

criteria, it is advised that the gluten-free diet should as a rule be maintained till after puberty, although temporary relaxation of the diet may be allowed to adolescents for personal and social reasons.

I am grateful to my colleagues Dr. O. H. Wolff and Dr. B. D. Bower, who have allowed me to include some of their patients in this report. Dr. J. M. French and the late Mr. Harold Salt were responsible for the estimates of fat, and Miss S. Littlejohn for the D-xylose excretion tests. Dr. R. Astley provided the radiological opinions and also assisted the registrars, Dr. M. Hallowell, Dr. Colin Miller, Dr. A. C. K. Antrobus, and Dr. R. Glass with the biopsies. Dr. A. H. Cameron reported on the biopsy specimens of small-intestine mucosa. Sister D. Horler did much accurate ward work in the collection of urine and faeces.

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IMMUNOLOGICAL STUDIES IN THE POST-CARDIOTOMY SYNDROME

BY

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The post-cardiotomy syndrome (P.C.S.) is an uncommon complication of heart surgery occurring after a latent period and recognized by fever, pleuropericarditis, raised erythrocyte sedimentation rate, and spontaneous resolution. Arthralgia and a tendency to relapse are less common features. Corticosteroid rapidly suppresses the disorder, and when used prophylactically prevents its appearance (Dresdale *et al.*, 1956). Mild symptoms are readily overlooked, especially when the onset is delayed for several weeks or months after operation.

The P.C.S. was first recognized as a complication of mitral valvotomy and was attributed to reactivation of rheumatic fever (Soloff *et al.*, 1953). However, its appearance after operation for congenital heart disease denied this aetiology (Ito *et al.*, 1958). It was also thought to be due to blood (or some foreign substance such as penicillin) in the pericardium, a view which was supported by reports of the P.C.S. as a complication of stab wounds of the heart (Segal and Tabatznik, 1960) and after implantation of a pacemaker (Dressler, 1962). However, it is now generally thought that a less direct process concerning hypersensitivity to antigenic material liberated by trauma is the more likely cause. Kaplan (1960) demonstrated a reaction between homologous heart tissue and factors in the serum of patients who had undergone mitral valvotomy. This suggested that trauma resulted in the production of autoantibodies, but his findings were not related to the P.C.S. Further support for this approach came from the work of Ehrenfeld *et al.* (1961), who found heart antibody-like factors in the serum of patients with different heart diseases, including one who had had mitral valvotomy and whose post-operative course was uneventful.

In this report we present the results of immunological tests on patients undergoing mitral-valve surgery, and we relate these to the subsequent clinical course. Our results strongly indicate the presence of a disturbed immunological mechanism in patients who develop the P.C.S.

Investigation

The Patients.—All of the patients studied, except one, had mitral valvotomy performed by the transventricular route (by Mr. Vernon Thompson or by Mr. Geoffrey Flavell). They were assessed pre- and post-operatively by us and with one exception have remained under close out-patient observation. Specimens of serum were taken from the patients pre-operatively, on or about the 10th and 30th post-operative day, and more frequently if the post-operative course was complicated. Tests were also made on blood from 12 patients after thoracotomy for non-cardiac surgery, from six patients after laparotomy, and on the sera from 35 healthy blood donors as controls.

The Test

We decided to use only the tanned-red-cell haemagglutination test in the present study. Fresh sheep cells were tanned by the method of Boyden (1951). Tissue extract was prepared by grinding fresh human auricular appendage (obtained at mitral valvotomy) with abrasive ("aloxite") in a solution of phosphate-buffered saline at pH 7.2. This was centrifuged and the supernatant fluid was diluted to approximately 1 in 20. The diluted tissue extract was then added to an equal volume of a 2% suspension of tanned red cells and allowed to stand at room temperature for 45 minutes. The sensitized cells were then washed three times with saline containing 1% guinea-pig serum at pH 6.4. The patient's serum and the guinea-pig serum were treated by heating to 56° C. for 30 minutes in order to remove complement, and by absorbing with fresh sheep red cells to remove non-specific agglutinating factors. The patient's serum was serially diluted with buffered saline and 1% guinea-pig serum, an equal volume of 2% sensitized red cells being then added to each dilution. Control tests were carried out by adding sensitized cells to saline without patient's serum and by adding tanned but not sensitized cells to patient's serum.

