

BLOOD MICROCIRCULATION IN THE LYMPH NODE DURING THE PRIMARY IMMUNE RESPONSE*

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There is constant recirculation of the small lymphocytes from the blood into the lymphatic tissues. The most important route of recirculation is the postcapillary venule (1-5). The small lymphocytes which enter the lymph node from the bloodstream are necessary for the immune response (6-8). Furthermore, it has been suggested that the microcirculation in the lymph node plays a role in antigen uptake (9) and in propagation of the immune response (10). The information concerning cellular interchange between the blood and lymphatic tissues was based on tracer studies, radioautographic examination, and electron microscopy.

In spite of the substantial recent information, our knowledge concerning the role of the blood circulation in the immune response is fragmented, and a more comprehensive morphological evaluation of the microvasculature still seems necessary.

This investigation was designed to determine the alterations of the microvascular morphology during the course of the primary immune response. The evaluation was based on microangiograms and histologic sections. Microangiography is a highly suitable method for a detailed study of the microvasculature (11). It permits an accurate, three-dimensional reconstruction of the capillary and postcapillary structures and can be correlated with the histologic findings.

Materials and Methods

The animal model utilized in this study is the popliteal lymph node of the rabbit challenged by typhoid-O antigen (12). In addition to the microangiograms, histologic sections and imprints (13) were obtained. The weight changes of the lymph node were recorded and antibody titers were periodically determined. Our observations ranged from 3 hr to 75 days. Our histologic findings, the cellular detail on imprints, the weight changes in the lymph node, and the antibody titers were essentially in agreement with previous studies (12-19).

General Plan.—31 male, New Zealand white rabbits, weighing approximately 2500 g, were injected with 0.5 ml of febrile antigen, *Salmonella* group D (typhoid O),¹ in the left hind footpad. The right side served as a control. At intervals from 3 hr to 75 days microangiography was performed. The removed lymph nodes were weighed, and imprints of the freshly cut lymph nodes were made. Contact microangiograms and histologic sections were obtained and correlated. Typhoid-O antibody titers from the plasma were determined (Table I).

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¹ Lederle Laboratories Div., American Cyanamid Co., Pearl River, N. Y.

Operative Procedure.—Under intravenous Diabotal² anesthesia, laparotomy was performed. Heparin³ (10 mg) was injected intravenously. Subsequently, two catheters (PE-190) were introduced into the aorta below the renal arteries. One was directed caudally and one cephalad. One catheter (PE-240) was placed into the inferior vena cava. 1000 ml of high molecular weight dextran (6% Gentran-75)⁴ was injected into the aorta. Free drainage of the venous blood from the venous catheter was permitted. The infusion pressure was 165 mm Hg. The infusion usually lasted 30 min.

Toward the end of the dextran perfusion, the animal's respiration and heartbeat ceased. The venous return became bloodless. At that time 1000 ml of 7% Micropaque⁵ suspended in high molecular weight dextran was injected at a pressure of 220 mm Hg. At the completion of the perfusion, the popliteal lymph nodes were carefully dissected and weighed. In some animals the nodes were cut, and imprints were obtained and stained with Giemsa stain. The lymph nodes were embedded in paraffin and serially sectioned. 6- μ histologic sections and 250–350- μ microangiographic sections were obtained. The histologic sections were stained with hematoxylin and eosin. The antibody titers were determined by the in-the-tube test.

Microangiographic Technique.—The thick sections were placed in close contact with Kodak high resolution⁶ photographic plates and radiographed with an AEG-50 (Machlett Laboratories, Inc., Stamford, Conn.) beryllium window X-ray tube. The technical factors were: 18 cm target-to-film distance; 20 mA; 18 kv; and 5 min exposure time. The micro-radiographs were developed in D-19 (Eastman Kodak Co.). Enlarged photographs ($\times 35$) of the entire microradiograph and histologic sections were initially obtained. Subsequently, for detailed study, some parts of the microradiographs were enlarged up to $\times 400$ using a light microscope.

RESULTS

The evolution of the immune response is considered here chronologically, and the microangiographic and histologic observations are correlated rather than discussed separately. For better understanding of the microvascular changes, the normal appearance is discussed in detail.

Vascular Pattern of the Normal Rabbit Lymph Node.—

Arteries: Usually one or two arteries with an average diameter of 140 μ entered the lymph node through the hilum. These vessels were straight and slender and showed a mild gradual decrease in diameter through two to four branchings usually with a branching angle of 45°. The average diameters were: first branch, 70 μ ; second, 40 μ ; and third, 25 μ . As they traversed the medullary cords, they gave off side branches. [Finally, they reached the subcapsular capillary arcade (20, 21).] An occasional artery pierced through the capsule. As they traversed the cortical portion of the lymph node, the arterial branches formed several large vascular units (Figs. 1 *a* and 4 *a*). A large vascular unit usually corresponded to a lobule. Lobules are subdivisions of the lymph node and are partially demarcated by fibrous tissue extending from the capsule (Fig.

² Diabotal (sodium pentobarbital); Diamond Laboratories, Des Moines, Iowa.

³ Lipo-Hepin (sodium heparin); Riker Laboratories, Northridge, Calif.

⁴ 6% Gentran-75 (dextran-75); Travenol Laboratories, Edison, N. J.

⁵ Micropaque; Picker X-Ray Corp., White Plains, N. Y.

⁶ Eastman Kodak Co., Rochester, N. Y.

1 *b*). The arteries were situated at the periphery of the lobules and had an average diameter of 20–40 μ . They terminated in the subcapsular-capsular capillary arcade. Within the large vascular unit several small vascular units sometimes were present. Often, these units represented a secondary nodule histologically. Characteristically, the arteries were located at the periphery.

Capillaries: Under the subcapsular sinus there was a dense capillary arcade 40–60 μ wide (Fig. 2 *b*). These capillaries averaged 11 μ in diameter. Some anastomoses between the subcapsular capillary arcades of adjacent vascular units were present.

Within the undifferentiated lymphoid tissues of the cortex there was a diffuse, significantly less dense capillary network. The capillary supply of the inner portions of the secondary nodules was rather sparse (Fig. 4 *a*). The capillaries of the pseudosecondary nodules were somewhat more dense and were often situated in a concentric fashion. The capillary branching was very often at right angles.

