THE CAPILLARY SYNDROME IN VIRAL INFECTIONS: TREATMENT WITH CITRUS FLAVONOIDS*

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INFLAMMATORY processes occur in many viral diseases, often in an acute form. The question as to whether the inflammation is a primary or a secondary phenomenon is still under discussion. Thus in certain viral infections, some workers have regarded the various alterations in the skin from their inception as the manifestation only of an acute inflammatory process. On the other hand, Rivers (1) has demonstrated that Purkinje cells in monkeys with louping-ill are lysed before clear evidence of inflammation appears. Of whichever nature viral inflammations might be, they often induce grave clinical complications which deserve the full attention of the physician.

One of the important features of viral inflammation is *the capillary syndrome*. This term was first introduced by Eppinger (2) in connection with the protein-leakage that occurs into the tissues. In viral inflammations, the endothelial cells of the capillary wall are often invaded by virus particles, the intercellular cement is degenerated and an increased capillary fragility appears. Through the damage to the capillary system, generalization of viral infection is enhanced and inflammatory phenomena intensified. In normal conditions, with a properly functioning capillary wall, the viral particles cannot penetrate into surrounding tissue for, as Danielli and Stock (3) have pointed out: "All the evidence available goes to show that the capillary wall in a normal tissue is comparatively impermeable both to serum albumin and to serum globulin." And since viral particles are, as a rule, larger than albumin molecules, they penetrate the capillary wall only when the pores of the intercellular cement are altered.**

The role of the capillary syndrome in viral infections seems to be much greater than has heretofore been recognized. Capillary damage and subsequent transudation into the tissues are present in many viral infections and have been proved experimentally and clinically.

Thus in viral hepatitis, caused by an epitheliotropic virus (Thaler's), there is a gross injury to the capillary system of the hepatic lobules and consequently severe disturbances in blood flow. These disturbances of blood flow, associated with capillary damage, apparently are the chief cause of the destruction of the cells of the central parts of the hepatic lobules. As Lyon (4) emphasizes: "The chief object of attack in viral hepatitis is the hepatic capillary bed." With the capillary wall once injured, transudation into the tissues takes place, and excessive acute hepatic necrosis may occur. In the fulminant form of the disease, an intense inflammatory response and profuse hemorrhages are present, according to Lucke and Mallory (5). In the subacute form of disease in which death occurs 3 to 6 weeks after onset, necrosis of the liver is less pronounced but phlegmonous inflammation and hemorrhage of the stomach and intestinal walls are often revealed on necropsy.

In poliomyelitis, there is a considerable reaction to neuronal necrosis among the various types of mesodermal cells participating in inflammation. Neighboring small venules, arterioles and capillaries are affected, perivascular cuffs are formed and edema is present (Bodian and Howe (6)). Although severe paralysis may occur without important vascular involvement, the presence of edema in poliomyelitis has been emphasized by numerous authors. Bower *et al* (7) found a decrease in the albumin content of the plasma in rough parallelism to the severity of the disease in acute poliomyelitis. They attributed great importance to the edema in this disease, which is caused by increased capillary permeability. All efforts, according to them, should be made to influence the dynamics of certain events in poliomyelitis in order "to break the vicious cycle of edema and anoxia and tend to reduce paralysis to that caused by the action of the virus on specific neurons."

As Lyon (4) points out, "in poliomyelitis, the degree of destruction of specific neurons may be at once due to direct viral action and due to edema as the sequelae of a primarily disturbed blood flow and, possibly, of lowered serum albumin." Recently, Letterer (8) experimentally showed that lesions of parenchyma of a similar nature can be produced by an increased capillary permeability, and especially without dysproteinemia. All these facts seem to indicate that the damage to the capillary system in poliomyelitis might be of a greater significance than has been realized heretofore.

In smallpox, the capillary syndrome is also present, according to Wolman (9), who found inclusion bodies and extracellular virus aggregates within the endothelial cells lining the blood vessels of various organs. The observations of Svertson and Hyman (10) suggest that in smallpox, increased capillary permeability with escape of protein through the capillary wall into the tissue spaces might lead to profound and consistent loss of plasma, to altered hemodynamics and peripheral circulatory failure.

