STUDIES ON THE MICROCIRCULATION OF THE SKIN IN DISEASE*

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In the past half century considerable attention has been directed toward the effects of systemic and local disease on cutaneous microcirculation. Capillaries, being the basic functional units of the circulatory system, are held suspect as the focus of primary pathology, or at least of important secondary changes, in many diseases. In humans the direct observational and experimental approach to the living capillary has naturally been limited to accessible areas: the conjunctiva, fundus oculi, and skin, as well as a few studies of mucosal surfaces. Observation of the microcirculation of skin has usually proven most feasible and has been the most widely used approach. In the past, the bulk of attention has been directed toward the capillaries of the nailfold because of the ease with which they can be observed. Their horizontal position, parallel to the skin surface, allows a view of more of their length than is possible in other skin areas. Recently, more emphasis has been given to studies of the microcirculation in other areas, especially the forearm.

Although density of capillary population per unit area has been evaluated in various normal skin areas and morphological observations made, especially in actual skin lesions, there is little information concerning the effect of systemic disease on the cutaneous capillary count. An evaluation was therefore undertaken of the microcirculation of the nailfolds and forearm skin using recently improved technics of keratin stripping and photography. The study included normal subjects and patients with several systemic diseases having known pathology in the cardiovascular system and in which changes in the small vessels might be suspected. The objective was to determine whether changes of pathogenetic or diagnostic significance occur, and to re-evaluate certain observations published in the past, particularly concerning the clinical value of these technics. Further, a number of skin lesions were examined and, because of the rather striking local changes seen in the microcirculation in some of these, a study was made of the response of the local microcirculation to controlled trauma and healing produced by burning, abrasion, and laceration.

HISTORICAL SURVEY

The first important microscopic observations of cutaneous capillaries in the living human were published by Lombard in 1912 (1) in a study of blood pressure in normal small vessels. The technic quickly became popular, especially in Germany and, soon after, in this country. Müller, Weiss, and associates published extensive observations on the morphologic changes in cutaneous vessels in many diseases (2, 3, 4, 5, 6), making numerous drawings and introducing the use of photography (7).

Much of the emphasis has been on nailfold capillaries; their development in infants was carefully studied and they were found to attain the adult form normally by about the sixth month (4, 8, 9). This development to adult form was found to be retarded in congenitally defective children, including mongolian idiots and cretins, the latter attaining the adult capillary form with thyroid treatment (10, 11). Considerable variations in appearance and numbers of capillaries in the skin of various areas of the body have long been recognized (4, 5, 12). Although age seems to have no effect on the number of visible capillaries (12, 13), the nailfold capillaries are felt by many observers to become slightly more tortuous in older people (9, 14). In spite of the fact that great variations in appearance of nailfold capillaries in the same and different normal subjects were recognized by many of the best early workers in the field, including Krogh (15), Brown (16), Boas (17), and Callander (18), and more recently by others (19, 20, 21), a great many studies have been published on a wide variety of physical and mental disorders which purport to show more or less pathognomonic changes in these capillaries. Recently, some of these conclusions have been criticized by Bosley (21), and it is evident that very thorough studies of normal capillaries, such as those by Gibson (22) and Walls (20), are necessary in a clinical laboratory before definitive abnormalities can be established in any disease. However, this should not be construed as suggesting that there are no well-defined abnormalities in any systemic or cutaneous diseases. The following is a brief review of some of the better studied conditions.

Raynaud’s Disease—There is unequivocal evidence of distinctive changes in Raynaud’s disease.

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The nailfold capillaries of involved fingers are dilated; there is a slow flow and clumping of the red cells. Cold exposure results in a tri-aphasic response, as described by Brown (23, 24) and others (14, 25); during the white phase, blood flow stops and many loops disappear; with cyanosis there is marked dilatation with continued complete stasis of flow, and in the red phase dilatation continues but flow is restored. Therapeutic sympathectomy results in narrowing of the capillaries and improvement in flow rate and skin temperature (26).

Scleroderma—Brown (27) distinguished the "primary" type as having a definite scarcity of nailfold capillary loops which were large and distorted, and the "secondary" type, with vasomotor changes, as having changes similar to those seen in Raynaud's disease (20). This seemingly paradoxical effect was thought to be due to a decrease in a capillary dilator factor along with arteriolar dilatation, resulting in increased flow rates.

Disseminated Lupus Erythematosus—Gilje described nailfold capillaries as dilated, uneven, with slow granular flow (28). Lawler and Lumpkin (29) did forearm capillary counts in uninvolved skin areas on four patients and found more than a fifty per cent decrease in number per square millimeter (see Fig. III). They even report a decrease of the same magnitude in discoid lupus erythematosus.