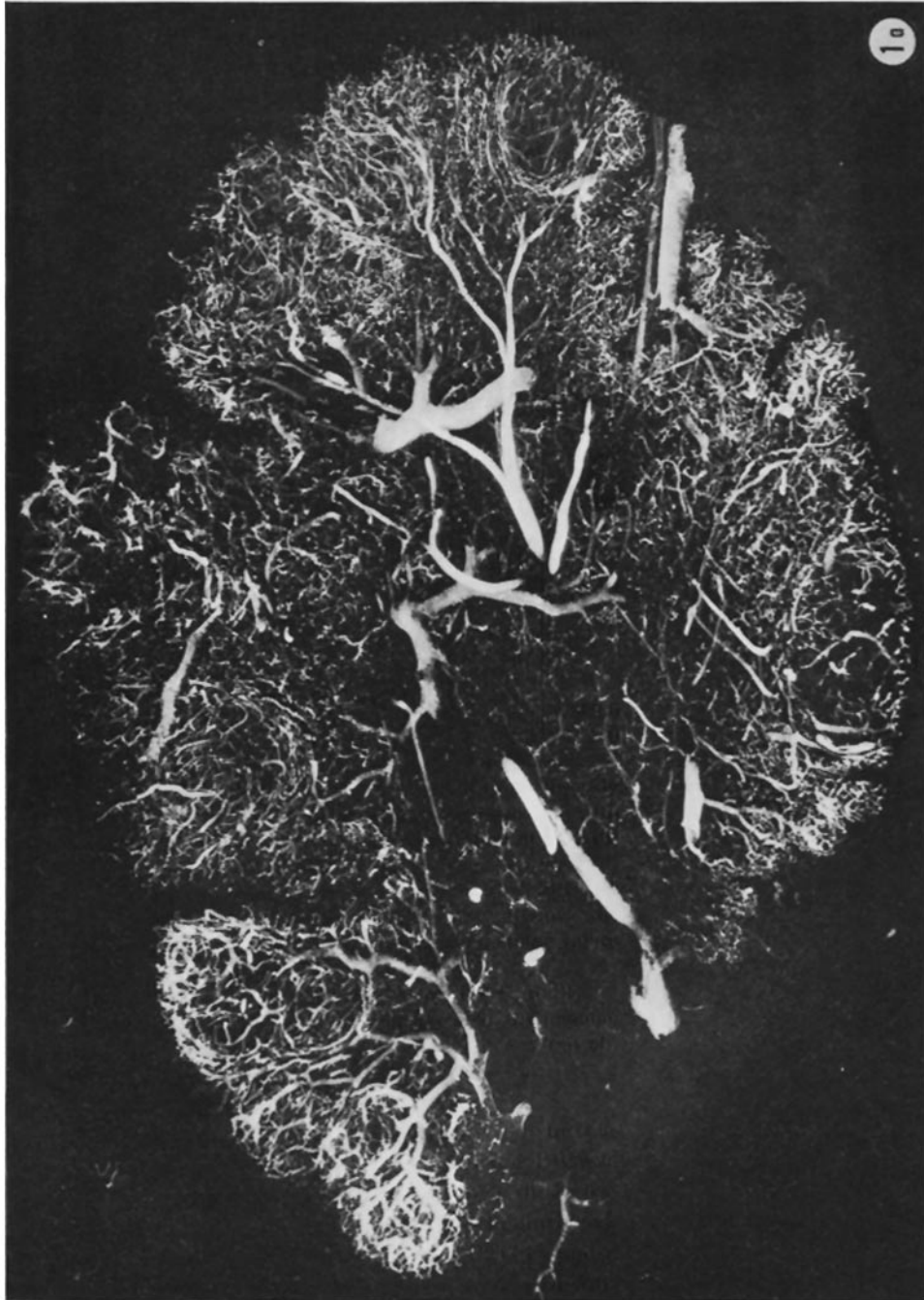
Within the medullary cords there was a very dense capillary network resembling the subcapsular arcade. The capillary diameter varied from 7 to 10 μ (Fig. 9 *a*).

Postcapillary venules: The postcapillary structures had a slightly granular appearance on the microangiograms due to the less complete mixing of the radiopaque particles (Fig. 3). This phenomenon facilitated their identification. Usually two to five capillaries formed a postcapillary venule. At the capillary-postcapillary transition there was a sudden increase in diameter (Fig. 2 *a*). From an 11 μ capillary an increase to a 15–30 μ postcapillary venule was not unusual. An interconnecting network of postcapillary venules was situated just under the subcapsular capillary arcade (Figs. 2 *b* and 9 *a*). These postcapillary venules were rather short, measuring approximately 60–80 μ in length and 15–30 μ in diameter. Their interconnections were nearly at right angles. The distribution of the postcapillary venules appeared random in the undifferentiated lymphoid tissues. Within the nodules the postcapillary venules again tended to be situated at the periphery. The postcapillary venules formed a large venule which ran a centripetal course and entered one of the main veins of the lymph node at the corticomedullary junction (average diameter, 140 μ). Several of these larger veins conjoined and left the lymph node through the hilum.

The venules of the medullary cords entered the larger corticomedullary veins. It was rare to observe a postcapillary venule originating from the medullary cords.

Vascular Pattern during the Immune Response.—

First 24 hr: At 6 hr there was a slight increase in the diameter of the capillaries of the subcapsular arcade of the involved side. The increase in size was more apparent in the areas where there was histologically a granulocytic reaction.



