THE EFFECTS OF SOME BIOLOGICAL ALKYLATING AGENTS ON CERTAIN MEASUREMENTS WHICH REFLECT HEMATOPOIETIC FUNCTION IN ANIMALS AND MAN

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ABSTRACT

The value of biological alkylating agents in the treatment of malignant disease is limited by the adverse effects they have on blood formation. A review of the development and properties of these compounds was made, and a study was carried out in which the effects of three clinically useful drugs were noted in a group of animals, and a smaller group of human subjects. Hematological studies were performed prior to and following the administration of the drugs. These measurements included determination of hemoglobin concentration, hematocrit, red cell count, total and differential white cell count, reticulocyte count, and platelet count. In addition to this, ferrokinetic studies were undertaken which employed a radioactive isotope of iron as a "tracer".

These studies included measurements of plasma iron concentration, estimation of the plasma half-life of the isotope and rate of plasma iron turnover, and observations on the rate of incorporation of radioactive iron into circulating red cells.

In comparing the results, differences were noted in the development of acute toxic signs, changes in the peripheral blood, and alterations in the ferrokinetic patterns. It is suggested that some of the factors which may have accounted for these differences included the route and method of administration of the drugs, alteration of tissue response in the host in diseased states characterized by abnormal proliferation of formed elements of the blood, and selectivity of action of the drugs which in turn may be related to differing chemical properties based on structural variation.

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GENERAL INTRODUCTION

The purpose of this study was to investigate and compare the effects of certain biological alkylating agents on measurements which reflect the ability of the organism to produce the formed elements of the blood. Abundant clinical and experimental evidence indicates that some of these compounds have a deleterious effect on hematopoiesis, and this is often the limiting factor in their therapeutic application (1). The exact mechanisms by which alkylating agents produce their adverse effects on blood formation are not well understood, and it was hoped that the present study would aid in the advancement of knowledge in this respect.

Three compounds were studied. Their structural formulae and standard nomenclature are shown in Table I. Alternate terminology is also included.

In the text these compounds will be referred to as follows:

I. Nitrogen Mustard

II. Chlorambucil

III. Busulphan

A more complete description of the physical, chemical, and biological properties of each is presented in the sections which follow.

Tests were performed prior to and following administration of the drug under consideration. These tests fell into two main categories, Routine Hematological Studies and Ferrokinetic Studies.

Routine Hematological Studies included estimation of hemoglobin and hematocrit, total red cell count, total and differential white cell count, platelet count and reticulocyte count. Methods and interpretation of results are discussed in the sections which follow.

The predominant feature of iron metabolism is its intimate and essential involvement in the synthesis of hemoglobin and the physiology of the red cell. By investigating the metabolic pathways of iron through the synthesis of hemoglobin and the incorporation of this protein in red cells it is possible

to gain information with respect to red cell production. The development of an artificial radioactive isotope of iron, Fe59, has greatly aided these investigations (2). The related tests employing Fe59 as a "tracer" in these experiments are grouped under the general heading of Ferrokinetic Studies.

Ferrokinetic Studies included estimation of plasma iron concentration, measurement of the biological half-life of Fe59 in the circulating plasma, calculation of the plasma iron turnover from these two measurements, and measurement of the incorporation of Fe59 into circulating red cells. These tests will be referred to in the text as Plasma Iron Concentration, Plasma T/2 Fe59, Plasma Iron Turnover, and Red Cell Incorporation Fe59. They are discussed in detail in the sections which follow.

Investigations were carried out on a group of mongrel pups and young dogs and on a smaller group of human subjects suffering from malignant disease. The selection of these subjects is discussed in the sections which follow. A brief summary of the clinical data pertaining to human subjects is also included.

Data obtained on experimental subjects is presented in tabular and graphical form. Comparisons were made between the means of values obtained before

treatment and at specified intervals of time following treatment. A general description of the experimental results is presented in a brief preamble, and particulars of the results in any animal or group of animals can be obtained by referring to the tables and graphs in the appropriate sections.