*Postgraduate Medical Journal* (March 1983) **59**, 152–153

# Discussion

CHAIRMAN: It seems that the cationic proteins will not damage the endocardium, but do obviously damage the muscle cell. Does that mean that the endocardial damage follows the myocardial damage?

DR SPRY: Dr John Davies is injecting eosinophil granule toxins into rats which have an established eosinophilia to see whether this leads to an inflammatory response which would amplify the damage and lead to fibrosis. At present these toxins produce myocardial necrosis but no fibrosis.

DR E. G. J. OLSEN: Your findings fit in with our restrospective studies. We found that necrotic and inflammatory changes preceded any endocardial changes. Therefore, the hypothesis and your proof fit in very nicely with the studies in man. I would like to ask whether the cationic proteins are not, by themselves, thrombogenic? Could it be that the endocardium is damaged as a result of the myocardial involvement? This and the additional action of the cationic protein explains the superimposition by thrombus which leads to the whole spectrum of the disease.

DR SPRY: Some of these proteins have a potent effect on the coagulation system.

Venge, Dahl and Hällgren (1979b) and Dahl and Venge (1979) in Sweden have shown that eosinophil cationic protein activates the Hageman system and the fibrinolytic system as well. Patients with hypereosinophilia also have a high incidence of thrombotic and embolic complications which is not a feature of tropical endomyocardial disease, suggesting that if damage to the heart in the tropics is due to eosinophil cationic protein, it develops with a slower time course. We now need to know where eosinophil granule proteins go to, after they have left degranulated eosinophils, and we also need to find possible inhibitors. Heparin can do this, and if a heparin-like molecule can be found, it could be considered for treating the rapidly progressive forms of eosinophilic endomyocardial disease. We have tried to reduce serum eosinophil cationic protein levels by plasma exchange and by giving heparin. Plasma exchange reduced the serum levels but had no clinical effect in one patient, and a course of heparin to a patient with widespread thromboembolic complications of the hypereosinophilic syndrome also appeared to have no benefit.

DR H.-D. BOLTE: I have some doubt about your interpretation of the increase in sodium transport on oxygen consumption. We have measured ATPase activity in myocardial cells and the ionic content of red blood cells. We know that by stimulating the ionic transport of sodium, the cell will shrink and, if the transport is decreased, the cell will swell. If the sodium content is decreased this could be evidence of an increased sodium transport activity.

DR SPRY: I understand that the only way that ouabain affects the cell membrane is through an inhibition of the sodium pump.

DR BOLTE: Ouabain decreases sodium transport, but we do not know in what way passive permeabilities are changed and so ouabain could, especially in high concentration, influence the passive permeability.

DR SPRY: Ouabain completely abolished stimulation of oxygen uptake.

DR BOLTE: Do I understand correctly that, with DNP and fluoride, you did not get a decrease in oxygen consumption?

DR SPRY: DNP increased the oxygen consumption of isolated rat heart cells. Fluoride and azide inhibited oxygen uptake. Ouabain inhibited it completely.

DR J. J. PUIGBO: Have you tried the calcium antagonist effect on this process?

DR SPRY: No.

DR BOLTE: How do you explain the fact that the inner layers of the myocardium are diseased preferentially?

DR SPRY: There are two possibilities. The first is that the metabolism of heart cells is different between the endocardium and other sites. The second possibility is that there is a different blood supply to the two parts of the heart. This could explain the localisation of necrotic lesions in the endocardium after injection of toxic amounts of adrenalin in rats. However the rat model of eosinophil granule protein induced heart damage shows widespread injury in the heart.

DR OLSEN: I think the explanation of why the change is limited, is due in part to the first suggestion you made. I think that the arrangement of the microcirculation and the metabolic differences are important.

DR P. J. RICHARDSON: The histological changes in the rat myocardium looked like myocarditis. Is there any suggestion that immunosuppressive therapy, either prednisone azathioprine combination or even cyclosporin A, might have any benefits in this particular condition?

DR SPRY: Yes. There is now circumstantial evidence from 3 of our patients and several in the National Institutes of Health (Bethesda) that low doses of steroids given continuously inhibit the progression of endocardial disease in patients with the hypereosinophilic syndrome. We have shown this using endocardial biopsies and post-mortem material. One patient with early lesions was treated for 6 years with low doses of steroids and still showed acute necrotic changes at post-mortem. This emphasises the importance of detecting early disease, as it may be treatable.

DR J. J. ACQUATELLA: We have a similar case; a patient with myocarditis and with a very high eosinophil count. She responded well to 10 mg of prednisolone and so far she has been followed for 3 years.

CHAIRMAN: Does this represent a change from your previous policy that immunosuppression is useful in limiting exacerbation but does not seem to prevent progression of the disease?

DR SPRY: We do not know whether immunosuppressive or cytotoxic drugs affect the progression of endomyocardial disease, in patients with hypereosinophilia, although steroids seem to have this effect. We discussed the question

of treatment further in our publications in the *Quarterly Journal of Medicine.*

CHAIRMAN: Professor Dubost, do you keep your surgical cases on steroids? We do not.

PROF. C. DUBOST: No.

DR SPRY: Once the stage of extensive fibrosis has been reached, it is unlikely that steroids could be beneficial.

DR OLSEN: Study of the effects of corticosteroids could also be an indication to undertake serial endomyocardial biopsies by bioptome as in our patients with myocarditis.

CHAIRMAN: Do you believe that if you have somebody with hypereosinophilia, you should then look at the eosinophils immunologically? If you find they are degranulated do you then put the patient on small doses of steroids long term?

DR SPRY: The presence of degranulated eosinophils in the blood is not sufficient, and an endomyocardial biopsy ought to be taken to make the diagnosis. However, many people would question whether invasive cardiac studies should be done in a patient who does not have any overt clinical evidence of cardiac disease.

DR BOLTE: We have observed some of our cases of EMF with decreased myocardial function, hypereosinophilia and a very high IgE concentration. Can you suggest a linkage between them?

DR SPRY: No. Other workers have noted this association in some patients who may have a type I allergic response underlying their hypereosinophilia.

DR BOLTE: I have seen well documented cases with characteristic findings of obliterative and obstructive myocardial disease associated with hypereosinophilia and with increased IgE concentrations. We could not, however, find eosinophils in the tissues and no hypereosinophilia in the myocardium.

Have you found increased levels of basic proteins in the plasma and with a normal eosinophil count?

DR SPRY: Yes, raised levels of serum eosinophil cationic protein have been documented by Venge *et al.* (1979a) in Sweden in patients who have several types of inflammatory reaction in tissues. They suggested that granule proteins which were released into tissues, could return to the circulation. In the past, we may well have overlooked the presence of degranulated eosinophils in histological sections. They are clearly seen in electron micrographs. The availability of specific monoclonal antibodies which bind to these proteins will enable us to detect them in tissues directly.

DR BOLTE: Are these proteins specific to the eosinophils or do neutrophils also contain them?

DR SPRY: They are specific for eosinophil granule proteins.

## References

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