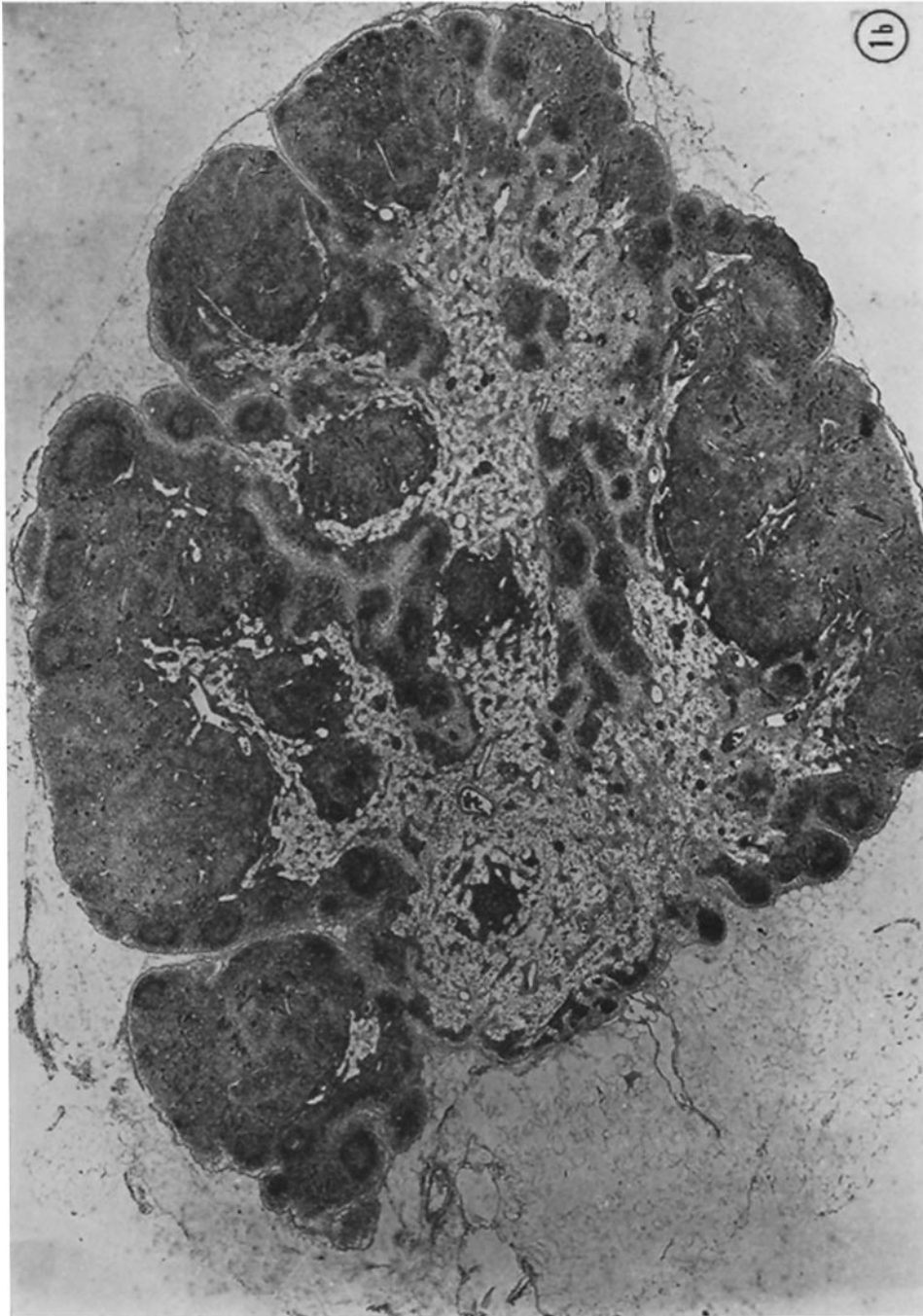


FIG. 1. (a) Microangiogram of normal popliteal lymph node (250 μ). \times 20. (b) Histologic section of Fig. 1 a (5 μ). Hematoxylin and eosin (H and E). \times 20.

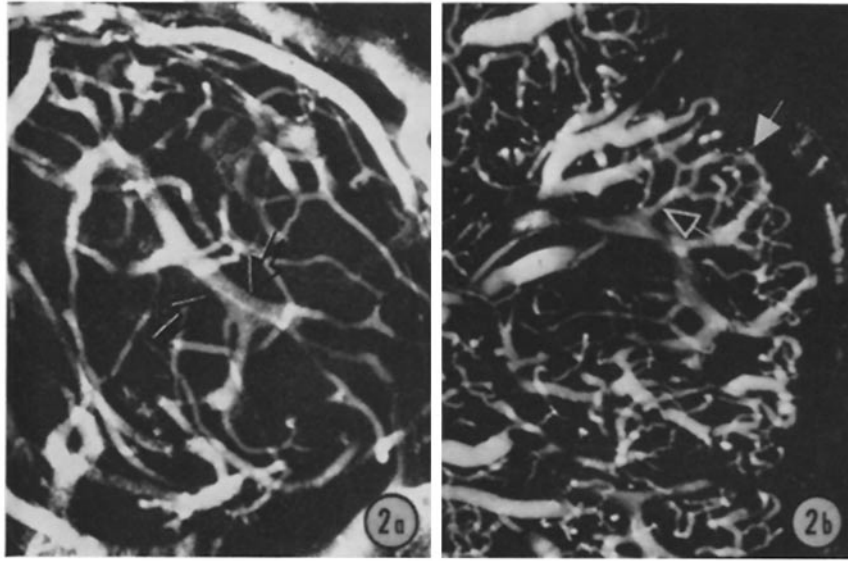


FIG. 2. (a) Pseudosecondary nodule from Fig. 1 a. $\times 100$. Arrows point to a postcapillary venule. (b) The subcapsular and cortical region from rabbit 16 (3 days). Solid arrow points to subcapsular capillary network. Open arrow points to formation of postcapillary venules. $\times 40$.