In this study heart tissue was stored at -20° C. and was used within two weeks, the extract being prepared fresh for each test. Each specimen of serum was tested as it was obtained and again when a series of sera from one patient was available, so that comparisons in titre could be made under the same test conditions. The results were read after two hours at room temperature and confirmed after standing in the refrigerator overnight. The criteria of positivity were those of Stavitsky (1954). In each test parallel observations were made using cells sensitized with rat heart and rat kidney which had been prepared in the same way as the human heart extract.

Results

All tests were negative in the controls and pre-operatively in the 36 patients who had heart operations (Table I). In six cases the test became positive post-operatively, while in 30 cases it remained negative (Table II). The test was considered positive when there was definite agglutination at a titre of 1/80 or greater. Results obtained with rat heart and human auricular appendage extracts gave essentially the same results, but usually slightly higher titres were obtained with human heart muscle. All tests gave negative results when rat kidney was used as antigen.

TABLE I.—Results of Haemagglutination Tests in Patients Before and After Cardiotomy and in Controls

| No. of Patients | Surgical Operation | Test Result | | |
|-----------------|-----------------------------------|-------------|--------------|------|
| | | Pre-op. | Post-op. | |
| | | | Neg. | Pos. |
| 36 | Cardiotomy | Neg. | 30 | 6 |
| 12 | Non-cardiac thoracotomy | — | 12 | 0 |
| 6 | Laparotomy | — | 6 | 0 |
| 35 | Healthy blood donors | — | All negative | |

TABLE II.—Results of Haemagglutination Tests Related to the Post-operative Course

| Post-operative Course | No. of Patients | Test Result | |
|------------------------------------|-----------------|-------------|------|
| | | Pos. | Neg. |
| Uncomplicated | 31 | 1 | 30 |
| Post-cardiotomy syndrome | 5 | 5 | 0 |

Since the antigen preparation was a crude saline extract, protein estimations were carried out on similar dilutions of various preparations; the results varied between 100 and 250 mg./100 ml. However, this variation did not appear to be important, since the results gave similar titres with various antigen preparations.

“ Positive Cases ”

Five of the six patients who had positive serological tests developed the P.C.S.; the relevant clinical and laboratory data are given below. In two the syndrome developed 8–10 days post-operatively, while in the others its onset was delayed for three weeks or more.

Case 1.—A married woman aged 48 developed fever, arthralgia, and central chest discomfort, accompanied by pericardial friction, an elevated jugular venous pressure, and oedema 10 days after mitral valvotomy. After seven days she was given prednisone (20 mg. daily); the symptoms disappeared within 24 hours. Pre-operatively the E.S.R. was 6 mm./1 hour and the tanned-red-cell test (T.R.C.T.) was negative. During the P.C.S. the E.S.R. rose to 30 mm./1 hour and the T.R.C.T. was positive at a titre of 1/160. One week after starting corticosteroid her E.S.R. was 12 mm./1 hour and the test became negative. Prednisone was continued for three weeks and the patient remained well. However, two months after operation her E.S.R. rose to 55 mm./1 hour and the T.R.C.T.

was again positive; at this time she was symptom-free, but one week later left pleuritic pain recurred together with arthralgia in the ankles and hands which lasted for four weeks and then subsided spontaneously. The T.R.C.T. again became negative and her E.S.R. fell to 5 mm./1 hour.

Case 2.—Seven days after mitral valvotomy a married woman aged 51 developed tricuspid incompetence which was not present before operation. Low-grade pyrexia persisted from the day of operation and pericardial friction developed. Before operation the E.S.R. was 10 mm./1 hour and the T.R.C.T. was negative. On the 10th post-operative day her E.S.R. was 71 mm./1 hour and the T.R.C.T. was positive at a titre of 1/160. On the 20th day, although resolution was already occurring, as indicated by an E.S.R. of 30 mm./1 hour and a T.R.C.T. positive at a titre of only 1/20, she was given prednisone (20 mg. daily). Fever rapidly subsided, the E.S.R. returned to normal, and the T.R.C.T. became negative. Tricuspid incompetence greatly diminished, but clinical evidence suggests that a minimal leak has persisted.