Rheumatoid Arthritis—There seem to be no significant changes in the nailfolds in uninvolved areas (30), though decreased numbers and constriction of capillaries have been described in swollen fingers and over Heberden's nodes (31, 14).

Glomerulonephritis—No consistent abnormality has been described in acute or mild chronic cases, but the nailfold capillaries in more severe chronic cases are said to show small contracted loops, a decreased number, and a high incidence of tortuosity (32, 14).

Arteriosclerosis—Brown felt that changes in nailfolds were not significant except in advanced cases when there was increased tortuosity (16). However, Wright and Duryee felt that the increase in tortuosity correlated only with age (14). Weiss and Frazier found that forearm capillary counts were not abnormal (13) (see Fig. III). Recently Davis and Landau described an abnormal pattern in the conjunctiva and nailfolds in arteriosclerosis (33): in 43% of 80 patients the nailfold capillaries were kinked and grouped in clusters. In addition, a greater number of rows and more of the sub-papillary plexus were visible than normal, and the arterial-venous capillary limb ratio was reduced. This pattern appeared in 20% of normals over 50 years of age, and in only 4% of younger individuals.

Hypertension—Though earlier observers noted a rather vague tendency to tortuosity (14, 32), no very specific changes have been described. Counts of forearm capillaries were normal (13). Davis and Landau describe no striking increase in morphological change, except for capillary narrowing in 22% of 100 cases (33, 34).

Congestive Heart Failure—Cardiac decompensation from any cause results in a dilated venous capillary limb, dilatation of the sub-papillary plexus, and a markedly decreased flow rate, as might be expected; this has been repeatedly observed and confirmed (3, 9, 35).

Polycythemia Vera—The capillary changes in this disease were carefully studied by Brown and associates (36, 37, 38). Capillaries and venules were distended and flow rate decreased, while the average number of capillary loops, counted over the first and second finger joints, increased by 50% or more over normal. However, only two normal cases are reported, and as can be seen in Fig. III, there is some discrepancy in the magnitude of increase in the two series.

Neurological Diseases—The studies of congenital defectives have already been mentioned. Epilepsy has also received considerable attention, and all observers have felt that a high percentage of idiopathic epileptics have bizarre, immature nailfold capillaries, similar to those seen infants (39, 40, 41, 42) the more severe and "deteriorated" cases supposedly being worse (45).

There is a disagreement about multiple sclerosis, some observers finding thickening of the intermediate portion of the nailfold capillary loops and general narrowing in about two-thirds of cases (44, 45), while another group, in an apparently better controlled series, found no significant difference between patients and controls (19).

In patients with migraine headaches, one group of investigators described increased tortuosity of nailfold capillaries in 90% of patients, with "blurring" of capillary edges during acute attacks (46), while another described an immature appearance, similar to that seen in epileptics, in 54% of cases (40), but again the adequacy of the control sample must be questioned.

Psychiatric Disorders—Many reports have appeared of abnormalities in a rather vague group originally described by Müller (4) as "vasoneurotic diathesis", and later as "neurasthenia" or "neurocirculatory asthenia." Apparently the patients are emotionally labile, have "vasomotor instability", blush easily, and have cold clammy hands. It is not clear just what current diagnostic category these patients would fit into. In any case, the reported abnormalities seem questionable, consisting of some increase in tortuosity of nailfold vessels, but the incidence of these changes is not impressive and suitable controls of comparable age are lacking in reported series (47, 48).

Among neurotic patients, one group with neurotic reactions did not show abnormalities, while 88% of "constitutional neurotics" (with a family history of neurosis) had over 20% abnormal nailfold capillaries (40). Other investigators describe a statistically significant increase in abnormalities in virtually all psychiatric diseases studied, particularly in severely disturbed patients (42), including schizophrenics (49, 50) and in affective disorders (51, 52). Some investigators even felt they could distinguish schizophrenics...
from manic-depressives: 72% of the former having the "immature" nailfold capillaries and 75% of the latter showing increased tortuosity (41). The validity of these observations, both in terms of occurrence of capillary changes of the types described in normals and their specificity in any disease process, requires confirmation in carefully controlled studies.

