certain patients nitrogen mustard therapy may produce serious or even fatal complications as the result of the presence of an anticoagulant (heparin ?) in the blood. This hemorrhagic effect can be neutralized *in vivo* and *in vitro* by specific antiheparin substances such as protamine, toluidine blue, and other thionine dyes. This observation is of further interest in drawing attention to the similarities in the biological effects of ionizing radiations and nitrogen mustards.

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[3] One-tenth mg/kg of body weight given daily for four days.

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Recovery of Pneumoencephalitis (Newcastle) Virus From the Air of Poultry Houses Containing Infected Birds

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This report describes the recovery of pneumoencephalitis virus from air contaminated as a result of natural infection. The viruses of poliomyelitis (*3*), influenza (*4*), and laryngotracheitis (*1*) have been transmitted by the exposure of susceptible animals to artificially contaminated air. It was assumed, therefore, that these and possibly other virus diseases may be transmitted by the air-borne route under conditions of natural infection, but the presence of virus in such air had not been demonstrated. In the case of pneumoencephalitis, field observations and laboratory experiments indicated the probable transmission of this infection by the air-borne route; hence, these experiments were undertaken to demonstrate