

Pyrexia after heart surgery due to virus infection transmitted by blood transfusion

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Pyrexia may follow any heart operation, especially an open operation, and in fact is invariably present for a number of days during the first one to two weeks. When fever persists or returns later, the possibility of numerous complicating conditions arises. If other conditions can be excluded, two particular diagnoses need to be considered; a pleuro-pericardial reaction (post-valvotomy syndrome) or bacterial endocarditis.

We have observed a further cause of continuing disturbance apparently due to a virus infection transmitted by blood transfusion. This takes the form of pyrexia developing just before or after the twenty-fifth post-operative day, *i.e.*, at about the usual time for discharge from hospital. It occurs after a variety of operations, both open or closed,

involving transfusion of widely differing amounts of blood (Table I).

In most cases the usual post-operative pyrexia had settled, and the later rise was sudden and disconcerting. The first patient in whom the condition

TABLE II
DAY OF ONSET, DURATION, AND INTENSITY OF PYREXIA

Case	Onset (post-op. day)	Duration of Pyrexia (days)	Maximum Temperature (°F.)
1	27	12	101 (38.4°C.)
2	25	24	103 (39.5°C.)
3	22	18	102 (39°C.)
4	No sudden rise	14	—
5		22	102 (39°C.)
6		25	100 (37.8°C.)
7		26	101 (38.4°C.)
8		23	100 (37.8°C.)
9	28	6	103 (39.5°C.)
10	28	10	102 (39°C.)
11	28	3	100 (37.8°C.)

TABLE I
DIAGNOSIS, TREATMENT, AND VOLUME OF BLOOD TRANSFUSED IN 11 CASES

Case No. and Sex	Age	Diagnosis	Operation	Volume of Blood Transfused (pints)
1. R.G. M	31	Coarctation of aorta	Resection and graft	10 (4.5 l.)
2. F.P. M	15	Fallot's tetralogy	Open total correction	15 (6.8 l.)
3. B.H. F	16	Fallot's tetralogy	Closed pulmonary valvotomy and infundibular resection	20 (9 l.)
4. S.G. M	5	Fallot's tetralogy	Closed pulmonary valvotomy and infundibular resection	2 (1 l.)
5. R.F. M	18	Fallot's tetralogy	Open total correction	8 (3.6 l.)
6. T.S. M	30	Aortic stenosis (valvar)	Open aortic valvotomy	8 (3.6 l.)
7. A.F. M	31	A.S.D. and pulmonary stenosis	Closure of A.S.D. and pulmonary valvotomy	8 (3.6 l.)
8. M.S. F	50	Aortic stenosis	Open aortic valvotomy	8 (3.6 l.)
9. P.S. F	7	Aortic stenosis (subvalvar)	Open resection of stenosis	6 (2.7 l.)
10. G.H. F	15	Fallot's tetralogy	Open total correction	14 (6.3 l.)
11. F.W. M	45	Aortic stenosis	Excision of aortic valve and homograft replacement	12 (5.4 l.)

was noted had been discharged from hospital and was re-admitted ill and febrile. In others the early pyrexia had persisted at a low level, the temperature then showing a further rise. The variations in the day of onset, maximum pyrexia, and duration are shown in Table II. The usual septic complications were excluded, including that of infective endocarditis, and in most cases it was assumed that a prolonged or delayed pleuro-pericardial reaction was responsible. However other changes developed that are not usually seen in this condition. These included generalized lymph node enlargement in all but case 2, and haematological examination showed a constant abnormality, an absolute lymphocytosis, many of the cells being typical of the abnormal lymphocytes seen in virus infections (Table III). Eleven patients have been observed to behave in this way. Two complained of sore throat at the outset, but cervical lymphadenopathy was noted in most cases with or without oropharyngeal symptoms, this being part of a general reticulo-endothelial disturbance. Two other patients developed splenomegaly approximately two weeks after the onset of the pyrexia.

A.S.D. = atrial septal defect.

