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FURTHER STUDIES OF A LYMPHOCYTIC HEMOGRAM AND ITS RELATION TO LYMPHOCYTOPOIESIS

II. VARIATIONS IN MITOCHONDRIAL CONTENT OF BLOOD LYMPHOCYTES IN RELATION TO THE PROCESSES OF REGENERATION OF THE LYMPHATIC APPARATUS OF RATS AFTER TOTAL BODY X-IRRADIATION*†

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In an attempt to establish a lymphocytic hemogram which might reflect changes in production and delivery of lymphocytes in lymphoid organs, the relationship between the average number of mitochondria in blood lymphocytes and the lymphocytopoietic activity in lymphoid organs has been pursued for the past several years in our laboratory. The earlier observations on rabbits by *Osogoe* et al. (1953) and *Awaya* (1956) have revealed that a marked rise in mitochondrial number in blood lymphocytes is linked with an extensive new formation of *Flemming*'s secondary nodules in lymphoid organs. This was observed not only in the normal course of postnatal development of the lymphatic system but also after stimulating this system by intravenous injection of foreign protein (ovalbumin).

Further observations on rats by the present author along this line also have demonstrated that in the normal course of the postnatal development of lymphoid organs, there occurs a significant rise in the average number of mitochondria in circulating lymphocytes, coincident with an extensive new formation of *Flemming*'s secondary nodules in lymphoid organs (*Imamura*, 1958).

The present work, in continuation of the previous observations on rats, is an attempt to determine whether or not a similar correlation is to be seen between the variations in mitochondrial number in blood lymphocytes and the processes of regeneration of the lymphatic system, subsequent to an extensive destruction of this system by a single large dose of x-irradiation on the whole body.

MATERIAL AND METHODS

Thirty-five healthy male albino rats of a subline of the Wistar strain, weigh-

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ing around 200 g, were used. They were fed on a standard laboratory diet* and water *ad libitum* supplemented once a week with cabbage or other vegetables.

The animals were subjected in a single whole-body exposure to X-irradiation from a *Shimazu* Deep Thereapy Machine. The dose received was 600 r, as measured in air. Radiation factors were: 160 kvp, 3 ma. 0.5 mm Cu + 0.5 mm Al, dose rate in air 32.2 r per minute at a distance of 23 cm. After irradiation, 11 out of 35 animals died within 10 days. Such animals were not included in the present study.

For staining mitochondria of lymphocytes, the same supravital technique with *Janus* green B and neutral red was used as in the earlier studies (*Osogoe* et al., 1953; *Awaya*, 1956; and *Imamura*, 1958). Detailed description of the procedures of staining and counting mitochondria in lymphocytes has been made in the previous cmmunication (*Imamura*, 1958).

Most of the other procedures emlpoyed (i.e., classifications of lymphocytes according to mitochondrial number and cell size, calculations of average number of mitochondria per lymphocyte and of mitochondrial index of lymphocyte, and other hematological and histological methods) were also the same as used in the previous study by the present author.

The secondary nodules in the lymph node were classified into 3 main types as described in the earlier studies (*Awaya*, 1956 and *Imamura*, 1958): (1) *Flemming*'s *secondary nodules* or *mature secondary nodules* are typical text-book secondary nodules composed of a pale-staining center and a surrounding dark-staining peripheral mantle of small lymphocytes; (2) *Solid secondary nodules* of *Groll* and *Krampf* (1920–21) denote nodules consisting nearly exclusively of densely packed small lymphocytes without pale-staining centers; (3) *Pseudo-secondary nodules* of *Ehrich* (1920) are enormously large masses of diffuse lymphatic tissue, often containing a few solid secodary nodules and/or *Flemming*'s secondary nodules in the periphery of the nodules toward their capsular surface. They are characterized by the presence of the post-capillary veins with high endothelial cells resembling cuboidal epithelium.

The early forms of the *Flemming*'s nodules were termed *immature secondary nodules* as in the earlier studies (*Awaya*, 1956 and *Imamura*, 1958). The mature *Flemming*'s nodules were divided into "active," "half-active," and "inactive" forms according to the cellular composition of their pale-staining centers. If they are almost entirely composed of densely packed, rapidly dividing, medium-sized lymphocytes, they are termed "active". In numerous nodules of adult rats, however, one-half is active while the other is not. Such nodules are called "half-active". The nodules are called "inactive" when their center is devoid of proliferating

* The diet consisted chiefly of unpolished rice, pressed barley and dried small sardines, with a small amount of cod liver oil and minerals ($CaCO_3$ + NaCl).

lymphocytes and composed mainly of reticular cells (Fig. 2 B-D, and Figs. 10–11).

The secondary nodules in the splenic white pulp were classified into two types, immature secondary nodules and mature secondary nodules. Neither solid secondary nodules nor pseudo-secondary nodules are discernible in the splenic white pulp.

OBSERVATIONS

After irradiation, both the total white cell count and the lymphocyte count sharply fell and were maintained at considerably low levels until the 10th day. Both values, however, began to rise from the 14th day on and had returned nearly to normal levels by the 21st day (Table 1 and Fig. 1).

The average number of mitochondria per lymphocyte also showed a sharp drop after 24 hours, but it began to increase from the 3rd day on and reached a maximal level significantly higher than the initial value ($P<0.01$) on the 21st day (Table 1 and Fig. 1). Thereafter, it gradually declined but did not drop below the initial level. The mitochondrial index of lymphocyte varied in the same fashion as did the average number of mitochondria per lymphocyte.

Differential counts of lymphocytes on the basis of classification of the cells according to mitochondrial number disclosed a shift of the predominating type of these cells from type III to type IV at 21 days, whereas the classification of lymphocytes according to cell size failed to reveal such a shift at any stage (Table 2).

Histological examination of the mesenteric lymph nodes and spleen 24 hours after irradiation revealed that the lymphatic tissue had been severely depleted of lymphocytes through a massive destruction of these cells. The damage was particulary severe in the *Flemming*'s secondary nodules (Fig 2 A and Figs. 3–4). Already at 24 hours their remnants were very small, and most of the nodules had disappeared completely within several days.

