Proceedings
of the
Society
for
Experimental Biology and Medicine

VOL. 42. NOVEMBER, 1939. No. 2.

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10905 P

Response of Hematopoietic Tissues to Artificially Induced Fever.

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In addition to affording a controlled method for successfully applying therapeutic hyperthermia in certain human diseases, artificially induced fever has proved to be a valuable technic for the

study of many fundamental physiologic phenomena. In this laboratory the interest has centered about the effect of radiotherm and hypertherm induced fever on the hemolytopoietic equilibria, first in experimental animals, and, later, in clinical patients.

In a series of rabbits the peripheral blood cell changes following varying degrees of fever for various periods of time have been correlated with the alterations observed in the blood-forming organs. It was found that a leucopenia persisted throughout the duration of the fever induction regardless of the method employed, and only during fever defervescence was leucocytosis of varying degree and duration observed. Furthermore, the leucopenic phase was participated in by all of the white cell elements, the lymphocytes reflecting earlier, and perhaps more profoundly, and certainly more persistently the inhibitory and destructive effects of the fever temperatures. Qualitatively the circulating lymphocytes became increasingly more pyknotic, less basophilic, older appearing cells as the duration of fever was prolonged until, in a rabbit, fevered continuously for 24 hr at temperatures ranging between 108°F and 109°F, they had all but disappeared. Postmortem studies were made of all lymph nodes and of the spleen, and it was found that practically every lymph follicle had disappeared, having been replaced by an infiltration of granulocytes and a great increase in highly phagocytic clasmatocytes with an excess of clear lymph. The sequence of events as reconstructed from a controlled series of animals, in which fever was maintained for varying periods of from 50 minutes to 24 hours, was as follows: lymphocytic nuclear karyorrhexis, cytoplasmic vacuolization, focal cellular necrosis, hemorrhage occasionally, granulocytic infiltration, clasmatocytic proliferation, and inhibition of lymphocytic regeneration with progressive hypoplasia so long as the temperature remained elevated. This is, of course, in conformity with the long recognized hypersensitivity of the lymphatic tissues to many diverse physical and chemical agents, including X-ray, radium, bacterial toxins, etc., and carries further, with added implications, the earlier suggestive experimental observations of Murphy and his associates[1] with dry heat (5 minutes at 55° to 65°C) in mice.

Conversely, however, the circulating granulocytes during this leucopenic period showed a steadily progressive nuclear "left shift", suggesting a constantly maintained delivery of new cells in an effort by the bone marrow to compensate for the increased exodus of polymorphonuclear neutrophils into the tissues under the new conditions. When the rabbit marrows were studied, the chronology of events

[1] Murphy, Jas. B., and Sturm, E., *J. Exp. Med.*, 1919, **29**, 1.

appeared to be as follows: occasional temporary myelocytic nuclear karyorrhexis was observed during the first hour of fever with more marked megakaryocytic damage, followed promptly thereafter by increased mitotic nuclear figures and myelocytic hyperplasia without progressive necrosis, and therefore with no increase in clasmatocytic activity. Immediately upon reducing the temperature, a granulocytic leucocytosis developed which persisted for some hours. By contrast, only after a considerable latent period of hours did young lymphocytes with deeply basophilic cytoplasm return to the circulation to reflect the gradual regeneration which was having to take place in the lymphopoietic tissues.

In those rabbits permitted to survive, the lymph nodes showed the maximum regenerative lymphocytic hyperplasia at the end of 56 to 72 hours post-fever. During 12 repeated feverings at therapeutic levels in the same animal at 3-5 day intervals, the circulating lymphocytes were invariably depressed temporarily while the granulocytes were stimulated, each, however, always returning eventually to the pre-fever equilibrium; and at autopsy no evidences of permanent damage could be demonstrated in any of the hematopoietic organs.

Therapeutic fever of 104°F to 106°F, induced in selected human patients with tertiary syphilis by means of the Kettering Hypertherm, produced a characteristic hemogram when followed by a series of repeated short interval (20 to 30 minutes) blood studies. During the period of fever after a longer or shorter leucopenic phase, a polymorphonuclear leucocytosis developed by tide-like increments of new granulocytes, their direct marrow origin being suggested by a progressive nuclear "left shift", and proved by serial sternal marrow studies. The highest post-fever counts ranged from 10,000 to 60,000 leucocytes at different times and in different individuals. Following the peak, the number of neutrophilic granulocytes decreased more rapidly than the total white count, due first to an increment of regenerating young monocytes and later to returning new lymphocytes. The leucocytic response was independent of the duration of the fever, and occurred following brief, as well as prolonged, temperature elevations. A much less striking granulocytic, nuclear "left shift" and myelocytic marrow hyperplasia accompanied the hypertherm induced leucocytoses than were observed after intravenous typhoid vaccine injections or malaria inoculata given at different times in the same individuals; and the leucopenia was more profound and the succeeding leucocytosis less marked with *B. typhus* and *Plasmodia malariae*.

Due probably to several factors, *e. g.*, anoxia, hyperpyrexic cell

damage, and increased metabolic requirements in inadequately prepared and fortified (glycogen, vitamin B_1) tissues, there arises during fever an increased need for granulocytic and clasmatocytic elements in the areas of resultant tissue injury and damage. To this demand the bone marrow promptly attempts response, and to the degree that the supply of available additional cells remains in excess of the increased emigration to the tissues, a peripheral leucocytosis of varying degree occurs without a striking individual nuclear "left shift". If, however, the delivery of new cells is unable to keep pace with the emigration rate to the damaged tissues, a leucopenia with increasingly marked "left shift" develops, and persists until production once again exceeds tissue demands. The much more sensitive lymphocytes are fragmented and destroyed, and their regeneration inhibited at the same fever temperatures.

Conclusion. Artificially induced fever within therapeutic limits destroys lymphocytes and inhibits lymphopoiesis in the normal experimental animal, while at the same time resulting in an increase and extension of marrow myelopoiesis, tissue clasmatocytosis and peripheral granulocytic leucocytosis. The character and nature of this profound effect of fever upon the cellular equilibria may indicate an accessory rôle in the strengthening or weakening of the body defenses—depending upon the particular circumstance—and should be considered whenever artificial hyperpyrexia is contemplated as a means of treating human disease.

10906 P

Bundle-Branch Block and the Monophasic Electrocardiogram.

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The accompanying investigations deal with the study of the alterations which are observed in the electrocardiogram when a bundle-branch block is added to a high take-off of the S-T segment and T-wave. Clinical observations have shown that in a recent coronary thrombosis with a high take-off, widening of the initial deflection occurs very rarely; this finding is not adequately explained by the difference in the blood supply of the specific tissues alone.

The combination of bundle-branch block and coronary thrombosis