Vascular Lesions of Rheumatic Heart Disease, with Special Reference to Rheumatic Activity

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In rheumatic fever and rheumatic heart disease the presence of the vascular lesions has been recognized by pathologists. Recently, frequent occurrence of Aschoff bodies in the atrial appendage has been observed at the mitral commissurotomy and in the majority of such cases, the rheumatic activity has not proved with clinical and laboratory examinations. Our studies also demonstrated that small vascular lesions were observed in the bulbar conjunctiva and synovial tissue, and there is a discrepancy between the presence of rheumatic activity and laboratory tests. Chronic rheumatic vascular lesions may persist in the inactive rheumatic heart disease. These vascular abnormalities can accelerate aging degenerative change of the blood vessels and bring out various damages to organs and tissues due to ischemic injuries.

The rheumatic fever is a disease of hypersensitivity with an attack of relatively short duration and is frequently associated with cardiac lesion, which is the most serious clinical complication of the disease. Lesions of the vessels represent a fundamental feature of the rheumatic fever, and have been described by numerous authors. Great majority of investigations was, however, made by pathologists on autopsied materials. In rheumatic fever, death is rare and exceptional outcome of the disease according to the clinical observations. The studies on the living subjects are, therefore, necessary in order to investigate the vascular change of the disease, in addition to the pathological studies of the autopsied materials.

In this paper, the results obtained in our laboratory are presented on the observations of vascular lesions of the rheumatic fever and rheumatic heart disease by biomicroscopy on bulbar conjunctiva and biopsy of the synovial tissue. The purposes of the present investigation are to obtain informations on the nature, distribution and clinical significance of small vascular lesions in the various stages of the rheumatic fever.

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MATERIALS AND METHODS

Bulbar conjunctiva was examined and photographed by ophthalmological slit lamp. No anesthesia was used and the examination was made in sitting position. The materials consisted of 55 observations of 36 patients with acute rheumatic fever and rheumatic heart disease. Of our rheumatic patients 12 were male and 24 were female, and there were 17 cases with acute rheumatic fever and 30 cases with rheumatic heart disease, ranging from the symptomless to the severest, from active to inactive, with various kinds of valvular lesions. As a control group bulbar conjunctiva was studied on 29 rheumatoid arthritis, 7 other collagen diseases, 22 diabetes mellitus and 65 normal subjects. In order to evaluate the activity of the disease, erythrocyte sedimentation rate (E.S.R.), serum C-reactive protein (C.R.P.), anti-streptolysin O titer (A.S.L.O.), mucoprotein and other protein fraction levels were measured.

In the other group, the synovial membrane of knee joints was biopsied with Polley's needle and was studied pathologically. The biopsied specimens removed from the suprapatellar bursa of the joints were observed with both light and electron microscope, especially on the small blood vessels of the synovial tissue. The materials consisted of 47 cases with rheumatic fever and rheumatic heart disease, who were thoroughly examined and investigated with the same procedure as described above. There were 19 males and 28 females, 17 rheumatic fever and 30 rheumatic heart disease of various stages with various valvular lesions. As a control, 19 cases of rheumatoid arthritis were examined. Autopsied materials were also investigated on the joint tissue to determine the value of biopsy method.

RESULTS

Bio-Microscopy of Blood Vessels in the Bulbar Conjunctiva

Among the intravascular findings in the bulbar conjunctiva, the blood sludge phenomenon was the most striking. The red cells were aggregated and clumped in the blood vessels, rate of blood flow was markedly reduced, and retarded flow of the large and rigid masses were observed without difficulties in either arterioles, venules and capillaries. Of rheumatic fever and rheumatic heart disease intravascular blood sludging was seen in 40% (22 of 55 obs.), in 47.1% (16 of 34 obs.) of rheumatoid arthritis, in 42.9% (3 of 7 cases) of other collagen diseases, 9.1% (2 of 22 cases) of diabetes mellitus and in 6.2% of normal subjects. It is likely according to the result, that the sludging of blood cells is due to inflammatory rather than degenerative process. The value of laboratory tests, such as elevated E.S.R. and positive C.R.P. was intimately related to the phenomenon, but normal E.S.R. and negative C.R.P. could be associated with the blood sludging.
Table I. Vascular Lesions in the Biomicroscopy of Bulbar Conjunctiva of Rheumatic Fever and Other Diseases