Regeneration of the lymphatic tissue in the mesenteric lymph nodes and spleen commenced from the 7th day on. The results of observation of the regenerative processes, particularly of the secondary nodules, are summerized in Table 3. Generally, the regenerative processes of the *Flemming*'s nodules followed the pattern of changes observed in the course of the postnatal development of the lymphatic apparatus (*Imamura*, 1958).

The first regeneration began at 7 days when a few immature secondary nodules of the *Flemming*'s type occurred in the cortical area. These immature nodules appeared as small isolated masses of densely packed, rapidly dividing, medium-sized lymphocytes and were initially "bare" without demarcating the outer zone of small lymphocytes (Fig. 2 B and Fig. 5).* They rapidly grew in size and

* These nodules are identical to the "bare germinal centers" of *Conway* (1937).

Table 1. Changes in blood counts and average number of mitochondrial per lymphocytes in the peripheral blood of rats after total-body X-irradiation.

Time after irradiation	No. of rats examined	RBC ($\times 10^4$)	Hb (%)	WBC	Lymphocyte count	Total No. of lymphocytes counted	Avg. No. of mitochondria per lymphocyte	Mltochondrial index of lymphocyte	Degree of development of secondary nodules* in mesenteric lymph nodes
Before	35	895	106	16548	11516	3500	10.10	3.42	±±
1 day	12	768	93	4133	991	1200	7.74	2.95	–
3 days	12	793	87	1695	562	1200	8.62	3.13	–
7 days	15	652	78	1746	749	1500	9.81	3.37	–
10 days	14	619	79	1728	1003	1400	9.76	3.35	–
14 days	15	590	78	4800	2658	1500	11.19	3.62	+
21 days	15	705	99	18266	7501	1500	12.95	3.95	++
28 days	12	813	106	15166	8291	1200	12.51	3.88	±±
35 days	6	782	112	12900	6835	1200	12.13	3.80	±±
49 days	6	1007	118	20766	12765	1200	11.50	3.68	±±
60 days	4	1076	118	20200	10870	800	11.36	3.67	±±
90 days	2	947	105	21400	12173	400	10.86	3.53	++

* Immature and mature forms of *Flemming*'s secondary nodules. See Table 3.

Table 2. Differential counts of lymphocytes in the peripheral blood of X-irradiated rats.

Time after irradiation	No. of lymphocytes counted	Classification of lymphocytes according to mitochondrial content						Classification of lymphocytes according to cell size*		
		I 0	II 1-5	III 6-10	IV 11-15	V 16-20	VI 21-	Small L.	Medium-sized L.	Large L.
Before	3500	1.0	7.8	51.8	29.0	7.6	2.6	80.7	17.6	1.6
1 day	1200	1.0	18.6	68.9	9.0	1.8	0.5	57.7	40.9	0.9
3 days	1200	1.0	15.9	59.1	18.0	3.9	1.9	57.5	37.7	4.7
7 days	1500	0.2	7.4	58.0	25.6	6.0	2.6	69.7	26.2	3.9
10 days	1400	0.5	8.9	56.5	24.2	7.3	2.3	68.0	27.7	4.3
14 days	1500	0	2.8	48.8	35.1	9.2	4.0	74.0	23.3	2.6
21 days	1500	0.2	2.2	33.0	39.1	16.8	8.6	62.4	32.1	5.4
28 days	1200	0.7	2.5	37.1	37.3	14.5	7.6	61.4	34.7	3.8
35 days	1200	1.0	4.9	37.8	32.4	14.7	9.0	68.2	28.2	3.4
49 days	1200	2.4	5.0	36.5	37.9	13.5	4.5	78.1	18.6	3.2
60 days	800	1.0	4.8	41.1	36.0	12.2	4.7	79.7	17.3	2.8
90 days	400	3.2	3.7	44.2	36.2	10.0	2.5	81.6	15.5	2.7

* Small lymphocytes measure less than 9μ; medium-sized lymphocytes, 9-13μ; and large lymphocytes, more than 1$\frac{1}{2}\mu$ in diameter in blood smears stained with *Giemsa*.

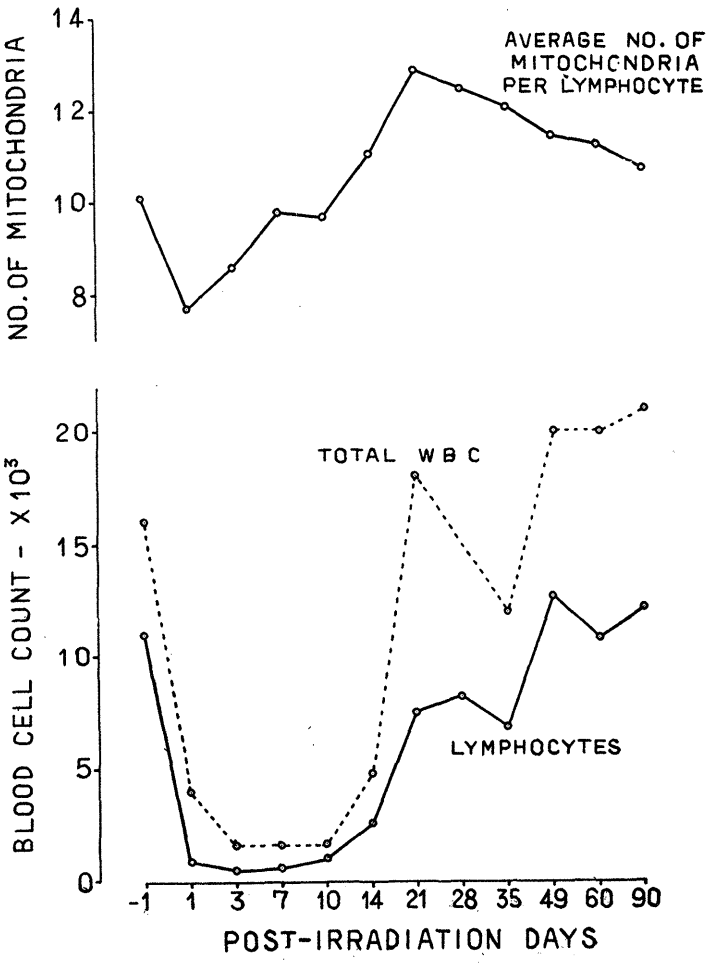

Fig. 1. Variations in the blood cell counts and the average number of mitochondria per lymphocyte in the peripheral blood of rats after exposure to 600 r of X-rays.

number during the period between 14 and 21 days after irradiation, so that the *Flemming*'s nodules had reached their full maturity by the 28th day (Table 3 and Figs. 7–8). As already mentioned, it was during the period between the 14th and 21 st days that the average number of mitochondria in circulationg lymphocytes sharply rose and reached the maximal level considerably higher than the normal values (Fig. 1). Thus, there exists a close paralellism between the regenerative processes of *Flemming*'s secondary nodules and a rise in mitochondrial number in circulating lymphocytes after irradiation.

