Viruses and myocarditis

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THE observations described here were made in the course of the work of the Regional Virus Laboratory, Glasgow, which provides a widely-used diagnostic service. Our investigations of cardiac cases have concentrated particularly on enteroviruses, the main group of viruses associated with acute myocarditis. Within this group the Cocksackie viruses have received particular attention, their well-known causal role in acute carditis and Bornholm disease being possibly related to their characteristic properties of causing acute myositis in experimentally infected newborn mice. Virological diagnoses were based on isolation of virus from faeces, and/or a four-fold or greater rise in neutralizing antibody titres in paired sera (rarely a four-fold fall in titre with acceptable time relationships) or an unusually high antibody titre without significant fluctuation. Unfortunately our first contact with a case is often too late in the course of infection for successful virus isolation or detection of rising antibody titre. The clinical diagnoses were those of the clinicians concerned, separating the categories of pericarditis (without recorded features of myocarditis) and myocarditis (including cases with features also of pericarditis).

Results

As a general illustration of our findings, the analysis is presented of twenty-three cases found during the period 1959-67 in which both clinical and virological findings gave acceptable evidence of an enteroviral aetiology for acute cardiac disease. They show the usual picture in that Cocksackie viruses of group B predominated (seventeen cases), these infections showing male excess of 12 : 5, an older age distribution (twelve cases over 10 years old) and a predominance of pericarditis over myocarditis (10 : 7). The other enterovirus infections (five Cocksackie virus A, one poliovirus) were mainly associated with acute myocarditis in female infants.

Cocksackie viruses of group A are less often implicated as causes of heart disease, though the greater technical difficulties of detecting most of them militate against successful diagnosis of these infections. We have reviewed elsewhere the evidence concerning this group of enteroviruses (Grist & Bell, 1969). Unlike Cocksackie viruses, echoviruses do not typically cause myositis or other disease when

inoculated into newborn mice. Nevertheless, significant differences have been observed between the associations of different types of echovirus with cardiac and Bornholm disease suggesting that some (notably types 6 and 19) may occasionally mimic Cocksackie viruses by causing illnesses of this type (Bell & Grist, 1970b).

Some problems of virological interpretation are illustrated by an adult male with acute pericarditis whose sera on the eighth and seventeenth days of illness showed diagnostic rising antibody titres to Cocksackie virus B types 1, 3, 4, and 6, high unchanging titres to type B2, and a low rise (<16 : 16) to type B5. These cross-reactions are fairly common and pose problems in specific interpretation; in this particular case the infecting virus was demonstrated to be type B3 by isolation from faeces. One of our echovirus 6 infections, a boy with acute pericarditis, also showed a cross-reactive antibody response, in this case to Cocksackie virus B3 (case 4: Bell & Grist, 1970a). In earlier days when it was technically too difficult to test for Cocksackie virus antibodies except on a very limited scale, one would have been happy to make a diagnosis of infection with a particular virus on the basis of a significant rise in titre of antibodies to that Cocksackie virus type. Our wider range of routine testing has shown that the situation is not so simple, though monotypic antibody responses are commoner in infants and young children.

Questions of pathogenic mechanism are raised by a female infant in whom Cocksackie virus A9 infection was demonstrated by virus isolation and rising antibody titre (case 3: Grist, 1966). She had acute carditis with persisting failure and cardiomegaly, and died 4 months later showing pathological features of severe interstitial myocarditis. Did the virus infection persist in the myocardium, or did it initiate some process which continued after the virus had disappeared?

In 1966 my colleague Dr Eleanor J. Bell introduced a simple microneutralization test for antibodies to group B Cocksackie viruses (Bell & Grist, 1970a) which revolutionized our approach by enabling us to accept for testing all specimens submitted from cases with suspected cardiac or Bornholm disease; previously we had been highly selective in accepting cases for examination because of the difficulty and

expense of serological tests by earlier techniques. Over a period of 5 years we examined 308 patients of a wide age range from infancy to old age, with a male predominance of 210 : 98. Based on the final diagnosis of the clinician concerned, with follow-up enquiry where required, each case was classified to my best ability within one of five categories: Bornholm disease (without cardiac features), acute myocarditis (including peri-myocarditis; excluding cases of vascular origin), acute non-bacterial pericarditis, other cardiac diseases, and non-cardiac diseases which had been suspected as being of cardiac origin when the initial specimens were submitted for examination.