<table>
<thead>
<tr>
<th>No. of observations</th>
<th>Rheumatic fever and rheumatic heart disease</th>
<th>Rheumatoid arthritis</th>
<th>Other collagen diseases</th>
<th>Diabetes mellitus</th>
<th>Normal controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>55 (100%)</td>
<td>34 (100%)</td>
<td>7 (100%)</td>
<td>22 (100%)</td>
<td>65 (100%)</td>
</tr>
<tr>
<td>Blood sludging</td>
<td>22 (40.0)</td>
<td>16 (47.1)</td>
<td>3 (42.9)</td>
<td>2 (9.1)</td>
<td>4 (6.2)</td>
</tr>
<tr>
<td>Arteriolar microaneurysm</td>
<td>26 (47.4)</td>
<td>13 (38.3)</td>
<td>2 (28.6)</td>
<td>11 (5.0)</td>
<td>13 (20.1)</td>
</tr>
<tr>
<td>Arborization</td>
<td>13 (23.6)</td>
<td>5 (14.7)</td>
<td>1 (14.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Arteriolar wavy irregularities</td>
<td>14 (25.5)</td>
<td>7 (20.6)</td>
<td>0 (0)</td>
<td>6 (27.2)</td>
<td>10 (15.4)</td>
</tr>
<tr>
<td>Arteriolar jaggy irregularities</td>
<td>5 (9.1)</td>
<td>2 (5.9)</td>
<td>1 (14.3)</td>
<td>3 (13.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Proliferation of capillaries</td>
<td>4 (7.3)</td>
<td>3 (8.8)</td>
<td>1 (14.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Tortuositues, hemorrhage etc.</td>
<td>5 (9.1)</td>
<td>2 (5.9)</td>
<td>0 (0)</td>
<td>9 (40.9)</td>
<td>2 (3.1)</td>
</tr>
<tr>
<td>Venous aneurysm</td>
<td>14 (25.5)</td>
<td>7 (20.6)</td>
<td>1 (14.3)</td>
<td>5 (22.7)</td>
<td>15 (23.1)</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>0 (0)</td>
<td>3 (8.8)</td>
<td>0 (0)</td>
<td>2 (9.1)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Figs. 1-4. Photomicrographs of vascular lesions in the bulbar conjunctiva.
Fig. 1. Blood sludging.
Fig. 2. Arteriolar microaneurysm.
According to Feinstein\textsuperscript{23} reactivation of subsiding rheumatic fever could be experimentally manifested after treatment with relatively large doses of prednisolone for 2 weeks. In our studies rheumatic heart disease without manifestations of rheumatic activity was treated with para-methasone 8 mg. daily for 7 days and then 4 mg. daily for 7 days, then the treatment was discontinued abruptly. The appearance of rebound phenomenon was examined by a number of clinical and laboratory procedures, including electrocardiography, and determination of serum protein pattern and acute phase reactants. In the period, during which rheumatic reactivity was expected, intravascular sludging newly appeared, or, in a case with the phenomenon already present, increased in intensity and range. Slight elevation of serum gamma globulin level was also observed, however, no other laboratory abnormalities proving rheumatic reactivity were found. It is assumed that the blood sludging in bulbar conjunctiva may be one of the most sensitive index to the presence of inflammatory process.

Microaneurysms of terminal arteries were also a frequent finding in the bulbar conjunctiva. In rheumatic fever and rheumatic heart disease their incidence was 47.4\% (26 of 55 obs.), and 38.3\% in rheumatoid arthritis, 28.6\% in other collagen diseases, 5\% in diabetes mellitus and 20\% in normal subjects.
From the correlation study between the age and the appearance of arteriolar microaneurysms, it was found that the microaneurysms were observed in 36.4% under 30 years of age, in 66.7% of the age group of 31 to 40 years, and in 57.1% over the age of 41 years in rheumatic patients. On the other hand, in normal subjects, the incidence of microaneurysm increased with the age. The figures were null under 30 years of age, 10% in the age group of 31 to 40 years, and 36.4% over 41 years of age. In rheumatic patients the aneurysms in the bulbar conjunctiva were found more frequently in the younger age group than in the older one, but the incidence of every decade was much higher compared with normal subjects. The increased incidence of arteriolar microaneurysms with aging suggests that some kind of aging process is the underlying cause of the lesion. The more frequent appearance of the lesion in every decade in rheumatic patients may possibly explain, that rheumatic inflammatory process accelerates the aging of blood vessels, at least in the bulbar conjunctiva.