After full development had been attained, the *Flemming*'s nodules gradually underwent regressive changes, which are characterized by a progressive increase in percentage of "half-active" and "inactive" forms. The *Flemmlng*'s nodules as

Tablle 3. Weights of the lymphoid organs and the degree of regeneration of secondary nodules in the mesenteric lymph nodes and spleen of rats after total-body X-irradiation (600 r). The activity of myelopoiesis in the splenic pulp is also roughly estimated.

Animal No.	Time after Irradiation	Body weight before irradiation (g)	Weights of organs (g)			Mesenteric lymph nodes				Spleen		
			Thymus	Mesenteric lymph nodss	Spleen	Solid secondary nodules	Pseudo-secondary nodules	Immature secondary nodules	Mature secondary nodules	Immature secondary nodules	Mature secondary nodules	Myelopoiesis
36	1 day	210	(0.19)†	0.28	0.48	±	+	−	±	−	±	−
37		200	(0.25)†	0.43	0.49	±	+	−	±	−	±	−
34	3 days	235	(0.21)†	0.40	0.53	+	−	−	−	−	−	−
35		235	(0.20)†	0.53	0.50	−	−	−	−	−	−	−
24	7 days	232	(0.14)†	0.30	0.60	−	−	+	−	+	−	++
25		190	0.05	0.30	0.28	−	−	−	−	±	−	+
21	10 days	211	0.10	0.33	0.87	−	−	+	−	+	−	±
22		206	—	0.33	0.40	−	−	+	−	+	−	+
19	14 days	195	0.15	0.33	0.71	+	−	+	−	++	−	++
20		186	0.09	0.15	0.28	+	±	+	−	±	−	++
11	21 days	183	0.06	0.17	0.58	+	+	++	+	++	−	++
12		181	0.12	0.24	1.30	+	+	+	−	+	−	+++
30		185	—	0.20	1.05	+	+	++	−	±	−	+++
31		195	0.10	0.23	0.55	++	+	++	+	++	−	++
9	28 days	177	0.17	0.45	0.41	+	+	+	+++	+	+++	+
10		154	—	0.25	0.70	+	+	+	++*	+	++	++
1	35 days	150	0.16	0.38	0.53	++	+	+	+++**	−	++*	+
4		164	0.20	0.31	0.87	−	−	−	−	−	−	−
32	49 days	220	0.18	0.40	0.54	++	+	+	++**	−	++*	++
33		215	0.18	0.55	0.55	+	+	−	+++**	−	+*	+
5	60 days	200	0.13	0.18	0.33	+	+	−	+++**	−	+**	+
27		228	0.17	0.27	0.45	+	+	−	++***	−	++**	−
7	90 days	209	0.08	0.18	0.45	+	+	−	++***	−	+**	±
26		210	(0.21)†	0.38	0.51	++	+	−	++***	−	+**	−

† Almost completely replaced by fat.

* The predominating secondary nodules are half-active forms with a few active secondary nodules.