Dermatologic Diseases—Skin lesions of many types have been studied with capillary microscopy since the advent of the technic. Nichau (53) reported studies of the microcirculation in areas other than the nailfolds and described changes in psoriasis, erythromelalgia, and Raynaud's disease. Saphier (54) in 1921 reported abnormalities in lichen planus, discoid lupus erythematosus, lupus vulgaris, and other diseases. While there are definite and often striking abnormalities in the microcirculation, the number of conditions which display actual pathognomonic changes is apparently small and the technic has not thus far proven very useful as a clinical aid in diagnosis. The most thorough early work in this country seems to have been done by Michael (60, 61), while more recently Gilje (28, 55, 56) and Davis and Lawler (57, 58) have described the findings in a number of conditions.

METHODS

The technics of keratin stripping, photography, and capillary counting have been described previously (59). Keratin was manually removed with cellophane tape, the stripped area coated with oil and a cover slip, and observed under a standard laboratory microscope. Photographs were taken using a 24 mm. microtessar lens at identical magnifications, and counts were made on the photographs using a measured area calibrated to the magnification. Nailfolds were not stripped since simply applying oil allowed a clear view of the vessels in most cases. Experimental burns were produced on the volar forearm with a heated platinum wire and lacerations and abrasions with razor blades.

RESULTS

Capillary Morphology and Counts—In 54 normal individuals of both sexes, aged 5 to 84, the average volar forearm count was 42 capillaries per square millimeter, with a range of 34 to 50 (Fig. 1). There were no significant differences between age or sex groups. At the nailfold edge the average count of the first row of capillaries (Plate I, 4) was 6 per linear millimeter, with a range of 4 to 8. As has been noted many times previously there is considerable normal variation in the morphology of nailfold capillaries and many observers find that the capillary loops tend to be somewhat more tortuous in older people. Local disruption related to occupation, manicuring, nailbiting and other forms of trauma probably has a marked effect, producing tortuosity of the vessels in the area of trauma, and occasionally thickening of the stratum corneum or the entire epidermis makes visualization difficult. Thus anything less than rather severe changes, consistently observed in all of a patient's nailfolds, must be interpreted with caution. In our normal group about one third had a slight degree of generalized tortuosity. There was a marked variation in visibility and apparent length of the

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<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of Cases</th>
<th>Ages</th>
<th>Forearm Count (per mm²)</th>
<th>Nailfold Count (per mm)</th>
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<tr>
<td>Normal</td>
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<td>5-84</td>
<td>42 (34-50)</td>
<td>6 (4-8)</td>
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<tr>
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<td>37-70</td>
<td>42 (35-47)</td>
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<td>Peripheral arterial Insufficiency</td>
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<td>18-70</td>
<td>40 (35-46)</td>
<td>6 (5-7)</td>
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<td>Glomerulonephritis (acute &amp; chronic)</td>
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<td>10-31</td>
<td>41 (35-47)</td>
<td>5 (5-6)</td>
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<tr>
<td>Hypertension</td>
<td>10</td>
<td>21-63</td>
<td>41 (37-47)</td>
<td>6 (4-7)</td>
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<td>Rheumatoid arthritis</td>
<td>11</td>
<td>26-57</td>
<td>48 (38-65)</td>
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<td>Idiopathic thrombocytopenic purpura</td>
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<td>17-72</td>
<td>46 (36-56)</td>
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<td>Systemic lupus erythematous</td>
<td>7</td>
<td>34-53</td>
<td>44 (39-50)</td>
<td>7 (6-8)</td>
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<tr>
<td>Psoriasis</td>
<td>6</td>
<td>39-63</td>
<td>45 (39-63)</td>
<td>6 (5-7)</td>
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<tr>
<th>Miscellaneous (1-3 cases each)</th>
<th>All had normal capillary counts and morphology.</th>
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<tbody>
<tr>
<td>Metabolic</td>
<td>Gout (2), Asymptomatic Hyperuricemia (2), Idiopathic Hyperlipemia (3),</td>
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<td>Porpuric Diseases</td>
<td>Von Willebrand's Disease (2), Pigmented Porpuric Disease (1),</td>
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<td></td>
<td>Thrombotic Thrombocytopenic Porpura (1), Henoch-Schönlein Purpura (1),</td>
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<tr>
<td></td>
<td>Waldenström's Hyperglobulinemia (1).</td>
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<tr>
<td>Miscellaneous</td>
<td>Reiter's Syndrome (2), Sjögren's Syndrome (1), Acromegaly (1), Generalized Ichthyosis (2).</td>
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loops and in prominence of the sub-papillary plexus, which is probably related to thickness and opacity of the epidermis.