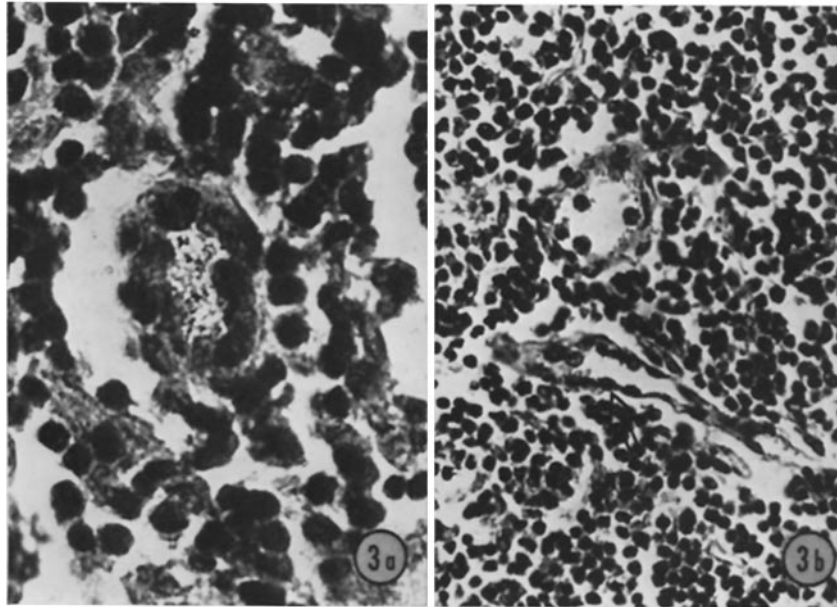


FIG. 3. (a) Cross-section of a high endothelial (HE) venule. Note the tall endothelium and the barium crystals within the lumen. 5μ section; H and E. $\times 300$. (b) Tangential section of an HE venule. The endothelial lining is not as tall as that of Fig. 3 a (arrow). 5μ section; H and E. $\times 120$.

By 12 hr there was a significant increase in the weight of the nodes. Straightening of the cortical arteries and veins coincided with cellular hyperplasia and histologic dissolution of nodules. No changes in the medullary cords could yet be observed.

Histologically the granulocytic reaction began at 5 hr and reached its height at 18 hr. The granulocytic reaction was perinodal and involved the subcapsular sinus and the superficial regions of the cortex. There was beginning dissolution of the germinal centers and evidence of diffuse lymphoid hyperplasia of the cortex with only minimal changes in the medullary cords.

1-3 days: At 24 hr (corresponding to the significant increase in size of the nodes), there was dissolution of the vascular units, and the larger arteries and veins were more evenly distributed throughout the lymphoid tissues (Fig. 4). The capillary diameter increased both within the subcapsular arcade and within the medullary cords. The density distribution of the capillaries increased throughout the lymphoid tissues.

By 48 hr the dissolution of the vascular units was almost complete. There was an increasingly dense capillary network throughout the markedly enlarged cortex without any avascular areas. The increased vascularity of the medullary cords became a prominent feature (Fig. 6 *a*). The medullary cord capillaries ranged from 15 to 20 μ in diameter.

On the 3rd day, in addition to the progressive hypervascularity, there were glomerulus-like tufts of capillaries at the cortical medullary junction measuring approximately 150 μ in diameter. These tufts histologically corresponded to developing nodules. There was a slight increase in the vascularity of the capsule.

Beginning on the 2nd day, an increasing number of plasmocytes were present within the medullary cords with progressive enlargement of these structures. Histologically, by the 3rd day the granulocytic reaction completely subsided. There was progressive cellular hyperplasia of the cortex with complete dissolution of the nodules.

4-9 days: The vascularity of the capillary arcades peaked at 4-5 days (Figs. 5 and 9 *b*). The markedly enlarged medullary cords on the 5th day showed many capillaries in the 25 μ range (Fig. 6 *b*). The width of the subcapsular capillary network increased. The capillaries maintained their regular outline and their branching characteristics; this tended to exclude neovascularity. By the 7th day occasional vascular units reappeared, and the vascularity of the medullary cords decreased slightly.

The peak of the plasmocytic response in the medullary cords occurred on the 5th day. Increasing numbers of plasma cells can be identified in the cortical areas also. Starting on the 6th day primary and secondary nodules began to reappear.

9-75 days: By the 9th day there was significant reconstitution of the vascular units (Fig. 7). Moderate enlargement of the subcapsular arcade still was seen

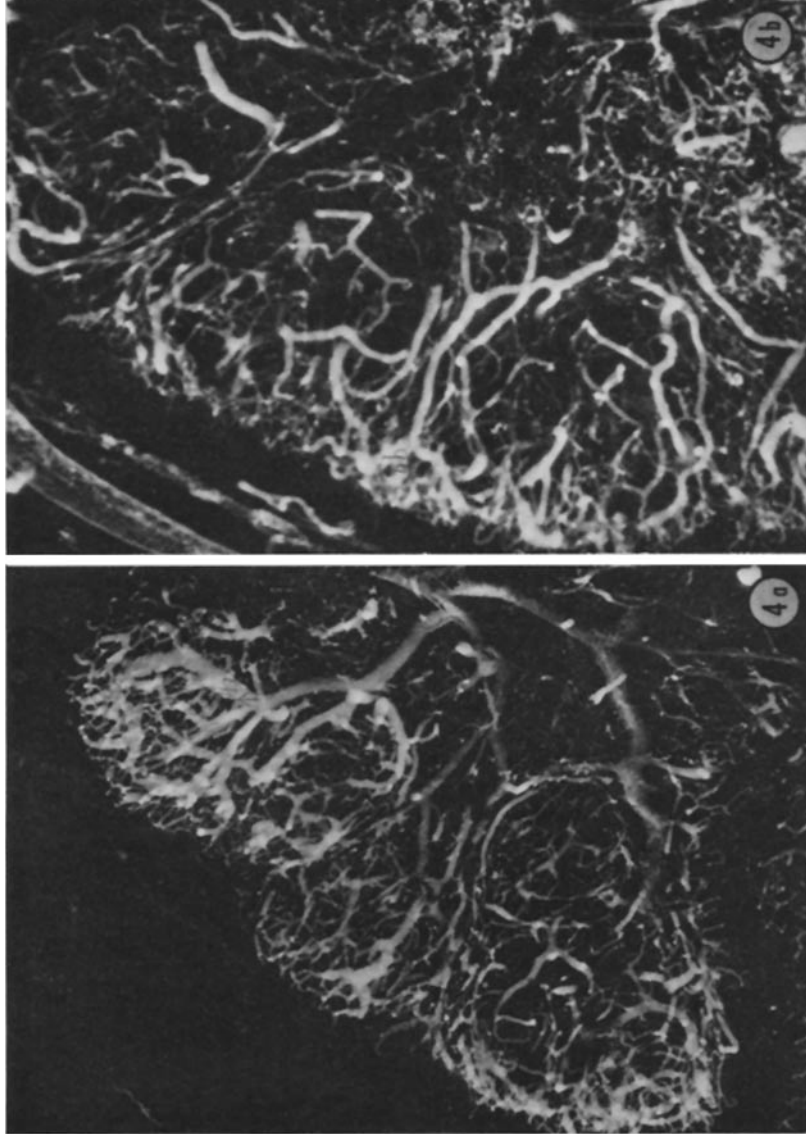


FIG. 4. (a) A large vascular unit from Fig. 1 *a* histologically corresponding to a lobule. $\times 32$. (b) Cortical area from rabbit 13 (24 hr). Note the dissolution of the vascular units and the prominent subcapsular capillary network. $\times 44$.