Another examination revealed that in rheumatic fever and rheumatic heart disease arteriolar microaneurysms were found in 51.4% (19 of 37 obs.) with obvious manifestation of valvular heart disease and in 38.9% (7 of 18 obs.) without it. The presence of relationship between arteriolar microaneurysm and valvular lesion, although slight, may suggest that hemodynamic factor also influences the pathogenesis of the vascular change.

The long term study of the same subject proved that in 2 cases microaneurysm appeared in the bulbar conjunctiva within the course of 6 and 15 months respectively. The patient was a 18-year-old female with rheumatic fever, who in the first attack showed temperature of 37.8°C, E.S.R. 64 mm. (one hour), A.S.L.O. over 333 Todd Unit, and revealed the picture of blood suldging in the bulbar conjunctiva. After 2 weeks, fever and other clinical manifestations, E.S.R. and other signs of rheumatic activity returned to normal. The biomicroscopic observation after 15 months from the onset revealed one new arteriolar microaneurysm in the conjunctiva, and the lesion persisted thereafter. The other case was a 42-year-old female with rheumatic fever, who showed a new aneurysm 180 days after the onset of the disease.

The incidence of venular aneurysm was 25.4% (14 of 55 obs.) in rheumatic fever as compared with 20.6% in rheumatoid arthritis, 14.3% in collagen diseases, 22.7% in diabetes mellitus and 23.1% in normal subjects. These results reveal that venular microaneurysms are due to inflammatory as well as degenerative process. This venular microaneurysm in the conjunctiva also has an increased frequency with the age and proves some relationship with presence of valvular lesion of the heart.
Another important abnormality in the conjunctival capillaries was called arborization, in which small blood vessels subdivided repeatedly and many thinned abruptly, giving a picture like the terminal branching of the walnut tree or the white poplar tree in winter. This kind of abnormalities was found in 23.6% (13 of 55 obs.) with rheumatic fever, 14.7% with rheumatoid arthritis, 14.3% with other collagen diseases, but none with diabetes mellitus or normal subjects. It is concluded that the arborization of the conjunctival terminal vessels may prove the relationship with inflammatory rather than degenerative changes. The age did not correlate to the abnormal C.R.P., A.S.L.O. or E.S.R. The arborization was less frequently demonstrated in the rheumatic cases with valvular heart disease than in those without it, and was more frequently associated with joint symptoms than the other symptoms.

Wavy and jaggy irregularities of outline of the arteriolar blood columns were also found in the bulbar conjunctiva, wavy ones in 25.5% and jaggy ones in 9.1% of rheumatic patients. Wavy irregularities of arterioles were also seen in 20.6% of rheumatoid arthritis, 27.2% of diabetes mellitus and 15.4% of normal subjects. This kind of change could be found in every decade of age in rheumatic fever group, and only in higher age in normal controls. The relationship between the wavy irregularities and age seems to be similar to that of arteriolar microaneurysms.

Among other arteriolar changes proliferation of capillaries was also found in 7.3% (4 of 55 obs.) of rheumatic patients, and hemorrhage in 3.6% (2 of 55 obs.), increased tortuosities 1.8% (1 of 55 obs.) etc. were also seen in the bulbar conjunctival arterioles of the disease, but their significance to the rheumatic process could not be determined, since they were too small in number in our materials.

In regard to the conjunctival venules, irregularities of venular contour, tortuosities and angularities, constriction and aneurysms were observed. Presence of the venular microaneurysms was stated above, and the other venular abnormalities were also too small in number for further correlation.

