SPECIFIC AND NONSPECIFIC BIOCHEMICAL PHASES OF IMMUNOGENESIS

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 55, No. 3,
pp. 69-72, March 1963
Original article submitted February 10, 1962

Studies of antibody formation during exposure of animals to ionizing radiation have shown that this process takes place in two phases: inductive (radiosensitive) and productive (radioresistant) [5]. The inductive phase of antibody synthesis differs qualitatively from the productive in its particular sensitivity to changes in metabolic conditions [4]. It is therefore easily disturbed in various pathological processes and, in particular, in the radiation syndrome.

It has been found [1, 2, 9] that the inductive phase of antibody synthesis consists of specific and nonspecific changes in the cells producing antibodies. The character of the nonspecific changes and the sequence of the specific and nonspecific changes remain unchanged during the inductive phase. These problems are of fundamental importance to the study of the mechanisms of specific protein synthesis.

We have studied the synthesis of antibodies to various antigens and the production of nonspecific γ-globulins for different relationships between the times of immunization and irradiation.

EXPERIMENTAL METHOD

In some experiments roentgen-ray irradiation was given before immunization by two antigens, and in others one of the two antigens was given before irradiation.

Nonspecific γ-globulins are the constitutional proteins of the organism, and the mechanism of their synthesis is established phylogenetically. The synthesis of these proteins is activated by antigenic stimulation as a result of proliferation of the cells responsible for protein production [3, 11]. Antibodies are a type of serum protein not usually present in the organism, and their inductive synthesis takes place independently of the formation of nonspecific γ-globulins [6, 7, 8].

Ionizing radiation acts as a specific inhibitor, capable of suppressing these processes at the crucial moment. Accordingly, by comparing the changes in the synthesis of antibodies and nonspecific γ-globulins during roentgen-ray irradiation, the depressing action of irradiation on the mechanisms of normal and specific protein synthesis can be studied separately.

Our investigations, conducted on 190 rabbits, comprised four series of experiments, in each of which the animals were immunized subcutaneously with Salmomella paratyphi B vaccine and human serum proteins, and irradiated with a dose of 1000 R. Control animals were (a) immunized but not irradiated, and (b) irradiated but not immunized. Irradiation was done by means of a type RUM-3 roentgen therapeutic apparatus, at 180 kV, 10 mA, filters 0.5 mm Cu and 1.0 mm Al, skin-focus distance 40 cm, dose rate 31 R/min, total dose 1000 R.

EXPERIMENTAL RESULTS

In the first series of experiments the animals were irradiated in a dose of 1000 R 48 h before immunization with both antigens. In these conditions antibody synthesis was greatly inhibited. For instance, at the height of antibody formation, i.e., after the third immunization, the titers of S. paratyphi agglutinins in the irradiated rabbits were on the average only 36% of those in the controls: the titers of the precipitins against human serum proteins were only 16% of the the controls (Fig. 1). The synthesis of nonspecific γ-globulins was equally depressed, for their concentration in the irradiated rabbits fell on the average from 1.18 to 0.85 g %.