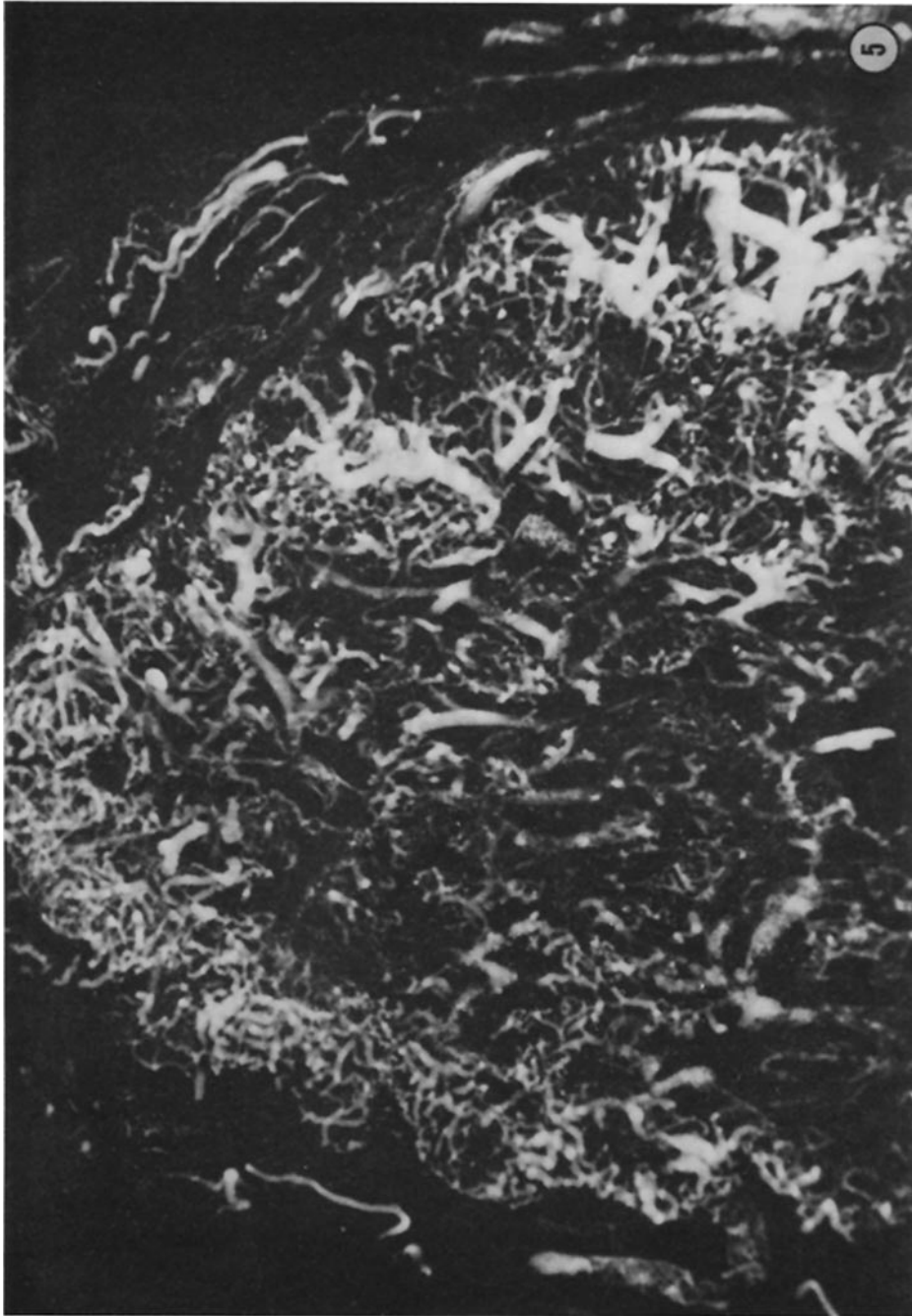


FIG. 5. Part of a lymph node of rabbit 22 (5 days). Note the increased vascularity of the subcapsular and medullary capillary arcade. X 44.

with only minimal increase in the vascularity of the medullary cords. A slight stretching of the cortical blood vessels was apparent.

At 15 days, the microvascular appearance returned almost to normal (Fig. 8). Minimal residual widening of the capillaries in the medullary cords was present (10–15 μ). At 75 days the weight of the lymph node was still increased, but the angiographic architecture had returned to normal.

Histologically, on the 9th day, there were numerous germinal centers present.

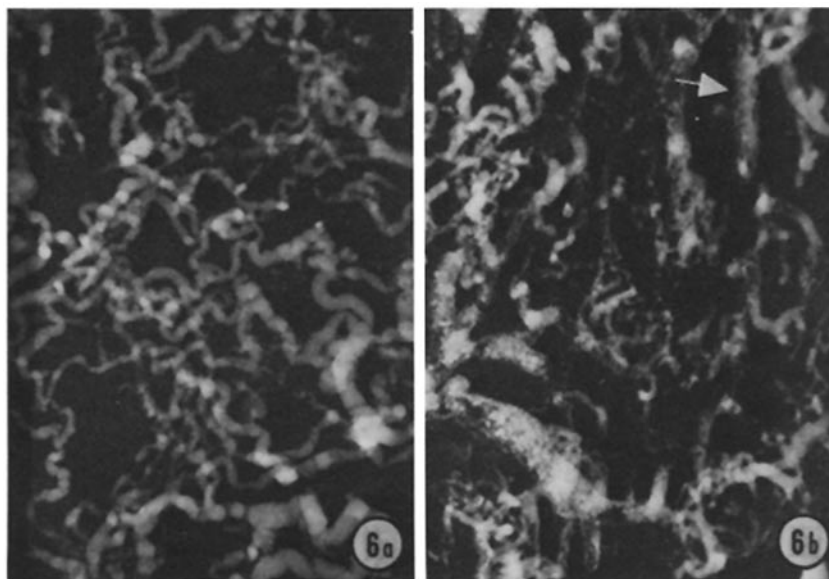


FIG. 6. (a) Medullary cord capillaries from rabbit 17 (3 days). The capillary diameter is 15–20 μ . \times 100. (b) Medullary cord capillaries from Fig. 5 (5 days). Markedly enlarged medullary cords are visible. Arrow points to a large venule. \times 65.