No significant deviation from the normal count range or average was found in any of the diseases investigated (Fig. I). There were two patients with rheumatoid arthritis, and one each with idiopathic thrombocytopenic purpura and psoriasis who had forearm counts above the normal range. Nailfold edge counts were remarkably consistent, and in none of the groups was there a significant or consistent deviation from the normal range of appearance. Sludging was only occasionally seen.

A number of patients with a variety of other diseases in which capillary changes might be expected were studied (Fig. II) and in none of these were significant abnormalities of count or morphology noted. However, in view of the small number in each group final conclusions must await accumulation of a larger series.

Capillary counts on stripped areas of the forearm showed a rather wide variation among normals, and in this connection it should be noted that this may be in part artifactual. The trauma of stripping plainly causes generalized vasodilatation of the area, and at times mild edema. The former, as in Plate I, 1, may tend to obscure some of the capillary loops against the background of dilated sub-papillary plexus, while the edema may serve to obstruct a clear view of all the vessels, as is suggested in Plate I, 2. These and other factors, such as pigmentation, difficulty in stripping all the keratin off, and limitations of depth of focus in the camera lens, make it evident that the counts are approximations. Thus any deviations to be considered significant must be consistent and well outside the normal range.

Skin lesions—Though this is not intended as a survey of skin lesions, some lesions not emphasized previously are included. The nailfold vessels of a case of dermatomyositis (in a Negro, Plate I, 3), are greatly dilated, enlarged, and reduced in number as compared with normal (Plate I, 4—same magnification). A lesion of necrobiosis lipoidica displayed prominent venules but many capillary loops are retained (Plate I, 5). A lesion of secondary syphilis (Plate I, 6) shows dilatation, a rather distinctive appearing tortuosity of the capillaries and venules, with marked sludging, which was not true of the vessels in uninvolved areas of the patient's skin. Accidental trauma, caused by burning, laceration, or abrasion produces a characteristic response in the microcirculation of the skin during healing. A burn, infected, and now healing (Plate II, 7), and a cat scratch (Plate II, 8) show the capillary capillaries around the edges of the lesion lining up and pointing in horizontally toward the center. Similar changes were produced in experimental burns (Plate II, 9); when the eschar comes off, vessels from deeper layers can be seen growing into the center of the burned area (Plate II, 10).

DISCUSSION

The range and average capillary counts on normal forearms and nailfolds in this study are consistent with those previously reported. In the three previous series of forearm counts, Wetzel and Zotterman found an average of 47 capillaries per square millimeter (12), Weiss and Frazier of 35 (13), and Lawler and Lumpkin of 51 (29). If the counts of these investigators are averaged (a total of 55 patients), the result (43.5) is almost identical with the average (42) in the present study, though the range is somewhat wider (Fig. III). It must be remembered that technic differed from ours in the two earlier studies; the counts were done directly, not from photographs, and keratin stripping was not performed, which may explain some of the lower counts. In none of the previous series, or in the present one, could any correlations with sex or age be found.

All of our averages and ranges were normal

PLATE I

1. Normal stripped area, volar surface of forearm, showing prominent subpapillary plexus. (Scale = 1 mm.; plates 1—6). Approximately 22X.
2. Normal stripped area, volar surface of forearm, with edema partially obscuring subpapillary plexus and capillary loops. Approximately 22X.
3. Dermatomyositis, nailfold, showing greatly enlarged and dilated capillary loops in reduced number (3 Per linear millimeter); contrast with Plate 4. Approximately 22X.
4. Normal nailfold (23 years old white male), showing typical capillary loop appearance with six capillaries per linear millimeter at nailfold edge. Approximately 22X.
5. Lesion of necrobiosis lipoidica on leg with prominent subpapillary plexus; many capillary loops are retained. Approximately 22X.
6. Papule of secondary syphilis on forearm. Note dilatation and tortuosity of capillaries and some venules of subpapillary plexus. Sludging is marked. Approximately 22X.
PLATE II

7. Accidental burn, infected, now healing, on forearm. Surrounding capillaries oriented horizontally toward center. (Scale = 1 mm.; plates 7-10). Reduced approximately 15% from 22X.

8. Accidental cat scratch on forearm showing horizontally oriented surrounding capillaries. Reduced approximately 15% from 22X.

9. Experimental burn on forearm, 6th day. Eschar is still present and characteristic change of surrounding capillaries can be seen. Reduced approximately 15% from 22X.

10. Same burn as in Plate 9, 10th day. Characteristic pattern of capillaries is fully developed. Reduced approximately 15% from 22X.
in the diseases studied. This finding in the patients with hypertension and in those with arteriosclerosis is in agreement with Weiss and Frazier (13). Our group of patients with peripheral arterial insufficiency did not include classic Raynaud's disease, so the finding of normal nailfold vessels does not conflict with previous studies.