Studies on the Punch Biopsy of Synovial Tissue

The noted findings of our 47 cases in the synovial membrane were as follows. Among 47 cases no abnormality was found in 17 cases (37.5%). In the other 30 cases with abnormality there were hypertrophy and proliferative changes of the synovial lining in 6 cases (12.8%), roughness in 7 cases (14.9%) and deposition of fibrinoid substance in 6 cases (12.8%) on the synovial surface, edema in 3 cases (6.4%), hyperemia in 4 cases (8.5%) and capillary proliferation in 4 cases (8.5%) in the synovial
### Table II. Small Blood Vessel Lesions in the Synovial Biopsy of Rheumatic Fever

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Rheumatic fever and rheumatic heart disease</th>
<th>Rheumatoid arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>47 (100%)</td>
<td>19 (100%)</td>
</tr>
<tr>
<td></td>
<td>17 (36.2)</td>
<td>14 (73.7)</td>
</tr>
<tr>
<td>Endoangitis</td>
<td>9 (19.1)</td>
<td>8 (42.1)</td>
</tr>
<tr>
<td>Periangitis</td>
<td>1 (2.1)</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td>Panangitis</td>
<td>3 (6.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Thromboangitis</td>
<td>6 (12.8)</td>
<td>6 (31.6)</td>
</tr>
<tr>
<td>Fibrinoid deg. of vascular wall</td>
<td>4 (8.5)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Figs. 5-9. Photomicrographs of synovial membrane.

Fig. 5. From 10 years of age male suffering from acute rheumatic fever, showing perivascular cell infiltration (left) and fibrinoid degeneration of the synovium (right). E.S.R. 120 mm. (1 hr.), A.S.L.O, 333 Todd Unit, C.R.P. (++). (Hematoxylin and eosin 150×)

Fig. 6. From 19 years of age female with tetralogy of Fallot, showing endoarterioitis with endothelial proliferation. E.S.R. 1 mm. (1 hr.), A.S.L.O. 333 Todd Unit, C.R.P. (+). (Hematoxylin and eosin 320×)
membrane. There was also fibrinoid degeneration, of the arteriolar wall in 4 cases (8.5%), of the collagen fibers of the subsynovial layer in 10 cases (21.3%) and of the synovial lining in 6 cases (12.8%). There was also cell infiltration, around the blood vessels in 6 cases (12.8%), in the synovium in 10 cases (21.3%) and in the subsynovial interstitial tissue in 3 cases (6.4%).

In regard to the vascular lesions, 15 of the 47 cases (31.9%) revealed any of the following abnormalities. There occurred endoangitis with endothelial proliferation and swelling, of which the majority was endoarteriitis, in 9 cases (19.1%), periangitis in 1 case (2.1%), panangitis in 3 cases (6.4%) and thromboangitis in 6 cases (12.8%). In 19 cases of rheumatoid arthritis endoangitis was in 8 case (42.1%), periangitis in 5 cases (26.3%), panangitis in null and thromboangitis in 6 cases (31.6%). These findings in the synovial specimen demonstrated that endoangitis occurred more frequently in rheumatic fever and periangitis in rheumatoid
arthrits. There was no difference in the incidence of angitis, between patients with or without valvular heart disease. Regarding the joint symptoms, there was a tendency that peri- and panangitis were more frequently accompanied with joint symptoms, and endoangitis with no or milder ones.

The relationship between the duration of the rheumatic disease from the onset and the incidence of vascular lesions was studied. The incidence of endoangitis and thromboangitis was highest in patients with duration of about one year, and less in cases with shorter or longer duration of rheumatic disease. It could be considered that inflammatory lesions of blood vessels in the synovium took about one year for the establishment, and subsidence of the abnormality occurred after that. The relationship between the value of serum acute phase reactant and the blood vessel lesions in the synovial tissue was investigated, and positive C.R.P. and abnormal value of A.S.I.O. accompanied, as a rule, the changes of blood vessels in the synovium.