The number of plasma cells within the medullary cords had decreased. At 15 days, the cortex was still enlarged, but it contained all the normal cortical elements. At 75 days there was still residual hyperplasia of the node, and the histologic pattern had returned to normal.

Extravasation of the Contrast Material within the Lymph Nodes.—Of the control lymph nodes, only two showed extravasation. In one instance the extravasation was only minimal and in a second node it was moderate. On the other hand, six lymph nodes on the involved side showed significant extravasation, and six additional lymph nodes revealed minimal extravasation. The extravasation occurred in experiments scattered throughout the observation period; there was no preference for the early or the late phases. These findings may indicate increased permeability or decreased pressure resistance of the small blood vessels during the immune response.

Changes in Weight.—The weight changes are tabulated in Table I. The weight was highest on the 5th day. Two lymph nodes revealed a weight increase 10-fold larger than the control side. There is no apparent explanation for this phenomenon.

Antibody Titer Determinations.—The antibody titers are summarized in Table I. The highest antibody concentration was found on the 5th day. Significant antibody production persisted until the 15th day.

Evaluation of the Imprints.—The imprints revealed large numbers of granu-

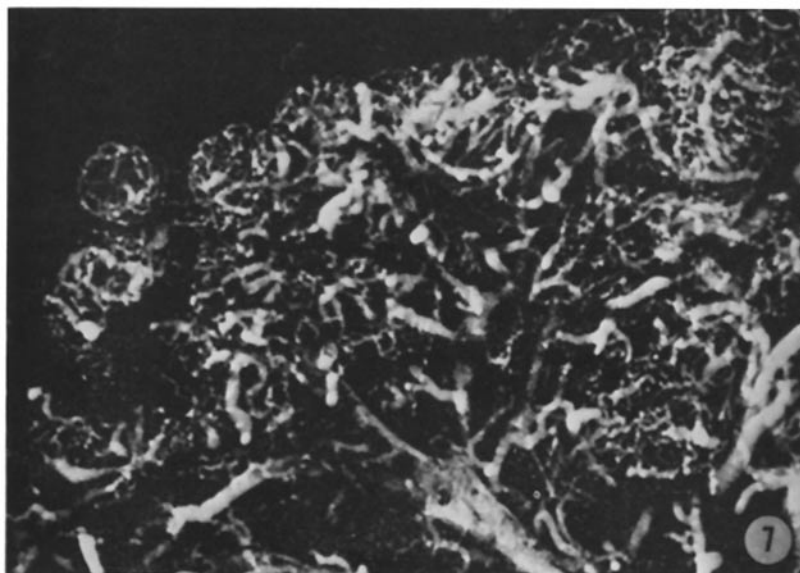


FIG. 7. Cortical region from rabbit 28 (9 days). There is reconstitution of vascular units corresponding to reappearing secondary nodules. $\times 120$.

locytes during the first 24 hr. After the granulocytic response had subsided on the 4th and 5th days, the small and medium-sized lymphocytes predominated. The highest level of plasma cells was recorded on the 5th day.

DISCUSSION

Technique.—In order to reconstruct the microarchitecture, sections thick enough to show the capillaries and postcapillary structures in continuity are required. The microangiographic method is suitable for this purpose. Because of the close contact of the tissue slices with the photographic plate and the relatively long target-to-film distance, the geometry of exposure is very favorable. The unsharpness can be kept to a minimum, and the size of the focal spot of the X-ray tube is almost irrelevant. The very sharp primary images, coupled with the very high resolution photographic emulsion, permit significant