Although our group was much smaller, we were unable to find the deviations from normal in the nailfolds of arteriosclerotics which were described by Davis and Landau (33). Furthermore, we have seen the picture they describe of an increased number of visible rows of capillaries and more prominent subpapillary venous plexuses in many normals of all ages and we cannot correlate it with any particular disease state.

The averages and range of forearm counts in the seven patients with systemic lupus erythematosus were entirely within the normal range; this is in disagreement with the results of a prior study of four patients (29). Also, our range of normal is considerably wider, as is that of Wetzel and Zotterman (12), and Weiss and Frazier (13).

Our observations in general indicate that there is a wide variation in the normal subpapillary capillary count presumably due in part to limitations of the current technics. Because of this wide variation any increase or decrease associated with pathologic conditions would have to be rather marked to be significant. The same is true of the morphology of the nailfold vessels: abnormalities there must be definite, consistent, and well-controlled to be considered significant.

The technic of capillary microscopy is especially useful when applied to skin lesions and to experimental studies of trauma and healing. The mechanism of the distinctive microcirculatory changes occurring in healing remains to be investigated, and in particular the intriguing possibility of a chemotactic factor capable of "attracting" the surrounding capillaries toward the wound warrants further study.

**SUMMARY**

An evaluation of cutaneous microcirculation based on forearm and nailfold capillary counts has been undertaken in a group of normal in-

<table>
<thead>
<tr>
<th>Number of Cases</th>
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<th>Knuckles</th>
<th>Hand-back</th>
<th>Forearm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wetzel &amp; Zotterman (10)</td>
<td>23</td>
<td>4-60</td>
<td>58 (34-76)</td>
<td>65 (39-93)</td>
</tr>
<tr>
<td>Brown &amp; Giffin (74)</td>
<td></td>
<td></td>
<td></td>
<td>15-40</td>
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<tr>
<td>Brown &amp; Sheard (75)</td>
<td>2</td>
<td>26-32</td>
<td>41 (25-53)</td>
<td>62 (38-108)</td>
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<tr>
<td>Brown &amp; Roth (43)</td>
<td>5</td>
<td></td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Weiss &amp; Frazier (73)</td>
<td></td>
<td></td>
<td>70</td>
<td></td>
</tr>
<tr>
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<td>20</td>
<td>12-51</td>
<td>35 (25-58)</td>
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<td>Hypertension</td>
<td>20</td>
<td>18-84</td>
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<td>Arteriosclerosis</td>
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<td>50-74</td>
<td>30 (17-39)</td>
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<tr>
<td>Lawler &amp; Lumpkin (80)</td>
<td>12</td>
<td>20-84</td>
<td>51 (49-53)</td>
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<td>Systemic L.E</td>
<td>4</td>
<td>11-40</td>
<td>24 (21-26)</td>
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<tr>
<td>Discoid L.E</td>
<td>13</td>
<td>29-56</td>
<td>22 (13-29)</td>
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<td>Average from Literature</td>
<td>55</td>
<td>4-84</td>
<td>43.5 (25-71)</td>
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<tr>
<td>Present Series</td>
<td>54</td>
<td>5-84</td>
<td>42 (34-50)</td>
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individuals and in patients with a variety of diseases. No significant variation in counts was found in any of the conditions studied, and the morphology of the nailfold capillaries was within normal limits. The application of the technic and its limitations in clinical medicine are discussed.

Capillary microscopy does reveal definite, though not always pathognomonic, changes in many cutaneous diseases, and is useful in the experimental study of local trauma and wound healing.

REFERENCES

37. Brown, G. E. and Giffin, H. Z.: Studies of


DISCUSSION

Dr. Herbert Mescon, Boston, Mass.: I believe from your Institute in the past has come a paper saying that there are gross abnormalities of the capillary's appearance in these pigmented purpuric eruptions, stasis, and perhaps even in lupus erythematosus. In your first chart you said that the appearance of all these were normal. Is there a misunderstanding on my part?

Dr. James G. Zimmer, (in closing): It is correct that previous studies done in our institution by other investigators did indicate a reduced number of forearm capillaries in systemic lupus erythematosus. We have been unable to confirm that finding in the present study.

In regard to pigmented purpuric eruptions, we had only one patient in this study, and the counts were done on the forearm rather than on the leg capillaries where the reported changes are seen, so we have nothing further to add to that.