DURATION OF THE EFFECT OF MEDICAMENTAL SLEEP ON INFLAMMATION

E. D. Klimenko

From the Laboratory of Pathomorphology (Head - Prof. A. A. Solovyev, Corresponding Member of the Academy of Medical Sciences, USSR), Institute of Normal and Pathological Physiology (Director - V. N. Chernigovsky, Active Member of the Academy of Medical Sciences, USSR), Academy of Medical Sciences, USSR, Moscow

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The character of the morphological changes caused by the inflammatory process in different functional conditions of the central nervous system has not yet been made sufficiently clear.

Many of the available sources of literature indicate the inhibiting influence of medicamental sleep on the local inflammatory process [2, 5, 9, 11, etc]. Studies have been conducted on animals, in which prolonged sleep is induced by repeated injections of narcotic agents, and then the action of various stimulants studied on this background. These researchers were interested in the effect of the actual sleep, and did not take into account any condition which might be retained or which might occur after the sleep had passed. We did not find any data in the literature regarding the duration of medicamental sleep's influence on the reactivity of animals, although such a problem must have arisen in the course of medicamental sleep therapy.

The purpose of our work was to investigate the character and duration of the inflammatory reaction at different time intervals after medicamental sleep. The stimulants we used to bring about aseptic inflammation were peach oil and rat's fat. Besides the special interest that these substances had for us in connection with other work we were doing, we considered that the duration of the reaction processes caused by the subcutaneous injection of fatty substances would be useful in solving the given problem.

Many researchers have studied the morphology of the inflammatory reaction which is caused by the injection of fatty substances into tissue (the so-called oleogranuloma) – W. von Leube, 1895; Wintermitz, 1903; V. Henderson and E.F. Crofutt, 1907; Henschen, 1914, V. V. Lauer [6], T. A. Pisareva [8], I. P. Vinogradov [3], G. A. Mokshanova, 1949, R. S. Braude and S. M. Gitman [1], and others.

The results of their works showed that subcutaneous injection of fat causes an inflammatory reaction similar to that caused by the injection of foreign bodies. The granulation tissue which arises as a result of this forms a nodule containing the injected substance, which divides into smaller nodules until, finally, the fatty substance is fully resorbed and replaced by scar connective tissue, sometimes with calcification. The speed with which the fat is resorbed depends on its derivation; according to the available data, vegetable fat is more slowly resorbed than animal fat (G. Brissy, Z. Binet and J. Verne; Veyrieres and Huerre).

EXPERIMENTAL METHODS

Our experiments were done with 70 white rats, weighing from 130 – 140 grams. The animals were fed the usual vivarium diet.

In each experimental series, one group of animals was injected with peach oil, the other with rat's fat (dose – 0.2 ml).

In the first experimental series, these substances were subcutaneously injected into the left flank 3 days after the sleep had passed. In the second series, the rats were injected after 7 days, and in the third, after 14 days. In all of the series, the morphological picture was examined on the 3rd, 7th, and 14th days, and, in a series of cases, also 24 and 48 hours after the fat injection.

We used a 2.5 solution of Barbamyl in a physiological solution as a hypnotic: 0.3 ml of this solution was injected subcutaneously into the rat's side at the level of the VIII – IX thoracic vertebrae. The hypnotic dose received caused sleep of varying durations, but these differences in duration were not reflected later outwardly in the general condition, behavior and weight of the animals.

We studied animals in which sleep had lasted from 2 hours to 4 hours 20 minutes. The microscopic material was fixed in a 12% solution of neutral formalin. The sections were stained with hematoxylin-eosin, and with sudan III for the fat.

EXPERIMENTAL RESULTS

The Morphological Picture in the Control Animals (not injected with the hypnotic). The first three days after the oil injection, the main mass of the oil concentrated in the central portions of the subcutaneous cellular tissue in nodules of different sizes, closely adjoining each other and surrounded by a considerable accumulation of polymorphonuclear leukocytes, most of which were in a necrobiotic condition. Nodules delimited by 1-2 rows of mononuclear, fat-containing cells were found in individual portions of the tissue. The remainder of the subcutaneous cellular tissue was infiltrated by a large number of mononuclear macrophages, many of which contained an inclusion of fat in the cytoplasm.

Later (after 7 days), the number of oil-phagocytizing, mononuclear cells increased. Due to the more intense resorption, the amount of oil in the subcutaneous cellular tissue decreased. The oil-containing nodules were mostly small and surrounded by 1-2 rows of macrophages, among which a few fibroblasts were found. In other places, single polynuclear cells were seen.