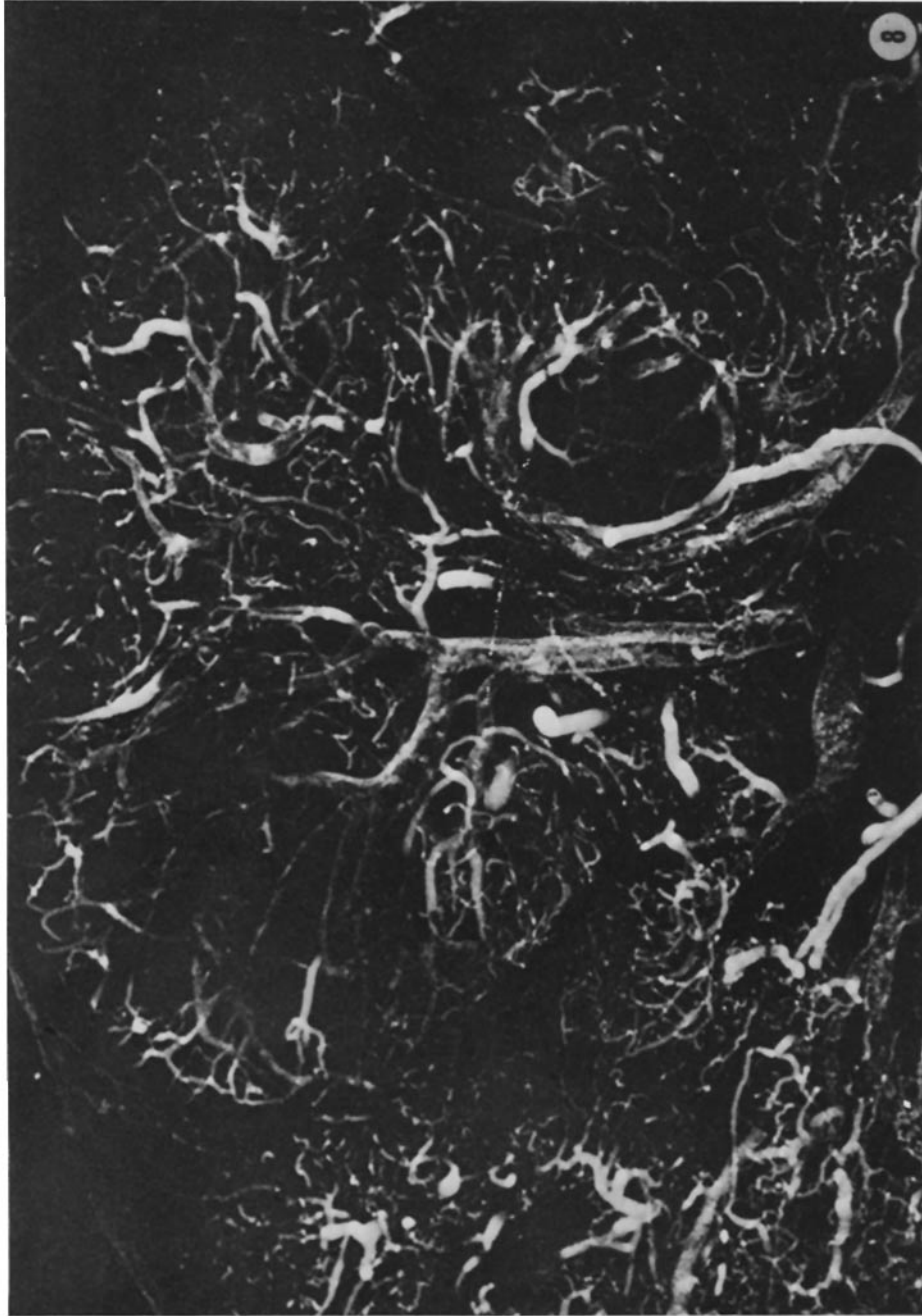


FIG. 8. Part of lymph node of rabbit 30 (15 days). The microvasculature has returned to normal. Slight stretching of the cortical blood vessels is visible. (The node is still enlarged.) X 90.

enlargement. In a $\times 100$ enlargement a 10μ capillary projects a 1 mm image which is more than sufficient for evaluation. The relatively thick tissue sections which can be examined offer an advantage of this method over clearing methods (20).

TABLE I
Weight Changes and Antibody Tilers

No. of experiment	Time interval	Wt. of nodes (mg)		Ratio Inv. wt. Con. wt.	Antibody titer
		Involved	Control		
		<i>mg</i>	<i>mg</i>		
1	3 hr	211.1	206.6	1.02	—
2	5 "	193.7	201.8	0.96	—
3	5 " *	—	—	—	—
4	6 "	417.7	325.5	1.28	—
5	7 "	262.6	231.4	1.13	—
6	9 "	282.3	300.0	0.94	—
7	10 "	982.1	297.2	3.30	—
8	12 "	285.8	195.2	1.46	—
9	12 "	600.0	300.0	2.00	—
10	18 "	469.4	173.7	2.70	—
11	18 " *	—	—	—	—
12	24 "	600.6	59.9	10.02	1:320
13	24 "	1119.7	387.5	2.88	—
14	48 "	1500.0	500.0	3.00	—
15	3 days	772.4	137.4	5.62	1:80
16	3 "	621.6	232.0	2.68	—
17	3 "	953.2	325.4	2.92	1:160
18	4 "	924.2	272.6	3.39	—
19	4 "	1300.0	400.0	3.25	—
20	5 "	868.6	240.3	3.61	1:5120
21	5 "	695.2	187.4	3.71	—
22	5 "	555.5	255.4	2.18	—
23	5 " *	—	—	—	—
24	6 "	1338.3	326.3	4.10	1:5120
25	6 "	1058.1	205.6	5.15	1:2560
26	7 "	579.9	41.0	14.10	—
27	7 "	900.0	300.0	3.00	—
28	9 "	403.8	160.9	2.51	1:2560
29	12 "	931.2	466.7	1.99	—
30	15 "	404.7	364.3	1.11	1:2560
31	75 "	300.5	106.4	2.82	Neg.

* Imprint only.

Because the popliteal lymph node is supplied by relatively small arteries and is far removed from the aorta, only the total body perfusion technique permits complete filling while producing relatively few artifacts. In a previous study we used plasma as the suspending agent for barium (11). More recently we observed that high molecular weight dextran is an ideal perfusing agent. The

lowest concentration of Micropaque which gave us consistently high-quality images was 7%. When plain dextran perfusion preceded the barium-dextran perfusion, the degree of filling was more complete.

In a perfusion experiment such as this there is some artifactual overdistension of the vessels. In our model, however, the right popliteal node served as the control for the left, and the perfusion was done through a distant site. Thus overdistension was of the same proportions in the control and in the involved node.

Complete serial sectioning of the lymph nodes for microangiography, with serial histologic correlation, is essential. Sections which are over 400 μ thick are difficult to evaluate because of the superimposition of the contrast-filled blood vessels. Stereo microangiography is helpful in separating superimposed structures.

Microvascular Changes.—The angioarchitecture of the popliteal lymph node is surprisingly constant. It is also noteworthy that the lymph node is a relatively vascular organ. The vascularity of the lymph node is much more apparent on microangiograms than on histologic sections (Fig. 1). The arteries are slender and straight, and they lack anastomoses below the capillary level. The veins are larger and intercommunicate freely. There is a very rich network of capillaries situated under the subcapsular sinus and throughout the medullary cords. These are adjacent to the intranodal lymphatic pathways: the subcapsular sinus and the medullary sinusoids. Within the undifferentiated lymphatic tissues of the cortex there is a fairly uniform, freely communicating capillary network.

The various nodules are less vascular. The center of a secondary nodule (germinal center) is almost avascular, and the larger arterioles and venules are displaced toward the periphery of the nodule. The larger nodules such as the pseudosecondary nodule are more vascular, showing a concentric arrangement of the blood vessels which indicate the growth process (Fig. 2 *a*).

During the primary immune response the first changes in the microvasculature involve the subcapsular and medullary cord capillary arcade (Figs. 5, 6, and 9). These vascular changes are more marked in those areas of the node in which the granulocytic infiltration is most prominent. The early vasodilatation may be a manifestation of inflammation. Between the 2nd and the 4th day of the primary immune response, there is a complete dissolution of the vascular unit. The appearance of the cortex of the lymph node resembles undifferentiated lymphoid tissues. The peak of the increased vascularity within the medullary cords occurs about the 4th or 5th day (Fig. 9 *b*). This coincides with the maximal plasmocytic response of the medullary cords.

