

A Mathematical Model of Neutrophil Production and Control in Normal Man

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Summary

A comprehensive mathematical model of neutrophil production in normal man is presented. The model incorporates three control elements which regulate homeostatically the rates of release of marrow cells to proliferation, maturation, and to the blood. The steady state properties of the model are demonstrated analytically. The basic equations of the model, which are nonlinear, have been integrated numerically. The solutions so obtained display graphically the dynamical response of the system to various perturbations, which simulate experimental investigations that have been made in the past of granulocytopoiesis. By an appropriate choice of values of the parameters characterizing the system, it is shown how most of the principal kinetic properties of the neutrophil production and control system are represented in a quantitative manner.

1. Introduction

The introduction of radioactive tracers as cell labels has led, inter alia, to a rapid accumulation of knowledge during the past 20 years or so of the kinetic behavior of the neutrophil and its precursors in the blood and marrow of man. Many investigations, too numerous to mention here, have contributed to this knowledge, and several excellent reviews of this subject may be found in the literature [1, 2, 3, 4]. The process of production of neutrophils is rather complicated, and many details of the process are as yet unknown. However, a fairly good qualitative or semi-quantitative description of the life history of the neutrophil exists. Concomitant with the study of particular aspects of this life history, there have been a number of attempts to describe such aspects theoretically in quantitative terms. Examples of mathematical models of this nature are those related to the distribution in number of neutrophil precursors in the marrow [5], the blood-granulocyte-specific-activity curve which follows the labeling of all neutrophils and their precursors [6], and the homeostatic regulation of blood neutrophil levels [7]. However, up to the present time, there does not exist a single comprehensive quantitative model representing both the steady state and

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the dynamical behavior of the neutrophil production system. By dynamical behavior, we mean the response of the production system to perturbations.

The purpose of the present work is to propose such a comprehensive mathematical model of the natural history of the neutrophil and its precursors which will simulate, more or less, all of the known kinetic aspects of this history. In developing our model, we make many idealized assumptions. These are made for the most part in the interest of simplicity, and because of the lack of quantified data. However, sometimes, as in the representation of the proliferative precursors of the mature neutrophil, we are forced to simplify the model because the data is not consistent with any simple proliferative scheme. Nevertheless, we believe that these simplifications do not invalidate the general utility of our model.

We first review, in section 2, the known quantified facts of granulocytopoiesis. Because the neutrophil is the most common granulocyte, the terms neutrophil and granulocyte are often used interchangeably in the literature, and we shall do so here. In section 3 we describe our model, which consists of five compartments, two, proliferative, and three, nonproliferative. Associated with each compartment is a partial differential equation for the cell density function, which describes the population in the compartment as a function of the variables age (or maturity) and time. The model also contains three feedback control elements which regulate homeostatically the rate of release of cells from the marrow to the blood, the rate of production, and the rate of release to maturation of cells in the proliferative pool.

Because of the control elements in the model, the model equations are nonlinear, and therefore cannot be solved in an analytic manner, in general. However, the steady state solution can be found, as shown in section 4. The steady state solution is useful for deducing many properties of the system, and is utilized in section 6, in conjunction with the known experimental facts, to determine the values of seven of the parameters. These seven parameters characterize the steady state behavior of the system.

A partial integration of the model equations can be achieved, so as to reduce the equation system to ordinary differential equations. This reduction is demonstrated in section 5. Numerical solutions of these equations, performed on a computer, which yield the populations in the compartments as functions of the time, following a given disturbance of the system, are displayed in section 7. A comparison of these solutions is made with the known semiquantitative behavior of the neutrophil production system, following a disturbance. This comparison provides information concerning the dynamical parameters of the system. The latter parameters serve to determine the dynamical response of the system to perturbations of the steady state cell populations.

We find that our model, although it oversimplifies certain essential details of the neutrophil production scheme, can be made to successfully simulate the significant quantitative details of granulocytopoiesis. The model forms the basis of a mathematical representative of the natural kinetic history of the leukemic state, which will be presented in a subsequent work.