In measles, the capillaries of the corium are damaged in the incipient stage of the disease, and petechiae and purpura often are present according to Miller (11). In cases of encephalomyelitis, the central nervous system shows, in the gross, congestion and petechial hemorrhages. Early cases show perivascular hemorrhages (Rake (12)).

In primary atypical pneumonia, the capillary syn-

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**The virus particles of foot-and-mouth diseases are exceedingly small, with a diameter of 12μ or about the size of small protein molecules. The majority of other viruses are larger.

drome is well pronounced. The pneumonic areas appear hemorrhagic, the bronchial mucosa inflamed, and bloody fluid may exude (Horsfall (13)).

In mumps, in the case of severe orchitis, there is marked congestion of blood vessels, punctate hemorrhages, edema and exudation (Enders (14)). In the viral disease of herpes simplex, "the corium of both skin and mucous membrane shows pronounced capillary dilatation and infiltration of inflammatory cells. . . . In the nervous system . . . there are local areas of dusky discoloration, studded with petechiae. . . . The appearance suggests encephalomalacia due to circulatory disturbance . . . and the capillaries show endothelial hyperplasia" according to Scott *et al* (15).

In virus A influenza, there is an inflammatory reaction in the submucosa, and often epistaxis. Brightman (16) found in experimental animals infected with influenza virus A, peribronchial lesions with congested alveolar capillaries and hemorrhages. In the common cold, vascular engorgement and edema of mucous membrane are predominant, indicative of an increased capillary permeability.

In rabies, vascular congestion, edema and perivascular hemorrhages are present. Strumpell's disease, or acute epidemic leuko-encephalitis, is characterized by predominance of large or small hemorrhagic foci throughout the central nervous system. "The pathologic picture in the CNS is one of congestion of arterioles and capillaries" (Olitzky (17)). Edema, vascular congestion and small hemorrhages are also present in St. Louis encephalitis.

This brief review of the capillary syndrome in viral infections suggests that involvement of the capillary system is much more frequent and common in these diseases than has generally been appreciated. It is possible that the damage to the capillary wall is one of the factors contributing to the generalization of viral infection. For, once the capillary wall is damaged, the viral particles penetrate unopposed through it and invade the surrounding tissues and organs of the organism. It is from this point of view that an attempt was made to apply a therapy which would prevent or minimize the capillary injury in certain viral diseases.

The work of Armentano *et al* (18). Bacharach *et al* (19), Scarborough (20), Griffith and Lindauer (21), Sokoloff *et al* (22), and others, have established the specific activity of vitamin P, otherwise known as bioflavonoids, in regard to capillary fragility phenomena. The usefulness of citrus bio-flavonoids in certain hemorrhagic conditions, in which an increased capillary fragility was present, such as in tuberculous hemoptysis, was emphasized by Sokoloff and Eddy (23). Puig-Muset (24) and Sokoloff *et al* (25), on the basis of their histochemical investigations, suggested that vitamin P has a specific affinity for the intercellular cement of the capillary wall.

Recently, C. D. McKeen (26) reported that the pressed juice of sweet pepper has an inhibitory influence upon the infectivity of cucumber mosaic, ringspot and tobacco etch viruses. Although the author does not specify the chemical nature of the inhibitory substance present in sweet pepper, it is well known that this vegetable is rich in bio-flavonoids.

In their clinical studies, Biskind and Martin (27) treated 23 cases of acute follicular tonsillitis, rhinitis, influenza and other upper respiratory infections of viral origin with citrus flavonoids with encouraging results. According to them, in all cases treated except two, "recovery occurred in from 8 to 48 hours, usually in 24 hours." In influenza and acute follicular tonsillitis administration of the flavonoids "led to recovery by crisis in 48 hours with profuse perspiration, rapid drop in temperature and subsidence of the pharyngeal [and other] lesions." The authors believe that the dramatic results which they have obtained with the flavonoids in treatment of viral upper respiratory infections "suggest that the flavonoids operate in the infections by decreasing capillary permeability."