During the later stages of the inflammatory reaction (after 14 days), quite a lot of oil remained in the subcutaneous cellular tissue, contained in nodules of various sizes, contiguous to each other and edged with one row of elongated fibroblast cells (Fig. 1).

The number of mononuclear cells decreased, and only some of them contained an inclusion of oil in the cytoplasm.

When rat fat was injected into the subcutaneous cellular tissue, the reaction was generally the same as when the oil was injected. The difference was that the fat injection caused a greater leukocyte infiltration, with sharply expressed phagocytosis the 3rd day after the injection. Due to the more intense resorption, an appreciably lesser amount of fat remained by the 7th day than remained after the same period with the oil injection (Fig. 2). At later intervals (14 days), one could see many small, loose-lying drops of fat and a small quantity of diffusely scattered cell elements in the subcutaneous cellular tissue.

Morphological Picture in the Animals Injected with the Hypnotic After the Medicamental Sleep Had Passed. When oil was injected into the rat 3 days after the sleep, the main mass of the oil appeared in the form of many large, coalescing drops, surrounded by a small number of polynuclear cells, some in a condition of disintegration. Individual oil drops of various sizes were found lying loosely in the subcutaneous cellular tissue. Mononuclear cells of the polyblast type predominated in the infiltration. However, there were as yet no phagocytes. At later dates (on the 7th and 14th days), the individual oil drops were observed to be delimited by 1-2 rows of mononuclear cells, and the quantity of cell elements gradually decreased; there was a slight increase in phagocytosis, which later ceased completely. Single polynuclear cells were found.

When the oil was injected 7 days after the sleep, the body reaction was somewhat more intense than in the early intervals (3 days). The oil-containing nodules were mostly small, and many of them were surrounded by 2-3 rows of elongated mononuclear cells; the smaller drops lay freely. There were no polynuclear cells. A small number of mononuclear cells were found, some containing oil. Later (on the 7th and 14th days), the proliferation process increased and the oil-containing nodules were surrounded by mononuclear cells of the fibroblast type, arranged in several rows. The number of mononuclear cells in the infiltration increased. However, along with the well-expressed proliferation processes in the central portions of the subcutaneous cellular tissue, on the 14th day we observed even more significant accumulations of polymorphonuclear leukocytes, most of which were in a necrobiotic condition. Phagocytosis was slight.

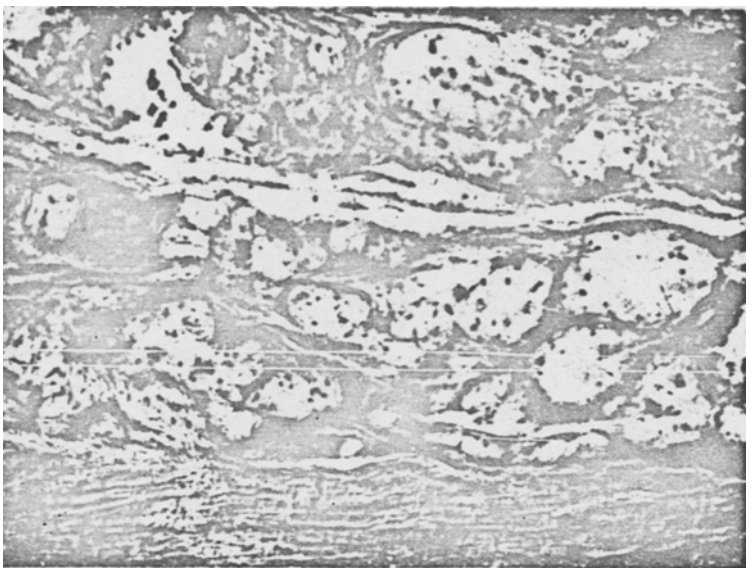

Fig. 1. Subcutaneous cellular tissue of a control rat on the 4th day after the oil injection. Many oil-containing nodules, separated from each other by narrow layers of elongated cells.