During the 3rd day of the immune response we observed glomerulus-like capillary tufts deep in the cortex, adjacent to the medullary cords. Histologically these tufts show a conglomeration of small lymphocytes. They average 150 μ

in diameter. One must consider that the blood supply has played a role in the formation of these nodules.

We assume that redistribution of the capillaries and postcapillary structures throughout the cortex of the lymph node facilitates increased interchange between the lymphatic tissue and the circulating blood.

After 7 days the appearance of the microvasculature returns to normal. The cortical lymphoid tissues again differentiate into nodules and the nodules have decreased vascularity in their centers.

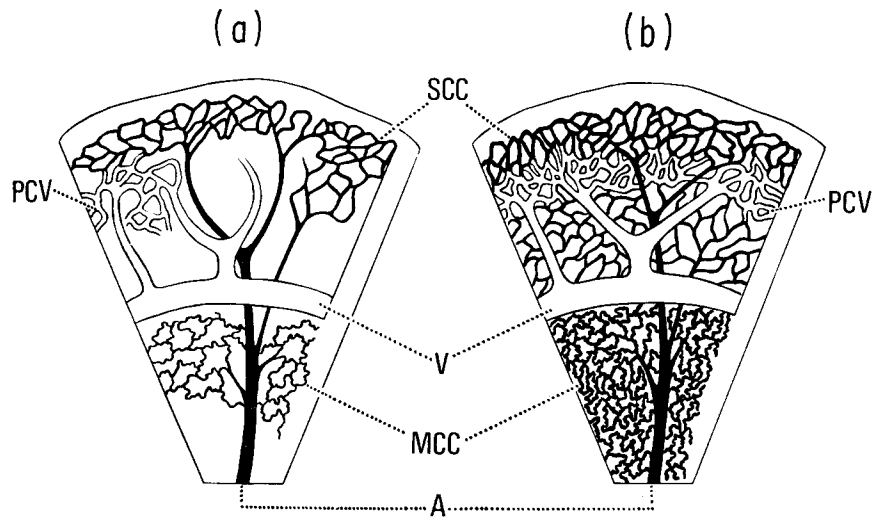


FIG. 9. (a) Diagram of normal microvasculature. SCC, subcapsular capillaries; PCV, postcapillary venules; MCC, medullary cord capillaries; A, artery; V, vein. (b) Diagram at height of microvasculature changes (4-5 days).

It has been postulated that the secondary nodules may develop from massive proliferation of high endothelial venules. This would explain their relative avascularity (22). Whether this is a valid assumption cannot be determined from our studies. An alternate explanation is that the forming nodules merely displace the capillaries and postcapillary venules. Even though the lymph nodes are still enlarged at 15 days, the pattern of the vascular supply has returned to normal.

The Postcapillary Structure.—The peculiar venules in the cortex of the lymph node, which have an unusually high endothelial lining (Fig. 3), have puzzled investigators for many years (23). It was once assumed that lymphocytes may enter the blood through these venules. The more recent studies, however, prove that the direction of migration is indeed from the blood toward the lymphatic tissues and that the lymphocytes move through the cytoplasm of this high

endothelium rather than between the endothelial cells (5). It has been suggested that antigenic stimuli initiate changes in the postcapillary endothelium (24) and eventually the hypertrophy of this endothelium forms the nidus of a secondary nodule (22). Reportedly the number of the venules showing the high endothelial lining is significantly increased during the 2nd and 3rd days of the immune response (9). In our study, however, we did not observe a definite correlation between the elapsed time and the number of postcapillary venules with the high endothelial lining. In several animals the number of high endothelial postcapillary venules increased. This increase was apparent, however, on both the involved and the control sides.

On the microangiograms it is easy to identify the postcapillary structures because of their granular appearance. The typical pattern is several capillaries forming a single postcapillary venule (Fig. 2). The diameter of this postcapillary venule is significantly larger than the capillaries from which it originated. It is apparent that the postcapillary structures are uniformly disseminated throughout the cortex of the lymph node. They are numerous in those areas of the cortex in which the capillary supply is rich, such as the subcapsular region. After correlation of the microangiograms with the histologic sections, it is quite apparent that the majority of the postcapillary venules do not have the unusually high endothelial lining. On the other hand, several postcapillary venules with normal endothelium may drain into a larger venule with a high endothelial lining.

The term "postcapillary venule" is inexact. One may refer specifically to the peculiar venule with a high endothelial lining or more generally to the postcapillary structures. For clarity of understanding, a distinction should be made between postcapillary venules and venules with high endothelial linings. It would be helpful to use the term HE (high endothelial) venules where the reference is made specifically to these structures.

During the capillary redistribution phase of the primary immune response, a redistribution of the postcapillary venules will also occur. This redistribution of the postcapillary venule can enhance the migration of the lymphocytes.

CONCLUSIONS

Microangiography performed after total blood replacement with contrast material provided complete visualization of the vascular structures of the lymph node.

Starting of the 2nd day, there is capillary redistribution throughout the cortex of the lymph node. The previously rather avascular nodules dissolve, and the cortical lymphoid tissue becomes uniformly vascular. Beginning on the 2nd day and reaching its peak on the 5th day, there is a significant increase in diameter and density of the subcapsular and medullary cord capillaries. 15 days after the antigenic stimulus, the appearance of the microvasculature returns to normal.

The postcapillary venules (the microvascular structures which follow the capillaries) are widely distributed throughout. Histologically, only a fraction of these venules have a high endothelial lining (HE venules). Therefore, it is suggested that among the postcapillary venules, those with high endothelial lining should be specifically denoted. Great individual variation in the number of HE venules was observed, and no correlation with the timing of the immune response could be established.

Whether the microvascular changes described lead to cellular change or are mere expressions of it cannot definitely be stated. However, the significant hypervascularity along the intranodal lymph pathways and the diffuse, even redistribution of the capillaries and postcapillary structures could greatly facilitate the humoral and cellular exchange between the circulating blood, the circulating lymph, and the tissues of the lymph node.

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