Postgraduate Medical Journal (March 1983) **59**, 184–185

Discussion

PROF. A. O. FALASE: You show some difference between EMF in England and India. Does it have different aetiologies or do you think other differences are important?

DR DAVIES: Yes, of course there are differences in genetic make up and to what they are exposed. Regarding aetiology in England, at least, we have good evidence that eosinophil granule products are toxic to heart cells. We know that EMF occurs in tropical regions where eosinophilia is common, but on the other hand EMF is still a relatively rare disease in these areas. What we are trying to discover are differences that exist between these patients and control subjects many of whom also have eosinophilia. We are also developing new techniques which we hope will enable us to look at very early disease.

CHAIRMAN: You did say that in India these patients showed granulated and not degranulated cells?

DR DAVIES: Yes. However, you have discovered degranulating eosinophils within the heart tissue of 2 patients with angiographically established EMF on whom Dr Vijayaraghavan and I were able to perform endomyocardial biopsies in Kerala, South India. Neither of these patients had a blood eosinophilia or peripheral degranulation. I would like to emphasise the very important point that a tissue eosinophilia can cause damage, in the presence of a perfectly normal blood eosinophil count. This has been impressed on me by a young boy with eosinophilic gastro-enteritis. He has not had a circulating eosinophilia for years, but we found a marked tissue eosinophilia on colonic biopsy. It appears that eosinophils can migrate towards tissue and cause damage within tissues in the absence of a circulating eosinophilia. I think that is a very important point.

DR E. G. J. OLSEN: Were these patients clinically in the earlier or the later phase?

DR DAVIES: They were in an advanced stage of the disease.

DR H. ACQUATELLA: Have you found a correlation between the degree of fibrosis in the left ventricle pathologically and the echocardiogram changes? It seems very strange to me that we have the fibrosis both on the left and the right side.

DR DAVIES: In our experience the disease is almost invariably biventricular. Sometimes the main haemodynamic problem is on the left side, caused by fibrosis of the posterior mitral valve leaflet giving rise to severe mitral regurgitation. These young people frequently do very well following mitral valve surgery.

DR P. J. RICHARDSON: With respect to biopsy, which ventricle would you choose when you biopsy, particularly patients with mitral disease?

DR DAVIES: We feel that it is probably not a good idea, especially in our English group who have arterial embolic problems, to touch their left ventricles with a bioptome. We have only done right ventricular biopsies, but in most cases this has been sufficient because the disease process is almost invariably biventricular.

DR SPRY: I am not clear why left ventricular biopsy is not being carried out for endomyocardial disease. This is of potential importance in India where the disease may be localized to this side of the heart.

DR DAVIES: There are no definite contraindications. In our limited studies done so far, we have simply chosen right ventricular biopsy as the quickest and safest procedure.

DR SPRY: What proportion of patients would you fail to diagnose if endocardial biopsy were restricted to the left side of the heart?

DR DAVIES: Only 2 out of nearly 50 Indian patients appeared to have isolated left ventricular disease.

PROF. FALASE: You did not comment on degranulated eosinophils in controls or patients.

DR DAVIES: There was no degranulation seen in either 28 patients or controls.

DR SPRY: We have carried out experiments with ^{111}In oxine-labelled eosinophils to see whether they go to the heart after intravenous injection in patients with eosinophilic endomyocardial disease. There was no preferential localization over the heart in 3 patients, which was disappointing. We would, of course, like to carry out similar experiments with labelled eosinophil granule toxins, but there are obvious reasons why we have not done this.

CHAIRMAN: Dr Davies has pointed out differences especially regarding emboli. Is it only because they have more thrombus or do you think there is a real difference between these groups of cases, in the U.K. and in India and Brazil? Is it just a matter of earlier recognition?

DR DAVIES: It would appear that the cardiac lesions are identical but the systemic complications are very different. I do not know why. It has been suggested that patients in this country are diagnosed earlier in the thrombotic stage and we are getting later cases in India, but some of the cases we saw in India were aged 5 and you cannot get a lot earlier than that.

CHAIRMAN: As Dr Spry has pointed out, we have not seen a case of endomyocardial disease associated with eosinophilia where there was no degranulation, and therefore I think that in itself is very strong evidence that eosinophils form the vital link in the pathogenesis of endomyocardial disease. Patients with EMF have been described in the tropics without eosinophilia. We suggested that there might be a significant number of degranulated cells in normal cell counts, and if the number is significant, endomyocardial disease will be associated. An Indian patient, as we learnt today, had a normal count, and significant tissue degranulation and therefore we have yet another link in our belief that the eosinophil is very closely linked in the pathogenesis of endomyocardial disease.

PROF. J. F. GOODWIN: It seems odd to me, on a slightly

peripheral issue, that in the U.K. patients have more in the way of extra-cardiac problems. Patients from the tropics have a massive eosinophilia. Is it therefore a question of mass action so that, if you have a massive invasion of eosinophils into the heart muscle, it will result in these problems.

CHAIRMAN: There are no differences from a pathological point of view in the heart and other organs in the chronic cases whether they came from the tropics or the U.K. The arteritic process, often cited as a difference, is a manifestation of an acute stage and that can be found in the heart and other organs in the tropics as well as in the U.K.

PROF. GOODWIN: You mentioned pro-coagulant properties. Were you referring to any eosinophil?

DR DAVIES: No, rather to substances released from degranulating eosinophils. Most people with high eosinophil count do not develop cardiac or other problems. Cardiac damage results from eosinophils discharging their toxic cationic proteins.

PROF. GOODWIN: We appear to have 2 unpleasant effects exerted by eosinophils. One is a specific one peculiar to eosinophils and that is degranulation and the release of toxic proteins; the other is the coagulant effects. Were the eosinophil proteins in the serum increased in the control patients?

DR DAVIES: We found very high levels of eosinophil proteins in both patients and controls in the South Indian series. This was not particularly related to the eosinophil count. This is interesting and we do not know yet how to interpret it.

DR SPRY: Those of us who have followed the eosinophil-endocardial disease work have assumed that patients have a toxin which damages the heart and that the degree of damage relates to the amount of toxins. An alternative hypothesis is that these toxins are released in all eosinophilic disorders, but that people who have endocardial disease lack an inhibitor. The eosinophil granule proteins which kill parasites and cells in culture are highly charged cationic proteins. They can be inhibited *in vitro* with heparin and other anionic substances. The presence of such potent toxins implies that inhibitory mechanisms should be available to prevent damage involving normal tissues. It would be interesting to look for these inhibitors in mast cells and serum from patients with and without endomyocardial disease. Recent work suggests that eosinophil cationic protein binds to several components in serum but it is not known whether these inhibit their effects on tissues.

CHAIRMAN: Dr Davies, what do you think is the relevance of IgE?

DR DAVIES: Our provisional work in South India suggests that patients have higher IgE levels than control subjects and also higher filarial antibody titres. These patients may well have been challenged by many other parasites for which we have not looked. It would be very likely that these patients would also have a significant eosinophilia especially in the early stages. IgE could be involved by inducing tissue degranulation at the onset of the disease, but this is only a hypothesis.

We really need to look hard for patients with very early disease, especially in the tropics.