Fig. 9. From 19 years of age male with acute rheumatic fever, showing arteriolitis. E.S.R. 66 mm. (1hr.), A.S.I.O. 333 Todd Unit, C.R.P. (+). (Hematoxylin and eosin 150×)

Fig. 10. Electron microscopic photograph of a small blood vessel in the synovial membrane from the same case of Fig. 9. Note that the swelling of endothelial cells nearly obstruct the vascular lumen. (4500×)
Electron microscopy added new knowledge to the cytology of the synovial tissue. Fig. 10 shows the cross section of a small blood vessel under high magnification in the subsynovial interstitial tissue. The specimen was taken from a case of a 19-year-old male with acute rheumatic fever of 20 days. With light microscopy of a the same specimen endarteritis was found as a striking picture. In this photograph 4 endothelial cells surround the vascular lumen, which is occupied by a fine precipitate of blood plasma. It is noted at the first sight, that the vascular lumen is narrow compared with the endothelial layer, so that the passage of blood cells may be disturbed. The shape of the endothelial cell is round with smooth inner surface and no protrusion such as villi or processus. The endothelial protoplasm contains numerous small vesicles of varying size, mitochondria and large vesicles, that is, endoplasmic reticulum, which is noted for the presence of Palade's granules on the surface. Pinocytes, as Palade,3) Moore and Ruska4) described, are not observed in the endothelial cells. A nucleus with high electron density is seen in a endothelium in the right side of the microphotograph. The basement membrane with high electron density surrounds the endothelial layer, and similar amorphous material also envelopes pericytes and muscle cells around the blood vessel.

Among the findings mentioned above, the swelling of endothelial cells with narrowed vascular lumen and slight increase in endoplasmic reticulum were noted in abnormal pictures. These findings were also observed in another specimen from rheumatic fever. In other microphotographs with electron microscopy abnormality in synoviocytes, fibroblasts, white cells and collagen fibers was found, which will be reported in another paper in details.

**Discussion**

The normal pattern of the small blood vessels in the bulbar conjunctiva has been established by ophthalmologist. It was, however, Knisely and his associates,5) who stimulated a growing interest to the other specialists in the visualization of conjunctival vascular system, and is now applied to the studies of various diseases, including rheumatic diseases6)7) especially of diabetes mellitus8)-10) and arteriosclerosis.11) Bulbar conjunctiva is both anatomically and embryologically similar to the subcutaneous tissue up to the present. The observation of fingernail with capillary microscopy was a routine procedure for the studies of small blood vessels, but is now substituted by the biomicroscopy of the bulbar conjunctiva, because of poor results and of technical difficulties. Blood vessels in the retina have been utilized for the same purpose, but detailed studies are
not possible because of difficulty in high magnification.

Biomicroscopic observation demonstrated 2 kinds of changes in the conjunctival blood vessels, that is, intravascular, vascular and perivascular. In diabetes mellitus, Ditzel\textsuperscript{10} reported that vascular changes consisting of irreversible degenerative and reversible vasmotor ones. He showed that the arteriolar change was the jagged irregularities in the configuration of the terminal arterioles, the capillary change was capillary elongation, and the venular changes were venular irregularities, venular sacculation and change in arteriolar-venular ratio. The intravascular change was aggregation of red blood cells, and the perivascular changes were edema, hyaline infiltration and hemorrhage.

In our examination on rheumatic fever the most noted intravascular findings was the blood sludge phenomenon (Knisely\textsuperscript{5}), or red cell aggregation (Ditzel\textsuperscript{13}). Knisely\textsuperscript{5} described that normal subjects never showed blood sludging in the bulbar conjunctiva, although Ditzel described the presence of such phenomenon in normal subjects during menstruation, aging and also unknown causes. Blood sludge phenomenon is a common finding in pregnancy, hypertension, tuberculosis, poliomyelitis, diabetes mellitus, myocardial infarction, neoplasms and various kinds of injuries. The possibility whether the presence of this abnormal picture was due to pathological change of red cells, blood plasma or blood vessel wall, had been questioned and the extensive studies of Knisely,\textsuperscript{5} Bloch,\textsuperscript{12} Thorsen\textsuperscript{13} etc. concluded that some kinds of plasma protein component adhered to and enveloped the surface of red cells resulting in clumping of red blood cells in the blood vessels.

Our observation revealed that sludging in conjunctival vessels was not a specific lesion to the rheumatic diseases, but occurred more frequently in rheumatic fever than diabetes mellitus and normal subjects. Abnormal pattern of serum protein associated with the rheumatic fever might possibly lead to the blood sludging and also to the abnormal E.S.R. and C.R.P. This is confirmed by the evidence that experimentally induced reactivation of rheumatic fever was accompanied with the simultaneous appearance of sludging and an elevation of serum gamma globulin level.