Case 3.—A man aged 47 had a mitral valvotomy, the early post-operative period being uneventful. However, blood taken on the 14th day and three months post-operatively gave positive results with the T.R.C.T. at titres of 1/80 and 1/160 respectively. Eight months after the operation general malaise, pleuritic pain, and ankle-swelling developed. He did not attend during this period, and when seen one month later his symptoms were already subsiding. However, x-ray examination showed a small pleural effusion and his E.S.R. was 30 mm./1 hour; this fell to 18 mm./1 hour over the next two weeks and the T.R.C.T. became negative.

Case 4.—This patient, a woman aged 33, had an early and uneventful recovery after mitral valvotomy. The T.R.C.T. on the 13th and 40th post-operative days gave positive results at a titre of 1/160. She returned to work as a midwife. Four

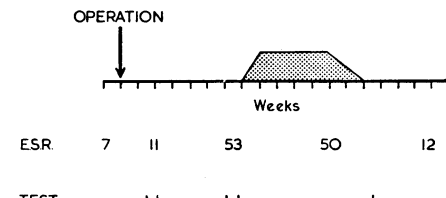


FIG. 1.—Case 4. Post-cardiotomy syndrome seven weeks after mitral valvotomy. (++ = strongly positive haemagglutination tests.)

months after operation she developed fever and pleuritic chest pain. She was found to have pleural friction and a slightly raised jugular venous pressure. Her E.S.R. was 50 mm./1 hour and x-ray examination showed a left pleural effusion. After recovery her E.S.R. was 12 mm./1 hour and the T.R.C.T. became negative. No recurrence of symptoms has occurred during the past year (Fig. 1).

Case 5.—Eighteen months after closure of an atrial septal defect the patient, a woman aged 22, developed fever and

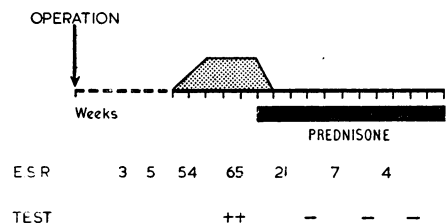


FIG. 2.—Case 5. Post-cardiotomy syndrome several weeks after repair of atrial septal defect. Strongly (++) positive haemagglutination tests become negative soon after cortisone administration.

precordial pain accompanied by pericardial friction, E.C.G. evidence of pericarditis, and raised jugular venous pressure. At this time her E.S.R. was 65 mm./1 hour and the T.R.C.T. was

positive at a titre of 1/160. After seven days she was given prednisone (20 mg. daily); the fever and chest pain disappeared abruptly. Her E.S.R. and E.C.G. rapidly returned to normal and the T.R.C.T. became negative. Prednisone was stopped after three months without incident and she has remained well (Fig. 2).

Case 6.—The patient was a woman aged 26. On the 13th day and six weeks post-operatively the T.R.C.T. was positive at titres of 1/20 and 1/80 respectively, but clinically there was no evidence of P.C.S. Further follow-up was not possible, as she left the country.

Discussion

It appears to us that there is very strong evidence for the view that the P.C.S. is due to hypersensitivity in the immunological sense. This evidence now comprises analogy with the clinical features of known collagen diseases, immunological tests, and a brisk therapeutic response to corticosteroid.

The clinical features appear after a latent interval varying from weeks to months (hypersensitivity takes time to develop). Pleuropericarditis is a common feature in various so-called collagen diseases, including rheumatic fever, rheumatoid arthritis, and systemic lupus erythematosus. The tendency to relapse, the raised E.S.R., and the favourable response to steroid are common to all. The same features are present in both the post-infarction and the post-cardiotomy syndromes and in both conditions serum factors which behave like organ-specific antibodies have been demonstrated. Assuming that the sensitized tanned red cells are carrying an antigenic moiety of heart tissue, then agglutination with patient's serum indicates the presence of a circulating antibody-like substance. Positive tests were not only obtained during the phase of activity, but in each case where tests were carried out positivity was found prior to the appearance of clinical features, and when the only other evidence of impending trouble was a greatly increased or rising E.S.R. It seems reasonable to conclude that there is a very close relation between the evolution of the syndrome and a circulating serum factor which reacts with heart tissue.