** The predominating secondary nodules are half-active forms with a few inactive secondary nodules.

*** The predominating secondary nodules are inactive forms.

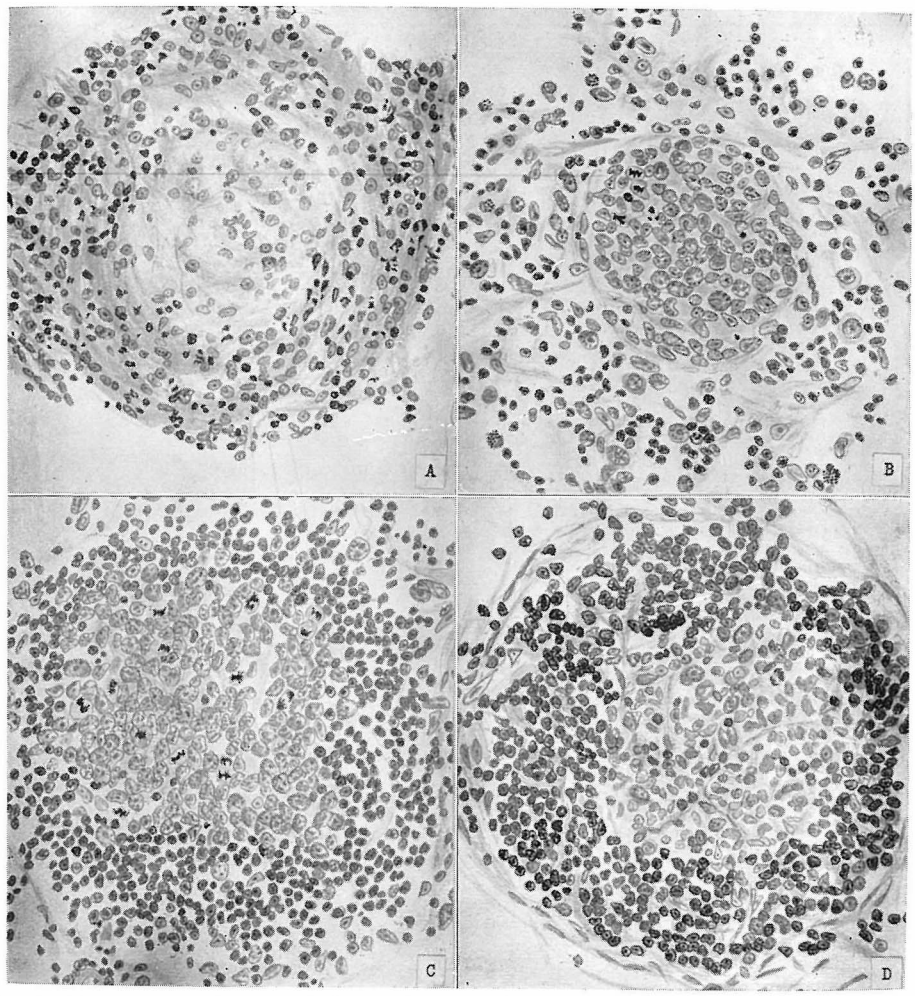

Fig. 2. The changes in the *Flemming*'s secondary nodules in the rat mesenteric node after exposure to 600 r of X-rays. A: Remnant of *Flemming*'s nodule containing a few epitheloid cells, 24 hours after irradiation. B: Newly formed, immature *Flemming*'s nodules without outer zone of small lymphocytes ("bare germinal ceter" of *Conway*), 14 days after irradiation. C: mature *Flemming*'s nodules with active center containing numerous mitotic figures and outer zone of small lymphocytes ("active" form), 28 days after irradiation. D: Mature *Flemming*'s nodule with inactive center devoid of proliferating lymphocytes and outer zone of small lymphocytes ("inactive" form), 90 days after irradiation.

a whole showed a tendency toward decrease both in size and number, and the histological picture returned to normal at 60 days (Fig. 9). It is important to emphasize here that the average number of mitochondria also showed a gradual decrease after 28 days.

The *Flemming*'s nodules in different stages of regeneration after irradiation was

essentially the same as described in the preceding paper (*Imamura*, 1958) dealing with the normal course of their postnatal development. In the earlier stages the "active" forms predominated, but in later stages the "half-active" and "inactive" forms gradually increased in number (Table 3; Fig. 2 A-D and Figs. 10–11).

In the mesenteric lymph nodes, in addition to regeneration of *Flemming*'s nodules, there was diffuse regeneration of the lymphatic tissue which was accompanied by the formation of solid secondary nodules and pseudo-secondary nodules (Fig. 6). The latter type of regeneration was somewhat delayed as compared with the nodular regeneration, and no qualitative changes comparable to new formation and maturation of *Flemming*'s nodules occurred during the period between 14 and 28 days after irradiation (cf. Table 3). Therefore, the diffuse regeneration can hardly be correlated with a marked rise of mitochondrial number in circulating lymphocytes at 21 post-irradiation days.

Of particular interest is the abundant occurreuce of plasma cells in the medullary cords of the mesenteric lymph nodes which may be regarded as one of the most striking features of the post-irradiation reactions (*Wohlwill* and *Jetter*, 1953). Here, it must be borne in mind that numerous plasma cells are normally present in the medullary cords of the rat mesenteric lymph nodes. However, replacement of lymphocytes by plasma cells after a large dose of X-irradiation took place on a very large scale as shown in Figs. 12 and 13, during the period between the 3rd and the 7th post-irradiation days. Thereafter, plasma cells gradually decreased in number and the histological picture of the medulla returned to normal at 60 days. A detailed description of this phenomenon will be made elsewhere.

Also worthy of notice is a hyperplasia of the reticular cells in the diffuse lymphatic tissue, notably the cortex, after irradiation. At 28 days these cell formed numerous small isolated cell nests. Some investigators such as *De Bruyn* (1948) are suspicious of a hyperplasia of reticular cells and claim that the prominence of these cells may be caused by depletion of lymphocytes. However, the present finding leaves little doubt in this respect, because repopulation of lymphocytes had taken place to a large extent by the time when a hyperlasia of the reticular cells became prominent. It is of interest to note here that a few fat cells were found scattered in the medulla of the mesenteric lymph nodes of a rat examined 21 days after irradiations (Fig. 14).

The regenerative processes of the *Flemming*'s nodules in the splenic pulp were essentially the same as seen in the mesenteric lymph nodes. The myelopoietic activity in the red pulp was greatly intensified during the period between 14 and 21 days after irradiation (Table 3 and Figs. 15–17).

Discussion

It is well known that the lymphatic tissue is the most sensitive to ionizing

radiation. After exposure to a single large dose of X-rays, the lymphoid tissue has been severely depleted of lymphocytes through a massive destruction of these cells within a short time. The experiment with X-rays, therefore, gives a good opportunity for studying the processes of regeneration of the lymphatic tissue and their relation to the changes in the lymphocytic blood picture.

The present observations have shown that the regenerative processes of the lymphatic tissue after irradiation generally follow the pattern of the postnatal development of this tissue. The most important finding is that during regeneration of the lymphatic tissue, there occurs an extensive new formation of *Flemming*'s secondary nodules, almost coincident with a significant transient rise in the average number of mitochondria in blood lymphocytes. This entirely agrees with the chief finding of the preceding study on the postnatal development of the lymphatic tissue in the rat (*Imamura*, 1958). However, it should be stressed here that after irradiation the *Flemming*'s nodules have reached their full maturity much earlier than they did in the postnatal development.

As regards the relationship between changes of the lymphocytic blood picture and of the lymphatic tissue after irradiation, a sharp drop of either the average number of lymphocyte mitochondria or the lymphocyte count may well be explained by a massive destruction of lymphocytes caused by irradiation. A similar drop in both values has also been observed after a single injection of 20 mg of cortisone acetate into abult rabbits by one of our collaborators, *Monden* (1956). This indicates that younger lymphocytes which contain a greater number of mitochondria than the mature and older forms are more sensitive to both X-irradiation and adrenalcortical hormone. This is further supported by the well established finding that the pale-staining centers of *Flemming*'s secondary nodules consisting chiefly of proliferating lymphocytes are the predilection sites of destruction of lymphocytes in response to various kinds of noxious agents.

The next finding upon which we lay a great stress is the earlier elevation of the mitochondrial number in blood lymphocytes as compared with the recovery of the lymphocyte count after irradiation. It was demonstrated that while the lymphocyte count was maintained at considerably low levels until the 14th day, the average number of mitochondria per lymphocyte began to increase from the 3rd on and thereafter rose sharply beyond the initial value. The regeneration of *Flemming*'s secondary nodules, on the other hand, commenced from the 7th day on and it also proceeded much faster than the recovery of the lymphocyte count. It can be stated, therefore, that a rise of the mitochondrial number in blood lymphocytes more closely reflects the regenerative processes of the lymphocytopoietic organs, the *Flemming*'s nodules in particular, than an elevation of the lymphocyte count.