TABLE III
HAEMATOLOGICAL AND SEROLOGICAL DATA

Case	W.B.C. (cells/ c.mm.)	Neutro- phils (%)	Lympho- cytes (%)	Atypical Mono- nuclear Cells	Paul-Bunnell Test
1	30,000	20	77	+++	Positive 1:32
2	8,500	25	72	+++	Negative 1:32
3	7,200	30	70	+++	Negative 1:32
4	6,000	44	44	+++	Negative 1:32
5	5,400	19	77	+++	Negative 1:32
6	5,000	38	51	+++	Not done
7	5,000	30	64	+++	Negative 1:32 on five occasions
8	16,600	20	74	++	Not done
9	8,200	57	37	++	Positive 1:32
10	13,200	30	58	++	Negative 1:32
11	8,400	31	66	25% of lymphocytes seen	Negative 1:32

The first case emphasizes many important features of this condition and is therefore fully described.

CASE REPORT

CASE 1 Mr. R. G. aged 31 was diagnosed as having coarctation of the aorta situated just above the diaphragm and associated with an aneurysm. He was admitted to hospital in October 1951 for resection and insertion of a homograft (Graham and Brock, 1952). His blood pressure was 240/160 mm. Hg. Neither spleen nor lymph nodes were palpable. The blood picture was normal: Hb 82%; W.B.C. 7,400/c.mm.; neutrophils 72%; and lymphocytes 26%. At operation on 1 November 1951 a homograft 5 in. (12.5 cm.) long was inserted. Two litres of blood were lost at the operation and this volume was replaced by transfusion. He received a total of 10 pints (4.1 litres) of blood. Post-operative anaemia was treated by further transfusion. When discharged on 2 December his cardiovascular state was excellent. He was afebrile. His blood pressure was 130/80 mm. Hg, good peripheral pulses being present. The blood picture was reported as normal: Hb 81%; W.B.C. 7,000/c.mm.; neutrophils 55%; and lymphocytes 37%.

Six days later he was readmitted with pyrexia of 100.4°F. (38°C.) and general malaise. Examination showed generalized lymphadenopathy but the spleen was not palpable. The blood picture on admission showed: Hb 78%; W.B.C. 30,000/c.mm.; neutrophils 22%; and lymphocytes 77%. The haematologist's opinion (Dr. R. L. Waterfield) was that there were many atypical mononuclear cells of the 'glandular fever' type. On 13 December a blood count showed: W.B.C. 22,000/c.mm.; neutrophils 8%; and lymphocytes 89%. The Paul-Bunnell test was positive at a dilution of 1:32.

A diagnosis of glandular fever (infectious mononucleosis) was made. He made an uneventful recovery, the pyrexia settling after 12 days. The maximum temperature reached was 103°F. (39.5°C.), the pyrexia

being first noted on the twenty-seventh post-operative day.

This case history is typical of the condition noted in the other 10 patients.

DISCUSSION

The initial diagnosis attached to this condition was that of infectious mononucleosis. Dr. Waterfield was adamant in his interpretation of the blood pictures in spite of repeatedly negative sheep-cell agglutination tests (Paul-Bunnell) except in the case just described in which it was positive at a dilution of 1:32, which is not necessarily significant. He maintains that the blood picture is a response to virus infection, although not necessarily specific for infectious mononucleosis.

As far as can be ascertained, no such condition has been described in this country, although a similar condition has been described in the United States. Wheeler, Turner, and Scannell (1962) describe six cases out of 50 open-heart operations that were succeeded by fever, splenomegaly, and atypical lymphocytes in the peripheral blood smear. Kreel, Zaroff, Canter, Krasna, and Baronofsky (1960) describe six cases in a study of the post-operative reactions to 20 open-heart procedures. They noted the presence of atypical mononuclear cells of the 'viral type' in the peripheral blood. In one case they found positive serological evidence to label it infectious mononucleosis.

Hoagland (1960), however, points out that it is incorrect to make a diagnosis of infectious mononucleosis without clinical, haematological, and serological agreement. He suggests that there are many virus infections that may simulate this condition, and confusion between them probably accounts for the concept that infectious mononucleosis is of 'protean nature.'

That the condition described is viral in origin appears to be acceptable as at no time has any causative organism been cultured. It seems reasonable to suppose that it is transmitted by blood transfusion for it has not been observed following major general operations in which smaller amounts of blood have been transfused.