We confirmed that the clinical features were relieved within 48 hours by cortisone, which also produced a negative T.R.C.T. It is of interest that premature withdrawal of cortisone was followed by an increasing sedimentation rate and a return to positive agglutination prior to clinical relapse (Case 1). Although the pathogenesis of the process is not understood, it is clear that the antibody is not a by-product of the inflammatory reaction but is closely related to its cause. Furthermore, if an antibody-like substance is not the result of the P.C.S. then its rapid elimination by corticosteroid indicates that this action of steroid is not merely the suppression of tissue inflammation in this condition. Indeed, the speed and effectiveness of small doses of corticosteroid in suppressing the clinical syndrome, causing a fall in the E.S.R. and negativity of the serological reaction, suggest that its action is more subtle and is concerned with the aetiological mechanism—a view which is supported by the apparently effective action of prednisone in preventing the appearance of P.C.S. when used as routine prophylaxis at the time of operation and in the immediate post-operative period (Dresdale *et al.*, 1956).

Individual susceptibility is a remarkable feature of this syndrome as in various forms of "collagen disease." We have no evidence concerning the nature of this susceptibility; no patient had evidence of active rheumatism or

hypersensitivity before operation and no special features characterized the surgical or anaesthetic techniques which were used in the affected individuals. It has been suggested that susceptibility to rheumatism has a genetic basis (Davies and Lazarov, 1960), but we really do not know why certain individuals develop rheumatic carditis after streptococcal infection while others do not. As the P.C.S. appears to be less rare in patients undergoing surgery for rheumatic heart disease than for those undergoing surgery for congenital heart disease it may be that rheumatic fever has already selected those more likely to react to an antigenic substance arising in the heart.

All positive tests obtained with human heart tissue were also positive with rat heart tissue, whereas rat kidney was invariably negative. Human kidney was not used. Thus whatever substance or substances are responsible for the reaction there appears to be organ specificity, though no individual (autologous) or species (homologous) specificity. However, as the initiating trauma concerns only host tissues, it seems reasonable to regard this as an auto-immunological reaction.

It has been suggested that the P.C.S. is less common than it was a few years ago. We consider that the apparent drop in frequency is due to an earlier tendency to include too many patients whose symptoms were due to the direct effects of operation (and these have diminished) and to a generally shortened duration of stay in hospital, so that delayed reactions tend to occur outside hospital and, when mild, are thus easily missed.

While the usual cause of a rise in jugular venous pressure in this condition is a pericardial effusion, it is probable that true heart failure sometimes occurs. Mounsey (1959) noted the delayed and unexpected development of tricuspid incompetence in six patients after mitral valvotomy. In one of our patients late tricuspid incompetence was accompanied by a rising E.S.R. (as in at least one of the six reported by Mounsey) and a positive T.R.C.T.; this raises the strong possibility that myocardial damage and failure under these circumstances may be due to local antigen-antibody reaction. Indeed, it is possible that patients who develop unexpected tricuspid incompetence or myocardial failure are examples of the P.C.S. in whom myocardial damage is the dominant feature.

It is tempting to consider that other aetiological forms of idiopathic pericarditis which tend to relapse have the same basic pathogenesis in which serous linings of heart, lungs, and possibly joints appear as special target organs in an immunopathological process. In these conditions the initial result may be provided by an infection such as with the Coxsackie virus or even by a vaccination. However, the most important aetiological factor seems to concern individual susceptibility. We have not been able to recognize any common factor which would label affected individuals or enable us to recognize features indicating their immunological incompetence.

Summary and Conclusions

Positive tests for heart antibodies using the tanned-red-cell test were obtained on six patients, five of whom developed clinical features of the post-cardiotomy syndrome. Tests were negative in 30 patients whose post-cardiotomy course was uneventful, and in 18 controls who had undergone lung surgery or laparotomy. The serum from 35 blood donors was also negative.