Again, the author wishes to emphasize here that the present findings confirm the earlier observations (*Osogoe* et al., 1953; *Awaya*, 1956; and *Imamura*, 1958)

and give additional evidence to support the view that a marked rise in mitochondrial number in blood lymphocytes takes place as a consequence of extensive new formation of *Flemming*'s nodules in the lymphoid organs. That an extensive new formation of *Flemming*'s nodules in the lymphoid organs indicates an increase in production and delivery of lymphocytes from these organs has been repeatedly emphasized in the earlier publications.

SUMMARY

1. In a series of young abult albino rats weighing around 200 g, variations in mitochondrial number in blood lymphocytes were observed in relation to the processes of regeneration of the lymphatic tissue, the *Flemming*'s secondary nodules in particular, after total body X-irradiation in a dose of 600 r.

2. Immediately after irradiation, there occurred a sharp drop of both the lymphocyte count and the average number of mitochondria per lymphocyte in the blood. The mesenteric lymph nodes and splenic white pulp were severely depleted of lymphocytes through a massive destruction of these cells. The *Flemming*'s secondary nodules had disappeared within several days.

3. During the regenerative processes of the lymphatic tissue, an extensive new formation of *Flemming*'s secondary nodules in the mesenteric lymph nodes and spleen was observed almost coincident with a remarkable transient elevation of the average number of mitochondria in blood lymphocytes, during the period between the 14th and 21st days after irradiation.

4. These findings provide a strong evidence to support the view that a marked rise in mitochondrial number of blood lymphocytes takes place as a consequence of extensive new formation of *Flemming*'s secondary nodules in the lymphoid organs, which, in turn, indicates an increase in production and delivery of lymphocytes to the blood.

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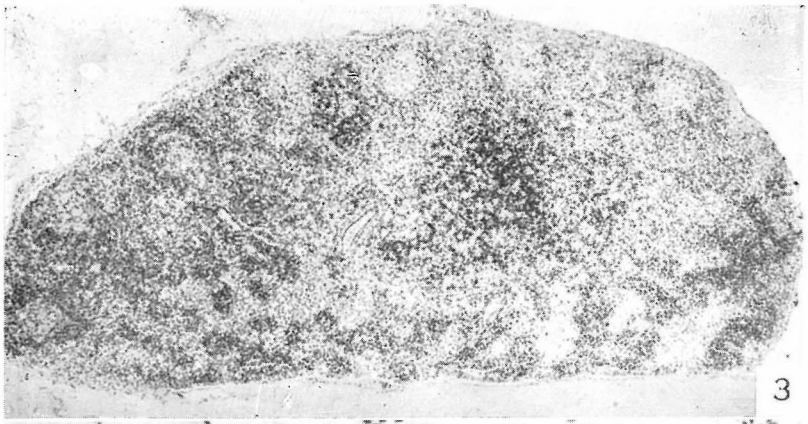
PLATE I

Explanation of Figures

Fig. 3. Mesenteric lymph node greatly depleted of lymphocytes. Several remnants of *Flemming*'s secondary nodes are to be seen in the cortex. Rat No. 36, 24 hours after irradiation. ×40.

Fig. 4. A remnant of *Flemming*'s secondary nodule in the same node as shown in Fig. 1. A few epitheloid cells having a distinct nucleolus are to be seen in the depleted center. ×200.

Fig. 5. Newly formed, immature *Flemming*'s secondary nodule without outer zone of small lymphocytes ("bare germinal center" of *Conway*). Rat No. 21, 10 days after irradiation. ×200.



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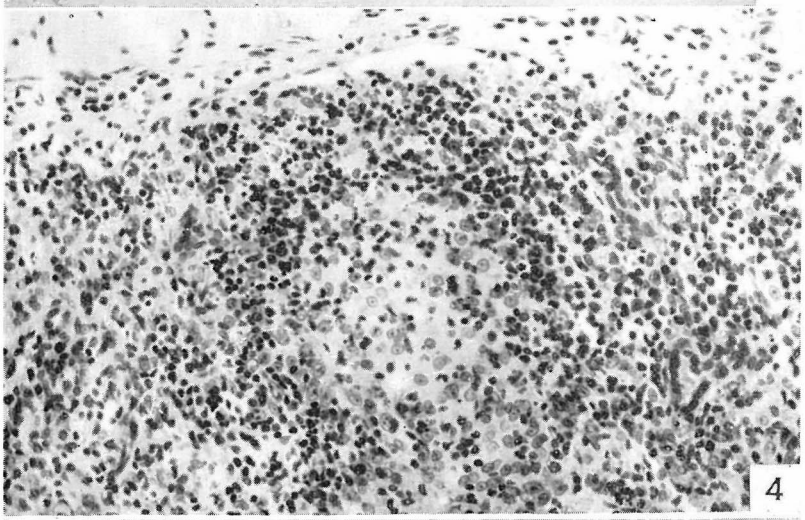

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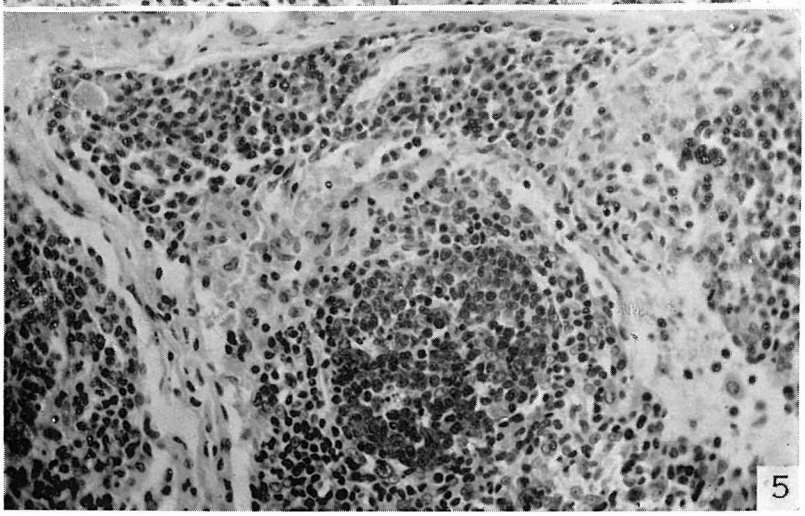