The demonstration of the transmission of infectious mononucleosis has always presented problems. Wising (1942) was able to demonstrate the condition in one out of five volunteers treated with intravenous heparinized plasma taken from infected patients. He was also able to demonstrate transmission of the disease to experimental animals by injection of lymph node extracts from infected humans. Markham (1957), however,

describes a patient who presented with florid infectious mononucleosis seven days after giving one pint of blood. The recipient was examined subsequently but no evidence of the disease was found.

The incubation period of the condition described appears fairly constant, *e.g.*, 25 to 28 days, but this does not compare with Paul's statement (1959) that the incubation period for infectious mononucleosis is five to 10 days. Hoagland (1955), on the other hand, states that it is longer, namely, 30 to 49 days.

One other virus disease which should be considered is infectious hepatitis, which produces a similar picture and whose haematological changes are easily confused, particularly in respect of the 'viral cells.' Although no chemical tests of hepatic function were performed on these patients, no clinical jaundice was seen during the course of the disturbance. Most of the open-heart operations are followed by a transient phase of jaundice which is due to haemolysis of red blood cells. This jaundice occurs, however, during the first two or three post-operative days.

It is interesting to note that of the 11 patients described here, three were submitted to operations without the use of extracorporeal apparatus. The machine used in the open-heart cases was a modified Kay-Cross disc oxygenator (Molloy and Lindfield, 1961). This rules out the view that this is a complication purely associated with the use of pump oxygenators.

As stated earlier, bacterial endocarditis must always be excluded, but repeated blood cultures in all cases were negative and the pyrexia resolved without treatment. Differentiation from the pleuro-pericardial reaction has been discussed earlier.

The possibility of an immune reaction should also be considered, particularly as the operations in cases 1 and 11 entailed the insertion of aortic homografts.

The immunological reactions to these grafts are being investigated.

CONCLUSION

The supposed causative agent in this condition has not yet been isolated. It is presumed from the clinical picture that it is a virus and that it gains entry at blood transfusion. It seems likely that the

virus may be that of infectious mononucleosis, but there are one or two differences between the two conditions.

The reason for its limitation to cardiac surgery is also unexplained, except that massive blood transfusion is used. Investigation of patients receiving comparable volumes of transfused blood without surgery may reveal further cases.

SUMMARY

Eleven cases of fever, generalized lymph node enlargement, and absolute lymphocytosis after cardiac surgery are described. It is thought that the illness is caused by a virus infection received in transfused blood.

The onset is approximately the twenty-fifth post-operative day.

The lymphocytosis is associated with the presence of numbers of atypical mononuclear cells comparable with those seen in virus infections, notably infectious mononucleosis.

No definite causative agent has been isolated.

The diagnosis should be considered in all cases in which continuing pyrexia, or pyrexia of delayed onset, is not due to bacterial endocarditis, pleuro-pericardial reaction, or the usual septic complications.

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REFERENCES

- Graham, A. J. P., and Brock, R. C. (1952). Resection of combined aneurysm and coarctation of the aorta with insertion of a homograft. *Guy's Hosp. Rep.*, **101**, 207.
- Hoagland, R. J. (1955). The transmission of infectious mononucleosis. *Amer. J. med. Sci.*, **220**, 262.
- (1960). The clinical manifestations of infectious mononucleosis. A report of two hundred cases. *Ibid.*, **240**, 21.
- Kreel, I., Zaroff, L. I., Canter, J. W., Krasna, I., and Baronofsky, I. D. (1960). A syndrome following total body perfusion. *Surg. Gynec. Obstet.*, **111**, 317.
- Markham, N. P. (1957). The failure of an intravenous blood transfusion to transmit infectious mononucleosis. *N.Z. med. J.*, **56**, 30.
- Molloy, P. J., and Lindfield, R. I. (1961). The technique of hypothermic perfusion. *Thorax*, **16**, 325.
- Paul, J. R. (1959). In *Viral and Rickettsial Infections of Man*, 3rd ed. Edited by T. M. Rivers and F. L. Horsfall. Lippincott, Philadelphia.
- Wheeler, E. O., Turner, J. D., and Scannell, J. G. (1962). Fever, splenomegaly and atypical lymphocytes. A syndrome observed after cardiac surgery utilizing a pump oxygenator. *N. Engl. J. Med.*, **266**, 454.
- Wising, P. J. (1942). A study of infectious mononucleosis from the etiological point of view. *Acta med. scand.*, supplement 133.