In our present studies, five cases of virus influenza were treated with the flavonoid compound combined with ascorbic acid.** The flavonoids were administered in a dosage of 200 to 300 mg. every three or four hours for 36 to 48 hours. In all the treated cases, the results of this therapy corresponded to those observed by Biskind and Martin. In two cases, in which acute tracheobronchitis was present, persistent cough subsided after 48 hours. There was rapid drop in temperature with profuse perspiration.

The following two cases may be given as typical in their response to the flavonoid therapy:

E. L., female, white, age 39. Past history revealed acute follicular tonsillitis with pharyngitis. Onset of the disease abrupt, with chills, nasal discharge, hoarseness, fever 104°. Persistent cough, muscular pain and general prostration. Complained of nose bleeds.

Examination: The nasal mucosa was swollen. The soft palate was red. Pulse: 120. There was no cardiac involvement. The urine showed a trace of albumin. WBC: 3600. Hirst test (serum-inhibition-of-hemagglutination) positive for virus A influenza.

Diagnosis: Virus A influenza. Moderate tracheobronchitis.

Treatment: Flavonoids, 300 mg every three hours for 48 hours. Total dose: 4.8 gm.

Results: Epistaxis arrested completely after six hours. 24 hours after the treatment was initiated: profuse perspiration, temperature normal, nasal mucosa slightly swollen but of a more normal appearance. Nasal discharge thickened. Cough subsided to a considerable degree but remained for another three days.

M. K., male, white, age 14. Past history showed chronic tonsillitis. Frequent colds. Onset abrupt, with chills. Excessive nasal discharge. Fever 103°, Extreme prostration, cough. Persistent epistaxis.

Examination: The nasal mucosa very red and swollen, bleeding easily. Pulse: 132. WBC: 6400. Urine: normal. Hirst's test (serum-inhibition-of-hemagglutination) positive for virus A influenza.

Diagnosis: Virus A influenza. Moderate tracheobronchitis.

**The preparation employed (C. V. P.®) is a combination of equal parts of the whole water soluble citrus bioflavonoid complex (22) and ascorbic acid. The dosage given in the text is that for the flavonoid component only.

Treatment: Flavonoids, 300 mg. every four hours for 48 hours. Total dose: 3.2 gm.

Results: Epistaxis arrested after five hours. Profuse perspiration took place 18 hours after the therapy was initiated with rapid drop of temperature to normal. Nasal discharge stopped. Nasal mucous membrane normal after 24 hours. Cough subsided after 48 hours.

COMMENT

In both these cases of virus A influenza, the infection responded promptly to flavonoid therapy. Epistaxis was arrested within five to six hours.

SUMMARY

The capillary syndrome is present in many viral infections and is involved in the inflammatory processes.

Citrus flavonoids, otherwise known as vitamin 'P' or capillary permeability factor, minimize the injury to the capillary wall induced by viral infections.

Five cases of virus influenza were treated with citrus flavonoids (C.V.P.) with encouraging results.

The therapeutic effect of flavonoids in viral infections might be interpreted as the result of improved functioning of the capillary system.

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SCURVY IN NEBRASKA: I. THE EPIDEMIC OF SCURVY AT CANTONMENT MISSOURI (FORT ATKINSON), NEBRASKA, 1819-1820

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LAST YEAR marked the bicentennial of the publication of James Lind's famous book in 1753 entitled "Treatise of the Scurvy." It was Lind's experiments upon twelve sailors afflicted with scurvy and described in this book which put final conviction to the fact that scurvy is a nutritional disease easily prevented and easily cured. In spite of the fact that the cause, the cure, and the prevention of scurvy were known even long before the time of Lind, this disease continued to be the cause of thousands of preventable deaths. Scurvy continued to be the sailor's calamity, the soldier's calamity (1), the explorer's calamity, the settler's calamity, the baby's calamity,

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