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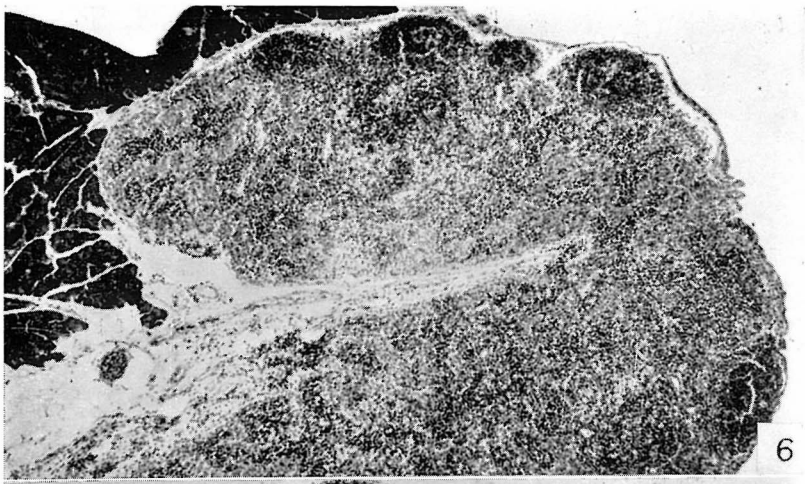
PLATE II

Explanation of Figures

Fig. 6. Solid secondary nodules developing in the cortex of mesenteric lymph node. Rat No. 20, 14 days after irradiation. ×40.

Fig. 7. Mature *Flemming*'s secondary nodules developing in the cortex of mesenteric lymph node. Rat No. 11, 21 days after irradiation. ×40.

Fig. 8. Mature *Flemming*'s secondary nodules in the cortex of mesenteric lymph node. Rat No. 9, 28 days after irradiation. The nodules have reached their full maturity. ×40.



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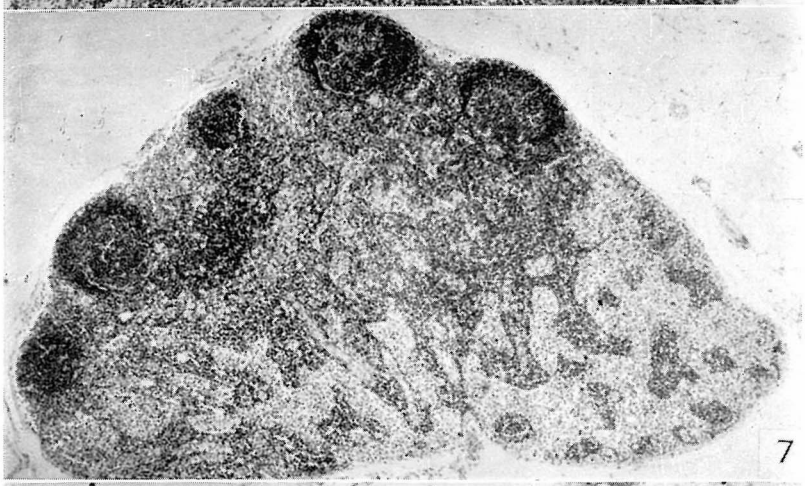

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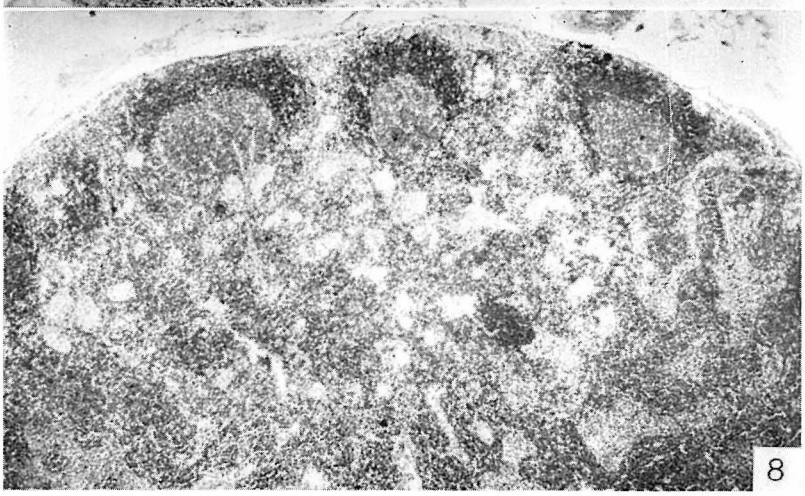

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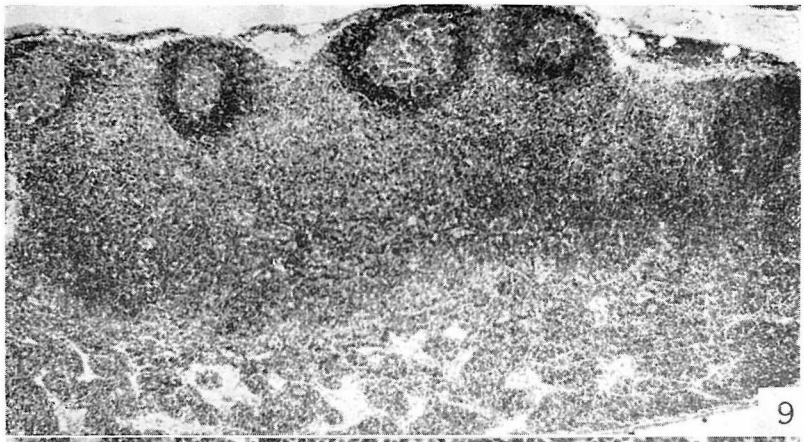
PLATE III

Explanation of Figures

Fig. 9. Mesenteric lymph node. Rat No. 5, 60 days after irradiation. The cortex of the node containing several large *Flemming*'s nodules is well developed and forms a large diffuse mass corresponding to a pseudo-secondary nodule of *Ehrich*, extending toward the medulla. × 40.