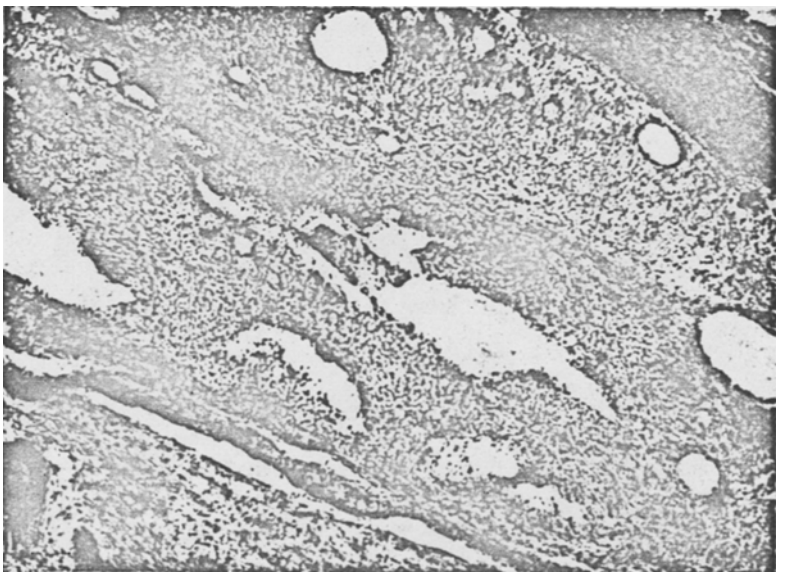

Fig. 2. Subcutaneous cellular tissue of a control rat after the rat fat injection. Massive leukocyte infiltration in the region surrounding the fat-containing nodules.

When the oil was injected 14 days after the sleep had passed, many round nodules of different sizes, surrounded by several rows of mononuclear cells, were observed in the subcutaneous cellular tissue of the rat at early dates (3 days); some of the cells contained drops of oil. There were large as well as small nodules

found. Later (after 7 days), the general quantity of cellular elements decreased slightly. At the same time, the number of cells around the individual nodules increased. Phagocytosis was more marked. The 14th day after the oil injection (i.e., 28 days after the sleep), the majority of the oil-containing nodules were small and situated slightly apart from each other. They were well delimited by 3-4 rows of elongated mononuclear cells, which included many fibroblasts. A large accumulation of lymphoid and histiocytic elements and fibroblasts was observed between the nodules. Individual cells contained inclusions of oil in the cytoplasm (Fig. 3).

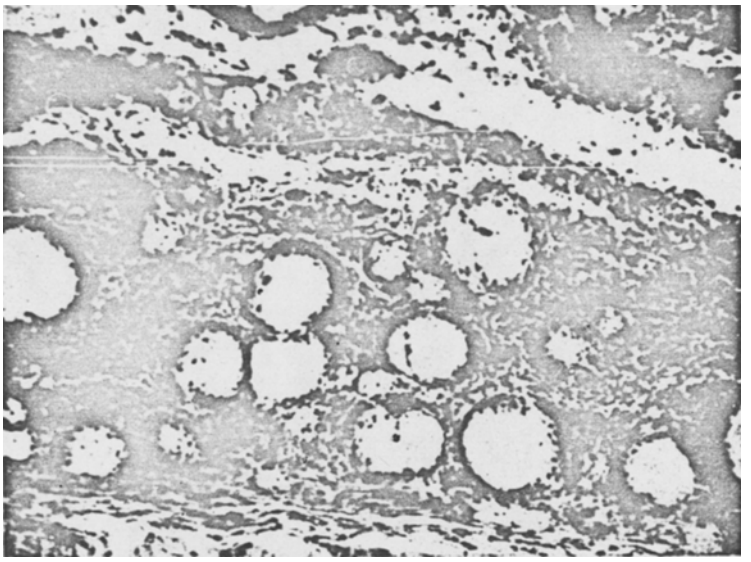

Fig. 3. Subcutaneous cellular tissue of an experimental rat on the 14th day after the oil injection. The injection was done 14 days after the sleep. The oil-containing nodules are well delimited by 3-4 rows of cells, and there is a sharply expressed proliferation reaction between the nodules.

There was a greater change in the reaction to rat fat after the medicamental sleep than in the reaction to oil (Fig. 4). While the injection of fat into the control caused a profuse leukocyte reaction with phagocytosis, in the experimental animals at the early intervals after sleep (3 days), the polymorphonuclear leukocytes were, in general, absent; there was only a small number of mononuclear cells, and phagocytosis was weakly expressed. The 14th day after sleep, the picture approximated that of the control, although there were also rather large nodules, edged with 1-2 rows of elongated fibroblasts, found among the small, fat-containing nodules, which indicated a certain delay in the resorption of the fat.

We have established that the reaction was more intense in the control animals than in the experimental. After the sleep, the intensity of the inflammatory reaction decreased; leukocyte migration was considerably less marked; the leukocyte wall around the individual drops of fat (oil) was absent or small, and phagocytosis was weakly expressed.