The abnormalities of arterioles in rheumatic fever were microaneurysm, arborization, irregularities of outline of arterioles, hemorrhage, tortuosities etc., which were due to various etiology. Arteriolar microaneurysm was a common observation in rheumatic fever. The development of new aneurysm in the course of the rheumatic fever was proved to take not a long time, only 6 to 15 months in our experience, but is not a specific lesion to this disease. Ditzel\textsuperscript{13} reported that microaneurysms were more frequently found in the venous than arteriolar circulation.
In our study venous microaneurysms were found less frequently in rheumatic fever and more frequently in diabetes mellitus than the arteriolar microaneurysm. The findings are also in accordance with Pickering’s work that hypertensive and arteriosclerotic vascular lesions were arterial, and diabetic ones were venous in retina.

The incidence of arteriolar microaneurysm in the bulbar conjunctiva increased with age in normal subjects and in rheumatic fever it was much higher in every decade. It is suggested according to our evidences that the appearance of aneurysms is promoted by some kind of aging process and accelerated further more by rheumatic inflammatory lesions. Our observation on the relationship between rheumatic fever and aging process seems, likely Ditzel’s view, that the degenerative and vasomotor changes of conjunctival blood vessels in diabetes mellitus are markedly accelerated as compared with normal aging.

The arborization of small blood vessels in the conjunctiva was, according to Davis, the most characteristic vascular lesion to the rheumatic fever. Our results also indicated that there was no vascular arborization in diabetes mellitus and normal subjects, although it was also found in rheumatoid arthritis and other collagen diseases. The pathogenesis of this lesion was not known, but inflammatory process of rheumatic fever in the conjunctiva could be the etiology of the arborization, since the relationship between this lesion and elevated E.S.R. was proved.

Wavy irregularities of outline of the arteriolar blood columns and venous aneurysms in the bulbar conjunctiva were other abnormalities which seemed to be aging degenerative lesions of blood vessels and accelerated by rheumatic process. Other kinds of findings were also demonstrated and they might show some relationship to rheumatic fever, but it could not be confirmed in the present studies.

Synovial membrane consists of 2 layers, the synovial lining and sub-synovial layer. On both embryological and histological evidence, it is regarded as connective tissue that has undergone certain modifications in functional and structural characteristics (Bennett). The inflammation of joints is one of the most common manifestations of the rheumatic fever, although it soon subsides to the complete restoration of the functions.

The punch biopsy of the joint tissue was introduced by Polley and a number of investigations were carried out on the synovial tissue of the rheumatoid arthritis. There are, however, few studies on the joint tissue of rheumatic fever since the joint symptoms of the disease are, as a rule, mild and usually subside in a short duration.

Our observation proved that there were many kinds of pathological findings in the rheumatic fever even in the stage with no manifestation of the joints, and the detail was mentioned above. Bennett described
the findings of hyperemia, edema, leucocyte infiltration and fibrinoid swelling as the articular lesions of the rheumatic fever, and no finding of small blood vessels in the synovium. Our study demonstrated various kinds of vascular lesions and their incidence was not low.

Endoangitis with swelling and proliferation of endothelial cells was the most frequent and characteristic in vascular lesion. This finding was less frequent in rheumatoid arthritis. Occurrence of endoangitis as well as thromboangitis was highest about one year after the onset of the rheumatic fever, and those vascular lesions might possibly take about one year for the establishment. These findings led to the conclusion that the vascular lesions were of chronic course, and persisted after all clinical symptoms and signs disappeared.

On the synovial specimens removed from acute rheumatic fever patients, small blood vessels were examined with electron microscopy. The swelling of the endothelial cells was a common feature, which was considered corresponding to the endoangitis in the light microscopy. The endothelial cells increased in volume, so that nearly obstructed the vascular lumen. The endothelium contained numerous fine structures of small vesicles, mitochondrias and endoplasmic reticulum in the protoplasm. Palade, Moore and Ruska described numerous vesiculated structures in the endothelial cytoplasms, which appeared to represent a continuous invagination and pinching off of the plasma membrane, and those vesicles, named pinocytes by the authors, were believed to be a transporting system of materials through the vascular wall. Our microphotograph did not show any microvesicle similar to pinocyte. The swelling of the endothelial cells indicates, therefore, the accumulation of fluid within the protoplasm, not by pinocytosis, but probably due to increased permeability of the cell membrane. The toxic substance or abnormal protein increased in the serum of rheumatic patients is considered responsible for the damage and increased permeability of the cell membrane. In addition to endoangitis, periangitis was also found in rheumatic fever, but less frequently than rheumatoid arthritis.