Fig. 10. A large mature *Flemming*'s nodule in mesenteric lymph node ("half-active" form). Rat No. 9, 28 days after irradiation. The upper half of its center is becoming inactive. × 200.

Fig. 11. A medium-sized mature *Flemming*'s nodule with inactive center devoid of proliferating lymphocytes ("inactive" form). Rat No. 1, 35 days after irradiation. × 200.



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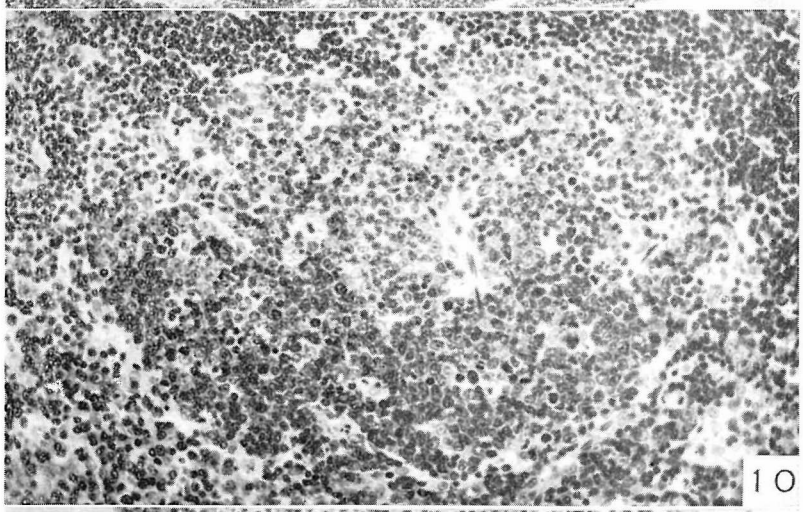

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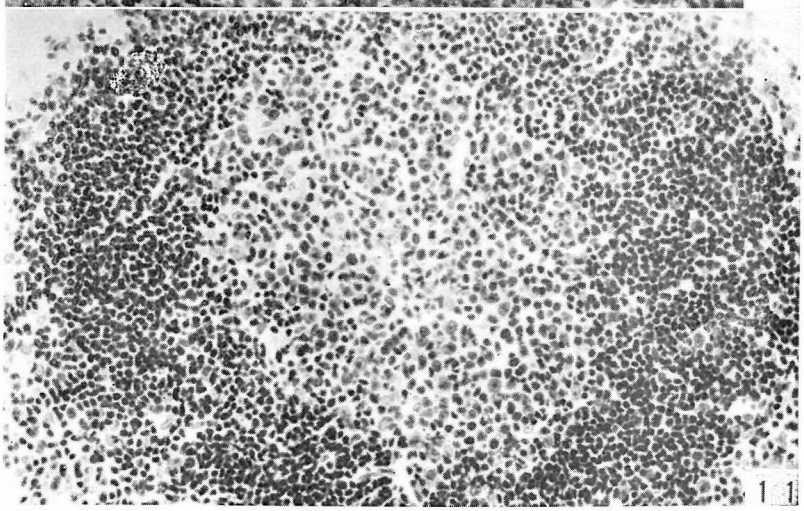

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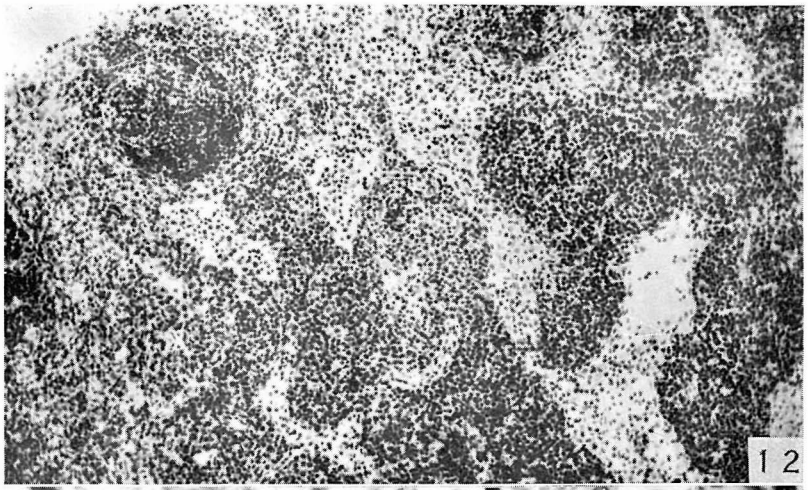
PLATE IV

Explanation of Figures

Fig. 12. Plasma cell infiltration in the medullary cords of mesenteric lymph node. Rat No. 34, 3 days after irradiation. The medullary cords are almost entirely filled with proliferated plasma cells. × 100.

Fig. 13. Plasma cell infiltration in the medullary cord of mesenteric lymph node. Rat. No. 25, 7 days after irradiation. The densely aggregated cells are composed almost entirely of proliferated plasma cells. × 400.

Fig. 14. A few fat cells scattered in the medullary cords of mesenteric node. Rat No. 31, 21 days after irradiation. × 100.



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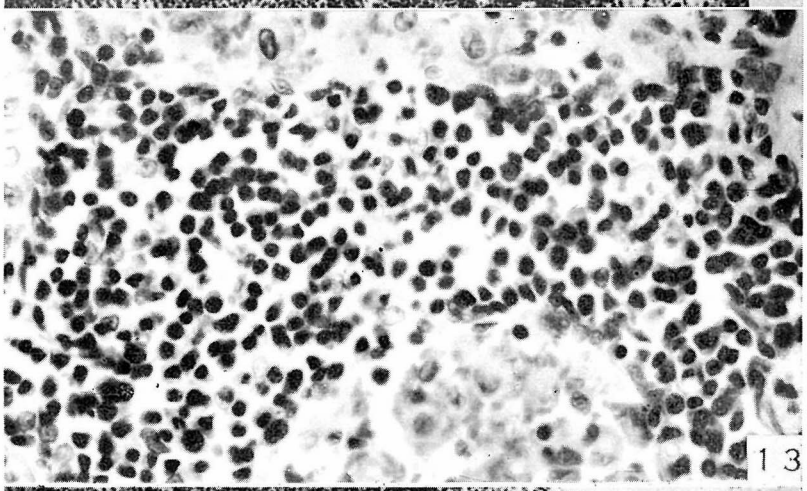