One must note that the character as well as the intensity of the inflammatory reaction was different. In the control, the leukocytic character of the reaction was marked, whereas, in the experiment, mononuclear cells predominated from the very first days.

The reactivity of the animals was more markedly changed when the stimulant was injected a short period after the sleep had passed (3 days) and remained changed up to the 7th and 14th days, but to a lesser degree. This was especially true of the later stages of inflammation, induced the 14th day after the medicamental sleep, when the original reactivity had apparently already been restored.

However, even in the very latest periods which we studied, for example the 7th and 14th days after the

oil injection (14 days after the sleep), a difference could be seen, as compared with the control, in the degree of the proliferative reaction, which after the sleep, i. e. under the conditions mentioned above of lowered reactivity, was more significantly expressed.

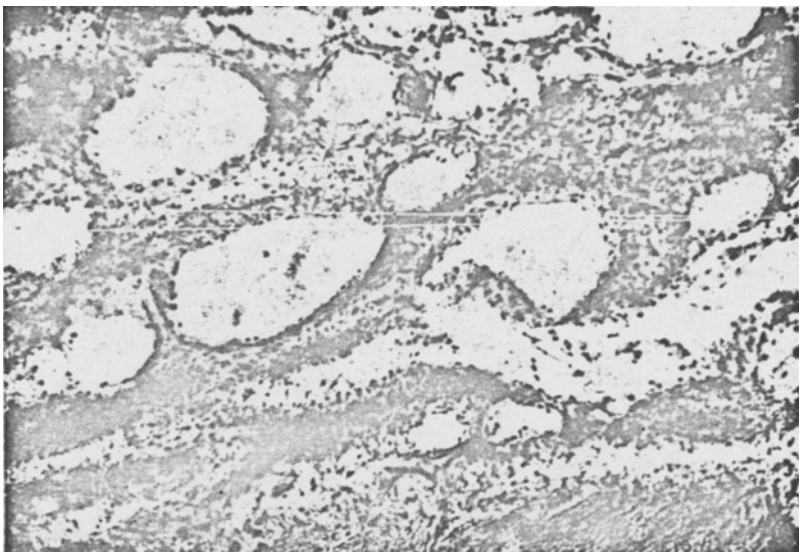

Fig. 4. Subcutaneous cellular tissue of an experimental rat on the 7th day after the rat fat injection. The injection was done 7 days after the sleep. In the region surrounding the fat-containing nodules, there are no polymorphonuclear leukocytes and only a few mononuclear cells.

This extremely interesting phenomenon needs further special study.

The reduced tonicity of the cortex evidently contributes to the different proliferative processes. I. P. Tereshchenko noted this in connection with the intensity of growth in grafted, malignant tumors.

In the laboratory of M. L. Borovsky, N. K. Georgiu [4] observed that the healing processes in the amputated stump of a dog were accelerated by the use of prolonged medicamental sleep.

Thus, from the data given, one can conclude that Barbamyl-induced sleep results in rather prolonged changes in reactivity. At least, such a conclusion follows from the character of the changes which we observed in the inflammatory reaction caused by the stimulants we injected. This reaction lingered, but its character changed toward a decreased intensity of the exudative processes and, inversely, towards the increase of the proliferative phenomena.

The duration of reactivity change can be associated with the duration of sleep, especially since, according to the data of O. Ya. Ostry and A. M. Monaenkov [7], the duration of the medicamental sleep alone can be a characteristic of the initial correlation of the principal nerve processes in the central nervous system, which is connected with this or that condition of reactivity.

It is obvious that, in cases of repeated medicamental sleep therapy, when establishing the dosage, one must take into consideration the after-effect of one-time medicamental sleep which we have mentioned; in this way, the greatest efficacy of the therapy used can probably be attained. This is especially essential in the case of inflammation, when it is necessary to regulate such a basically protective reaction as inflammation so as to eliminate its harmful effect on the organism, which often occurs when this reaction is excessively intense.

The duration of the effect of medicamental sleep on the character and development of an aseptic inflammation brought about by the subcutaneous injection of fatty substances (peach oil, rat fat) in different intervals after the sleep (3, 7, 14 days) has been studied.

In all the experimental variants the inflammatory reaction lingered, and intensity of the exudative processes decreased, whereas proliferative phenomena increased. Reactivity of the animals was found to be higher if the stimulants were injected shortly after the sleep. In the latest intervals under observation (14 days) a difference in the morphological picture could nevertheless be observed in comparison to the control animals.

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* In Russian.