Rheumatic fever is a disease of hypersensitivity and the blood vessel lesions are the most important and characteristic to the disease. The examination on the autopsied cases shows various kinds of abnormality in blood vessels, which were reported by a great number of pathologists. Klinge stated in his anatomical studies that the inflammatory lesions of rheumatic fever usually occurred around small blood vessels in organs and tissues, and these abnormalities changed into perivascular scarring after subsidence of rheumatic inflammation. The focal lesions of arterioles, venules and capillaries are demonstrated in heart, lung, pancreas, kidney, ovary, testicles and skin.
The incidence of blood vessel lesions and its relationship to the clinical and laboratory findings have not been studied in living human with rheumatic fever and rheumatic heart disease, and there can be discrepancy between post mortem and living materials. Recently frequent occurrence of Aschoff bodies was recognized in the endocardium of the left atrial appendage, when mitral commissurotomy was employed in the treatment of rheumatic heart disease.\(^{(20)-(23)}\) In the majority of these cases, however, the clinical and laboratory findings which proved rheumatic activity were not present. Since Aschoff bodies had been considered true evidence of the rheumatic activity, disagreement became evident between the presence of this lesion and clinical and laboratory findings.

Our observations on the bulbar conjunctiva and synovial membrane of the living rheumatic fever patients demonstrated the frequent occurrence of various vascular lesions in cases with no apparent clinical and laboratory evidence of rheumatic activity. The chronicity of these vascular abnormalities both in the conjunctiva and synovial membrane was also stated above. Those evidences prove the subclinical existence of the blood vessel lesions. It is concluded that the laboratory tests utilized for the demonstration of the rheumatic activity are not sensitive enough and a negative test does not necessarily exclude the presence of rheumatic activity. The history of rheumatic fever is, therefore, the most important aid for the diagnosis of rheumatic heart disease, but it must be realized that unfortunately half or more patients attending rheumatic heart disease clinics have no acceptable history of rheumatic fever, carditis or chorea. Attempts to improve the laboratory tests are greatly needed.

The aging degenerative process of blood vessels are proved to be accelerated by the addition of rheumatic inflammation and, as Klinge\(^{(19)}\) stated, arteriosclerotic change can be established on the damaged blood vessels. Ischemic damage of organs and tissues due to anoxemia is possibly brought out by the vascular change, and various symptoms and signs can be modified by the presence of subclinical rheumatic fever. The incidence of such modification must be high, since rheumatic fever is one of the most common diseases.

The prevention and treatment of chronic vascular disease of rheumatic origin is an important problem awaiting urgent investigation. The routine control of rheumatic activity with corticosteroid and salicylic acid is not quite satisfactory. It is important to recognize that low grade rheumatic activity and incidious morphologic changes may persist in rheumatic patients and they can not be detected by current diagnostic tests.
SUMMARY

(1) Bio-microscopy of bulbar conjunctiva and examination of the punch biopsy of synovial membrane demonstrated various kinds of blood vessel lesions in rheumatic fever and rheumatic heart disease.

(2) These lesions were observed not only in cases with manifestations of rheumatic changes, but with no apparent clinical and laboratory evidence of rheumatic activity, too. It would be suggested that laboratory tests of the present day were not sensitive enough to indicate the presence of mild rheumatic inflammation. Incidious morphologic changes of blood vessels might exist in rheumatic heart disease patients with no evidence of rheumatic activity.

(3) The prevention and treatment of those vascular lesions are important, since the vascular changes can accelerate aging degenerative process of blood vessels to bring out early appearance of arteriosclerosis, and can also cause various damages to organs and tissues, which are ischemic injuries due to anoxemia.

REFERENCES