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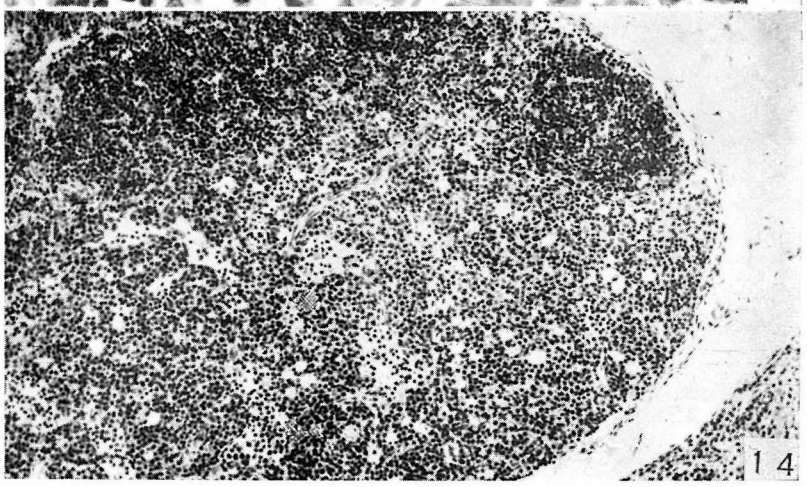

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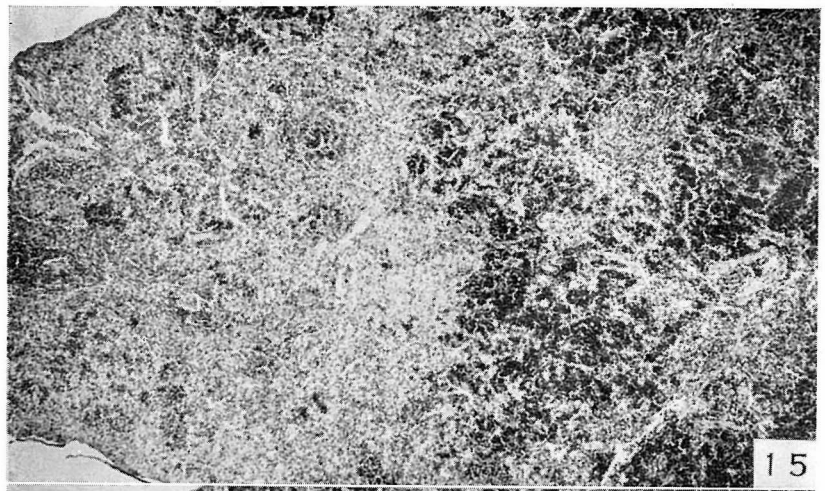
PLATE V

Explanation of Figures

Fig. 15. Spleen of Rat No. 24, 7days after irradiation. There is no sign of regeneration of the white pulp. A slight degree of hyperplasia of erythroblasts is seen in the red pulp; they appear as dark staining cell foci. ×40.

Fig. 16. Spleen of Rat No. 30, 21 days after irradiation. An advanced stage of regeneration of the white pulp. the erythropoietic activity is greatly intensified and the red pulp is almost completely filled with erythroblasts. ×40.

Fig. 17. Spleen of Rat No. 27, 60 days after irradiation. The final stage of regeneration of the white pulp. The erythropoietic foci is no longer seen anywhere. ×40.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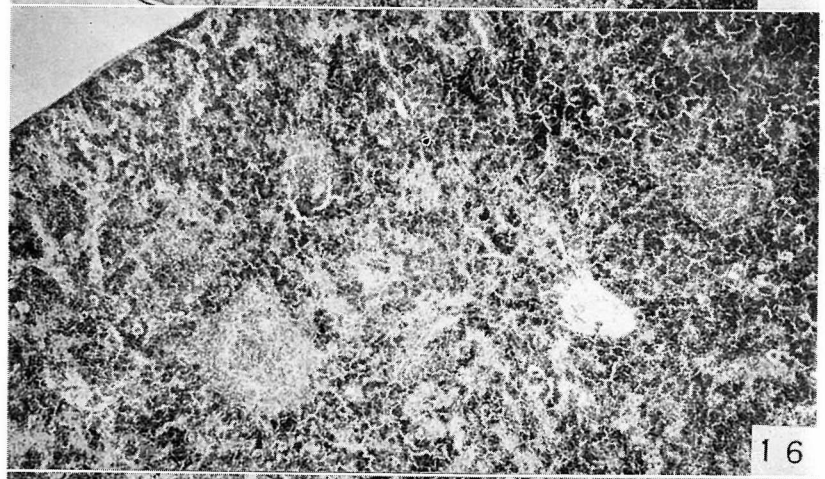
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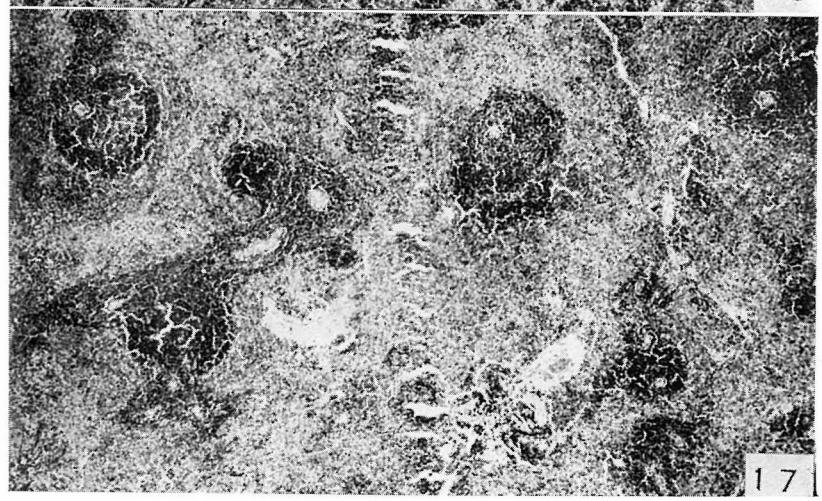
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