In Table 1 these cases are tabulated according to the virological findings: (a) those in whom virus isolation and/or four-fold or greater rising antibody titre provided unequivocal evidence of current enterovirus infection, (b) those with static antibody titres of 256 or more to one or more of the six group B Cocksackie viruses, i.e. titres so high as rarely to be found except after recent infection with one of these (or occasionally other) enteroviruses, (c) those with borderline titres of 128 (sometimes 'significant' but often found as residual titres in the general population) and (d) those with insignificant titres of 64 or less.

It can be seen that cases with definite or probable evidence of infection comprised (combining virological groups a and b) fifteen (72%) of those classified as Bornholm disease, twenty-seven (48%) of those with acute myocarditis, thirteen (21%) of those with acute pericarditis, thirteen (11%) of those with other cardiac diseases, and five (11%) of the non-cardiac group. In effect, the first and last groups provide positive and negative virological control groups against which to evaluate the others. The descending order of virological 'positivity' from Bornholm disease through myocarditis and pericarditis to the 'other-cardiac' and non-cardiac groups is not significantly changed by analysing the data by age-groups and is therefore not due to different age-structures of the diagnostic categories; the order is also unchanged for each of the separate years

1966-70. Although we cannot make a precise evaluation of the role of enteroviruses from these figures, it seems clear that viruses of this group contributed at least one-third of the cases classified as acute myocarditis and at least one-tenth of those classified as acute pericarditis.

Because of the limited range of even our extended battery of virological tests, and because many cases come to attention too late to provide satisfactory virological evidence, our findings must underestimate the contribution of enteroviruses to this problem. It may be noted that Levi & Proto (1971) estimated from their experience that Cocksackie viruses probably caused about 300 cases of carditis per year in the Italian province of Brescia (population about one million). It is also interesting that a London epidemiologist, Professor Rose, drew attention a few years ago to errors in classification of fatal pericarditis, contributing to a persisting and even higher reported mortality-rate for 'rheumatic fever' in adults in England and Wales despite the precipitous decline in the figures for younger people (Rose, 1966). It appeared likely that a non-rheumatic group, probably 'acute pericarditis, not otherwise specified', was being misclassified as 'rheumatic' by the Registrar General. Could these fatal, adult cases of acute non-specific pericarditis be of enteroviral origin?

There may be an analogy with paralytic poliomyelitis, another enteroviral infection with which our ecological relationship changed during the first half of this century as a result of improved hygiene and living conditions. It is believed that the delay of primary infections until older and adult ages led to the consequent emergence of the new phenomenon of epidemic paralytic poliomyelitis involving these older groups. Cocksackie viruses and other enteroviruses spread in the same way as polioviruses, and would be expected to share this ecological change whereby more primary infections and associated diseases are to be expected in older and adult age-groups than a few decades ago. It is, therefore, distinctly possible that enteroviral heart disease of adults is genuinely increasing in developed countries.

TABLE 1. Results of tests for enterovirus infection in cases of suspected cardiac disease

Disease group	Number of cases in each virological group*				Totals
	(a) definite	(b) probable	(c) borderline	(d) negative	
Bornholm disease	8	7	1	5	21
Acute myocarditis	10	17	7	22	56
Acute pericarditis	3	10	10	39	62
Other cardiac diseases	3	10	13	97	123
Non-cardiac diseases	1	4	4	37	46
Totals	25	48	35	200	308

* (a), Cases of virus isolation and/or rising antibody titre; (b), cases with antibody titre 256 or more to one or more group B Cocksackie viruses; (c), cases with highest antibody titre of 128 to any group B Cocksackie virus; (d), cases with antibody titres of 64 or less to group B Cocksackie viruses.