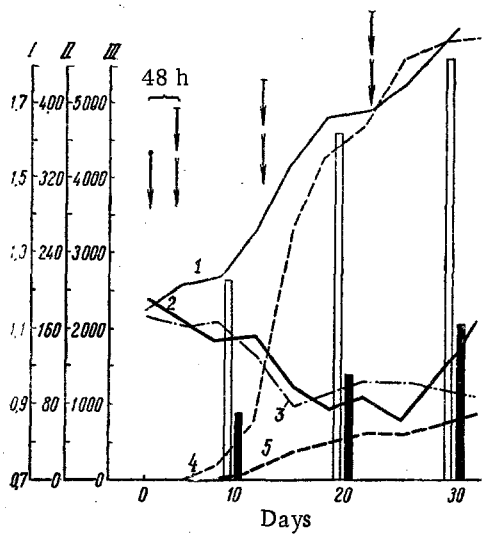

Fig. 1

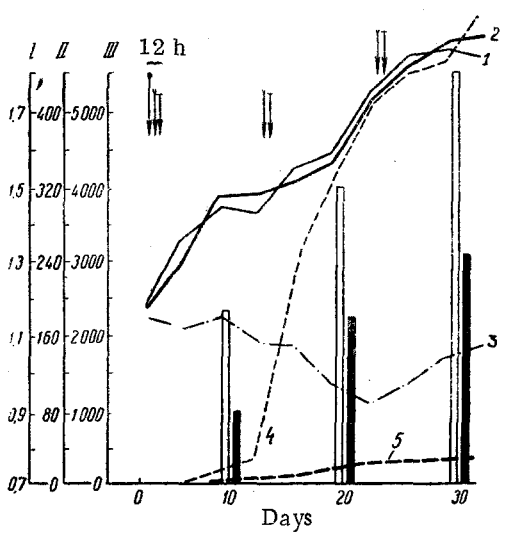

Fig. 2

Fig. 1. Irradiation in a dose of 1000 R given 48 h before immunization with Salmonella paratyphi B. vaccine and human serum protein. 1) γ-globulins of control rabbits; 2) γ-globulins of irradiated and immunized rabbits; 3) γ-globulins of rabbits receiving irradiation only; 4) precipitins of control animals; 5) precipitins of irradiated rabbits; unshaded columns) agglutinins of control animals; black columns) agglutinins of irradiated rabbits; arrow with circle) irradiation; remaining arrows) immunization. Legend for verticle axes: I) globulins (in g%); II) titers of agglutinins; III) titers of precipitins.

Fig. 2. Irradiation in a dose of 1000 R given 12 h before immunization with Salmonella paratyphi B. 1) γ-globulins of control rabbits; 2) γ-globulins of irradiated and immunized rabbits; 3) γ-globulins of rabbits receiving irradiation only; 4) precipitins of control animals; 5) precipitins of irradiated rabbits; unshaded columns) agglutinins of control animals; black columns) agglutinins of irradiated rabbits; arrow with circle) irradiation; remaining arrows) immunization. Legend for verticle axes: I) globulins (in g%); II) titers of agglutinins; III) titers of precipitins.

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These results demonstrated a marked depression of the function of the cells producing antibodies and nonspecific γ-globulins 48 h after irradiation, which thereafter became refractory to antigenic stimulation.

In the second series of experiments the animals were irradiated 12 h before the first immunization with S. paratyphi B, and 24 h before injection of the human serum proteins. In these experiments the synthesis of antibodies against both antigens was considerably inhibited. Meanwhile the production of nonspecific γ-globulins, induced by antigenic stimulation, took place equally intensively as in the control animals (Fig. 2).

These results are especially interesting, for they show that 12 h after irradiation with LD_{50} doses, the biochemical changes characterizing the inductive phase of antibody synthesis can no longer occur in the antibody-producing cells. Meanwhile the mechanism of normal protein synthesis continues undisturbed, as a result of which the cells are capable of responding to immunological stimulation by the active production of nonspecific γ-globulins.

In the third series of experiments rabbits were immunized with a single dose of S. paratyphi B. vaccine 48 h before irradiation in a dose of 1000 R, after which the two antigens were injected simultaneously, at intervals of 10 days. In these conditions both nonspecific γ-globulins and antibodies against S. paratyphi B. first administered before irradiation, were produced normally. The synthesis of precipitins against human serum proteins, first administered after irradiation, was considerably inhibited by comparison with the controls (titers 1:6400 in the control group and 1:600 in the irradiated rabbits) (Fig. 3).