In some patients antibodies were detected prior to the evolution of the clinical features (the others were not tested

until the disorder was apparent). In all cases the test became negative with spontaneous or steroid-induced resolution.

It is concluded that the circulating substance responsible for a positive test is not the product of the P.C.S. but is closely related to its pathogenesis. No evidence was obtained concerning the nature of the individual susceptibility which is a feature of this condition.

It is a pleasure to thank Professor C. Barwell and Dr. R. G. White for their helpful advice and for providing us with laboratory facilities.

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SERUM CHOLESTEROL LEVELS AFTER MYOCARDIAL INFARCTION

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Although absolute proof is lacking that hypercholesterolaemia is a cause of atheroma, lowering of the serum cholesterol is regarded by many as a useful objective in the management of ischaemic heart disease. Patients who have had a myocardial infarction are particularly eligible for such therapy. It is known that the serum cholesterol falls after myocardial infarction (Biörck *et al.*, 1957), but the pattern of the fall and of the subsequent rise has not been clearly established, and it is not certain how long after an infarct maximum levels are attained. Such information is necessary in order to time the start and so assess the maximum efficiency of hypocholesterolaemic therapy.

The aims of this study were threefold: firstly, to observe in detail the serum cholesterol level after myocardial infarction; secondly, to establish how long after an infarct maximum levels were reached; and, thirdly, to detect any possible relation between change in cholesterol level and other disordered blood levels.

Methods

The problem was investigated in two phases, the first including the 22 days after an acute myocardial infarction, and the second the period from the 22nd day until the 20th week. Serum cholesterol was estimated in duplicate by Henly's (1957) modification of the method of Zlatkis *et al.* (1953) and the mean value taken. If duplicates varied by more than 15 mg. the estimation was repeated.

Phase I

The subjects were 14 men aged 42 to 65, who were admitted on the first day of a first myocardial infarction, so far as this could be determined from the history, and who had no evidence of reinfarction during the 22-day period of observation. All had electrocardiographic proof of acute myocardial infarction. Nine were treated with anticoagulants (phenindione with heparin initially, then phenindione alone). In five patients anticoagulants were contraindicated because of a history of dyspepsia or proved peptic ulcer. Two of the patients had intravenous nor-adrenaline for 24 hours because of severe hypotension.

Serum cholesterol was estimated on the 1st, 3rd, 6th, 9th, 12th, 15th, and 22nd days of the illness. On the first day

blood was taken as soon after admission as possible, and on the subsequent days at 9 a.m. The erythrocyte sedimentation rate (E.S.R.) and packed cell volume (P.C.V.) were measured frequently during this period. In 10 of the patients the serum glutamic oxaloacetic transaminase (S.G.O.T.) levels were estimated on the first, second, and third days of the illness.

Serum cholesterol was also estimated in a controlled group of seven men of comparable age, on the 1st, 3rd, 6th, and 12th days of admission. These seven comprised four minor haematemeses not requiring transfusion, two with acute myocardial ischaemia not amounting to infarction, and one cerebral infarction.

Phase II

Serum cholesterol was estimated in 10 male patients, satisfying the clinical criteria already described, on the 22nd and 29th days after infarction, and at follow-up visits 8 and 12 weeks after the infarction. Six of these 10 were also seen during the 20th week after infarction. All had discontinued anticoagulant therapy on discharge from hospital at the 29th day and were on no special dietary management. At out-patient visits blood was withdrawn between 11 and 11.30 a.m., the patients having had a light breakfast at 8 a.m.

Results

Phase I

The serum cholesterol levels, maximum percentage fall in cholesterol, maximum E.S.R., and highest S.G.O.T. readings of the infarct patients are recorded in Table I, and the cholesterol results are charted in Fig. 1. The results in Table I are grouped according to whether the patients received anticoagulants or not. The cholesterol readings of the control group are given in Table II and charted in Fig. 1.

There is a sharp fall in the serum cholesterol level after a myocardial infarction. This reaches its lowest about the 6th day and is highly significant (mean difference = 65.0 mg.; S.E. of mean = 7.05; $P < 0.001$). The fall seems to occur immediately, and even by the third day the mean fall of 35.7 mg. is significant (S.E. of mean = 5.2; $P < 0.001$). This