References

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Discussion

PROFESSOR WATERSON: The last three papers raise the question of a possible direct or indirect viral aetiology for COCM. The idea of a virus infection as something which either kills the patient in the acute phase or from which a rapid and complete recovery is made has become increasingly inadequate as we have developed better methods of studying viruses and it is quite clear that there may be chronic persisting infections with viruses and also that we have to consider the question of antibodies. Now antibodies are only good if they are in the right amount at the right time in the right place. One possible result of a chronic persisting viral infection, or even of an acute virus infection in which the patient recovers, is that antibody which is left may act upon tissue (and cardiac muscle is not exempt) either because of cross-reaction between tissue antigens and the virus which caused the infection, or because of the effect of immune complexes of the virus or one of its antigens and the antibody. Our real trouble is at present that we do not have the evidence on the cases of COCM. At one end we have acute virus infections, at the other end the known cases of COCM and what we have to do is to see if the two are associated.

DR BRIGDEN: Is there here a possible meeting place between virologists and geneticists? Competence to handle an immunological problem is presumably genetically determined. I have seen two or three suggestive familial episodes. In one of these, for instance, a man died in 1953 with the typical histological changes of idiopathic myocarditis. Last year I saw his son with a history of fever and chest pain, diagnosed as having myocarditis. Coxsackie virus antibody tests were carried out, and suggested that he had Coxsackie myocarditis. This happened in Sydney, Australia; he returned to this country in heart failure, and died in London just after he left the Heart Hospital. His heart showed the same histological changes as his father's. This is the second time we have seen and encountered this phenomenon, and I wonder therefore whether in studying patients we think might have myocarditis, we should take cognizance of familial history since there might be determinants in the family which sensitized the particular myocardium to an infective insult.

PROF. GRIST: I think this is a very reasonable speculation. There is also another possible mechanism. Some viruses will incorporate into their own outside membranes, host antigenic material, which it then presents to the host in a different configuration. This may stimulate an autoimmune tissue antibody reaction by the host to what may be some of his own antigens, but presented in a peculiar way. This is not true of the enteroviruses such as Cox-

sackie but it is known to occur in some of the arbovirus group prevalent in tropical countries. There has been speculation regarding some of the tropical heart diseases of arboviruses.

DR BRIGDEN: May I raise another point? Are not some potentially cardiotropic viruses helped to damage the heart if it is weakened by some other noxious process? I think George Burch showed in experimental animals that in potassium depletion studies a non-cardiotrophic virus could produce a lethal myocarditis. As clinicians, we often feel that many factors are operative in myopathies.

DR JANE SOMERVILLE: I know viruses are 'in' and bugs are 'out', but I would like to ask if there is any evidence that diphtheria causes a late cardiomyopathy. We know it causes myocarditis in death and I wonder if there is any evidence whether we do see cardiomyopathy with this as an aetiology.

PROF. BENGTSOON: Diphtheria toxin is one of the common classical agents giving myocarditis, but I have never heard anything specifically about cardiomyopathy. However, since diphtheria as a disease disappeared just at the moment when this became of interest, I don't know anybody who has taken this connection into consideration.

DR SHAPER: Diphtheria has not disappeared from all areas, and in many parts of the tropics diphtheria is still a problem and skin infections with diphtheria organisms are very common. However, one would hesitate to say merely because many of the cardiomyopathies are common in tropical countries where diphtheria is also common that they are necessarily related.

PROF. WATERSON: One could test for diphtheria antitoxin in these patients' sera.

DR JANE SOMERVILLE: There was a case, a patient with idiopathic cardiomegaly and a history of diphtheria 10 years earlier. Some of the prisoners-of-war in the Far East had idiopathic cardiomyopathy; they did have a lot of diphtheria and one wonders if it played a role. Dr Brigden had two patients with histories of diphtheria with myocardial involvement documented by the Army 18-20 years before they presented with cardiomyopathy.

DR M. J. DAVIES: Could I ask what attempts should be made to try to isolate virus at necropsy in case of sudden death of young persons where myocarditis is a possibility?

PROF. GRIST: By a battery of tests we have isolated many viruses from the tissues of infant cases of sudden death, but interpretation is difficult because young children commonly have virus infections anyway and we cannot get controls. It is questionable whether much