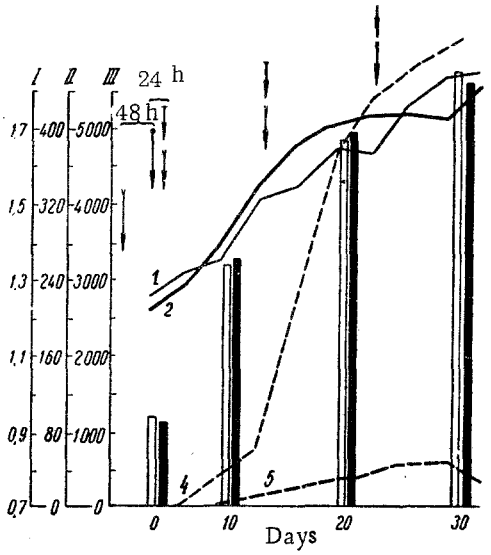

Fig. 3

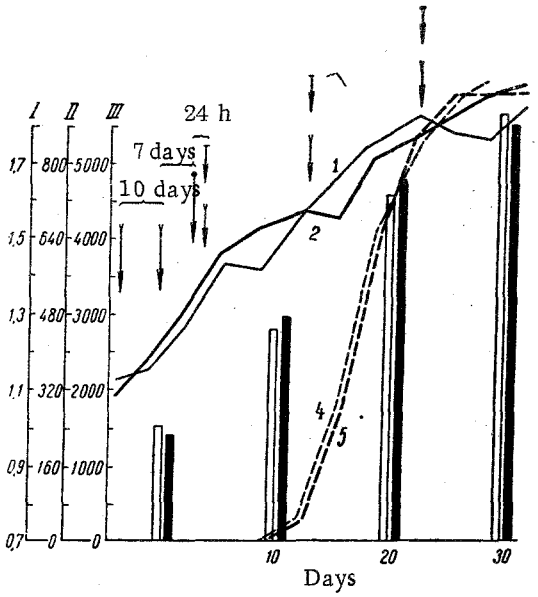

Fig. 4

Fig. 3. Irradiation in a dose of 1000 R given 48 h after immunization with a single dose of S. paratyphi B. 1) γ-globulins of control rabbits; 2) γ-globulins of irradiated and immunized rabbits; 3) γ-globulins of rabbits receiving irradiation only; 4) precipitins of control animals; 5) precipitins of irradiated rabbits; unshaded columns) agglutinins of control animals; black columns) agglutinins of irradiated rabbits; arrow with circle) irradiation; remaining arrows) immunization. Legend for verticle axes: I) globulins (in g%); II) titers of agglutinins; III) titers of precipitins.

Fig. 4. Irradiation in a dose of 1000 R given 7 days after immunization with two doses of S. paratyphi B. 1) γ-globulins of control rabbits; 2) γ-globulins of irradiated and immunized rabbits; 3) γ-globulins of rabbits receiving irradiation only; 4) precipitins of control animals; 5) precipitins of irradiated rabbits; unshaded columns) agglutinins of control animals; black columns) agglutinins of irradiated rabbits; arrow with circle) irradiation; remaining arrows) immunization. Legend for verticle axes: I) globulins (in g%); II) titers of agglutinins; III) titers of precipitins.

Apparently the inductive phase of synthesis of agglutinins against S. paratyphi B. took place successfully during the 48 h between immunization with S. paratyphi B. vaccine and irradiation. On the other hand, the inductive phase of synthesis of the second antibody against the antigen injected for the first time after irradiation could not take place because of the development of radiation changes in the antibody-producing cells.

In the fourth series of experiments irradiation was preceded by immunization with two doses of S. paratyphi B., given in the course of the 10 days before irradiation. Under these circumstances the synthesis of agglutinins against S. paratyphi and of nonspecific γ-globulins, which started before irradiation, continued no less intensively after exposure to a dose of 1000 R. The marked protective action of the preliminary irradiation in respect to the formation of precipitins against human serum proteins, injected after irradiation, could also be observed (Fig. 4).

These results suggest that the inductive phase of antibody formation takes place in two phases. The first (nonspecific) phase consists of the proliferation of mesenchymal cells, resulting in stimulation of the production of constitutional serum proteins (i.e., nonspecific γ-globulins). This period does not exceed 36 h in duration.

The second phase of antibody formation (the inductive phase proper) consists of modification of the γ-globulin generator [5] or of nucleic acids [10] by the action of the antigen. It is the second, inductive, phase which is radiosensitive.

The subsequent biochemical changes developing in the cells after the conclusion of the inductive phase of synthesis lead to the appearance of qualitatively new properties in the antibody-producing cells. They become radioresistant, as a result of which they are able to carry out intensive synthesis of antibodies against the antigen injected after irradiation.

SUMMARY

Studies of the antibody synthesis in various antigens and of the production of nonspecific γ-globulins in various ratios of immunization periods demonstrate that the inductive phase of antibody formation occurs in two stages: the first – nonspecific one – consisted in the proliferation of mesenchymal cells, resulting in an intensified production of γ-globulins; the second stage of immunochemical reconstruction (inductive phase proper) consisted in the modification (under the effect of antigen) of the proteosynthesis mechanisms, due to which antibody formation takes place.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
