CHRONOBIOLOGICAL EVALUATION OF LEUKOCYTOSIS CURVES

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The methodology of the study of reactive leukocytosis has evolved historically and now takes the form that the magnitude or intensity of the response is established by the investigator depending on the degree of deviation of the parameter studied from its initial values. The modern division of the states of vital processes into health, predisease, and disease is based precisely on this static principle [1, 5].

In textbooks and practical manuals the static limits of the height of reactive leukocytosis typical for various states are given, but such data must be used with caution: Leukocytosis is essentially the time course of the change in number of leukocytes, and expression of the dynamics of a function by a straight line is an abstraction [2, 8]. It is preferable to express changes in different biological values in the form of curves, for curves can show fluctuations of these values around the initial level [9]. It is also logical to represent reactive leukocytosis not as a straight line, or even as a smooth curve, but in the form of a more complex shape, resembling in our opinion a damped oscillation. If this is so, the results of measurement of reactive leukocytosis in an individual on any randomly chosen day ought to differ considerably from each other. How should the investigator proceed in this case? Which of the different values characterizing reactive leukocytosis should be taken as the basis?

In relation to diagnostic enzymology, Wilkinson [7] suggests making serial measurements and using not one, but many tests. In practice this is not always possible, and even if it is, it involves additional expense.

We consider that this question of the correct evaluation of reactive leukocytosis can be dealt with more simply. The present paper describes an attempt to describe chronologically and to compare the time course of different forms of reactive leukocytosis. Their subdivision was based on the well-known principle of dependence of the intensity of the response on the quality of the stimulus, its dose, its point of application, and the original state and species of the animal.

EXPERIMENTAL METHOD

Experiments were carried out on 87 mongrel dogs of both sexes. The experimental animals were divided into six groups. Two stimuli were used separately: an emulsion of turpentine (equal proportions of resinified turpentine and horse serum) and general hypothermia in a bath with ice until the rectal temperature fell by 1°C below its initial value. The animals of group 1 received a single injection of turpentine emulsion in a volume of 0.3-0.5 ml into the inferior ganglion of the vagus nerve (36 dogs), animals of group 2 received an injection of 1.0 ml of the emulsion into the thigh muscle (eight dogs), those of group 3 received 0.5 ml by injection into the lung (four dogs), group 4 received an injection of 0.3-0.5 ml of emulsion into the right tonsil (24 dogs), and those of group 5 (four dogs) were intact animals exposed once to general hypothermia; the 11 dogs of group 6 were animals with an experimental model of chronic suppurative lung disease (CSLD), and also were exposed to general hypothermia. Every day after exposure, for 14 days at the same time of day the total number of leukocytes was counted in 1 μl blood by the standard method in a Goryaev's chamber or on an automatic "Picoscale" automatic blood cell counter. The results were subjected to statistical analysis. All graphs were plotted from mean data.

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Fig. 1. Trajectory of leukocytosis in dogs of group 1.

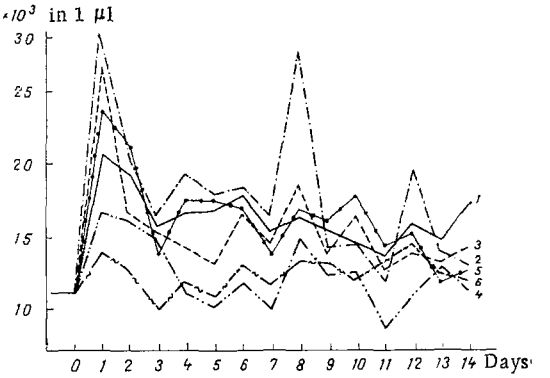

Fig. 2. Trajectories of leukocytosis in dogs of all six groups.

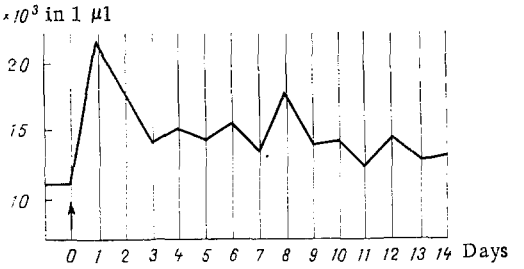

Fig. 3. "Biological norm" of reactive leukocytosis in dogs.

EXPERIMENTAL RESULTS

The dynamics of the leukocytic response plotted from mean data for the animals of group 1 is shown in Fig. 1. Broken curves reflecting reactive leukocytosis of this type can be interpreted differently. Usually when the individual response with natural fluctuations of this kind in the number of leukocytes is described, these fluctuations are attributed either to technical errors or to unconsidered influences of various external and internal factors on the body, i.e., these fluctuations are ignored on account of tradition. However, is such an interpretation valid?

Comparison of reactive leukocytosis in dogs of all six groups (Fig. 2) show that the quantitative characteristics of the leukocytosis differ in different groups, but the general trajectory of their changes is preserved. To explain this coincidence, it is insufficient to cite the action of various external environmental factors, for the experiments were carried out at different seasons and not simultaneously. If the idea of a specific effect of the turpentine emulsion on the character of the reactive leukocytosis is accepted, this assumption is invalidated by the results of experiments with general hypothermia of intact and sick animals (groups 5 and 6). The trajectories of the changes in number of leukocytes in the animals of these groups coincide with trajectories of animals of the first four groups.

The mean error when counting leukocytes is ±7% [3, 4], and the same count with an automatic analyzer gives a scatter of between 2 and 27% [11], but exclusive importance cannot be attached to this factor because the investigations were conducted over a period of time, and a possible mistake by the investigator would have to be repeated constantly without having any significant effect on the trajectory of leukocytosis.

On the basis of these results we concluded that fluctuations in the leukocyte count during reactive leukocytosis are not random in character but obey a definite rule. In our view this rule is of not only theoretical but also practical importance. If we examine leukocytosis curves (Fig. 2) by the traditional method, i.e., without a chronobiological approach, and having taken as the basis, for example, the leukocyte counts on the 2nd, 5th, 7th, and 14th days, we should apparently confirm the generally held view that the magnitude of this parameter depends on the quality, strength, and localization of the stimulus and the state of the organism.

However, by adopting a dynamic approach to the study of leukocytosis curves, we found that the trajectory of reactive leukocytosis does not depend on strength, type, or localization of the stimulus or the state of the

animal. We consider that the trajectory of reactive leukocytosis is a more stable characteristic than its amplitude, and it evidently reflects the "biological norm" of response of the leukocyte system to a stimulus. This "biological norm" of reactive leukocytosis was obtained graphically by averaging data for all 87 dogs on each day of the investigation (Fig. 3). In practice this graphic representation of the "biological norm" enables the behavior of reactive leukocytosis to be predicted in any randomly chosen time interval. Successful prediction naturally depends on how correctly we determine the shape of the curve reflecting the established general rule.

There is reason to suppose that this rule also extends to reactive leukocytosis in man.

Data in the literature indicate that 24 and 48 h after myocardial infarction the blood serum is distinguished by leukocyte-inhibiting properties. After 72 h, i.e., on the 3rd day, the leukocyte-inhibiting properties of the serum changed to leukopoietic. Agreement with our own data is evident if it is recalled that the quantity of leukocyte-inducing factor in the blood is indirectly proportional to the number of leukocytes [10].

The aim of this paper is to draw the reader's attention to the great potential value of the chronobiological approach to evaluation of a particular function in the response of the organism as a whole.

Determination of the "response norm" for one particular function is not a difficult task, for the specific trajectory of its change with time is a stable characteristic, independent of the dose and quality of the stimulus. Conversely the amplitude, universally called the intensity of the response, a quantitative measure, is a labile characteristic. It depends both on the dose and on the quality of the stimulus and also on the state of the individual. For practical purposes, when using the "response norm" the investigator makes fewer mistakes by defining the state (intensity) of the function of an individual at a given moment of time, for he knows what period of time in the response is characterized by an increase and what period by a decrease. When interconnection and interdependence between reactive leukocytosis and other functions of the body in time are established, the trajectory of reactive leukocytosis as described above may be called its kinetics.

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