# Surgical and immunological aspects of Takayasu's disease

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## Summary

*Forty-five patients with Takayasu's disease were studied between 1972 and the end of 1979. Operative treatment was less frequently needed for aortic arch disease than for descending aorta disease. Correct evaluation may be difficult in the latter till the time of operative exploration. Children with significant stenosis need early operation and a 'plasty' type of repair is favoured over bypass grafts. Contrary to some descriptions, the disease process can affect the region of the aortoiliac bifurcation, needing surgical management based on established principles. Correct evaluation can make operative treatment safe and rewarding for those patients who need intervention as the recurrence rate of the disease process has been low in surgically treated patients. Immunologically the patients show defective T-lymphocyte function, increase in the serum level of IgG, and a reduction in serum complement constituents C3 and C4, indicating the possibility of formation of a complement-binding immune complex. Histochemical studies show deposition of IgG and PAS-positive material in the intima and probable deposition of IgM and IgA in the junctional area of media and intima, with total destruction of the elastic lamina. A hypothesis for the pathogenesis of the disease is presented.*

## Introduction

John Hunter discovered collateral circulation, but he also established its limitation in ensuring normal growth. His concept has become true for the crippling occlusive vascular disease affecting the young that has come to be known as Takayasu's disease. The aetiology, pathology, and clinical features of this disease, which is prevalent in Asia but is seen sporadically all over the world, have received wider attention *(1–6)* than its surgical treatment *(7,8)*. Some authors *(4)* have even considered it largely beyond the scope of surgery because of the high mortality in all reported series. A fresh look at the whole problem has been undertaken for evaluation of the role of surgical treatment on the background of haemodynamic and immunological abnormalities and to try to obtain an insight into its pathogenesis.

## Clinical material

A total of forty-five patients with Takayasu's disease were investigated in Calcutta between 1972 and the end of 1979. Out of these, 25 had aortic arch disease with affection of the subclavian–brachial and/or carotid circulation, 14 had affection of the descending aorta, and there were 6 cases of aortoiliac obstruction which have been included in the series of Takayasu's disease because they showed the same clinical and histological pictures. The existing clinical classifications of Takayasu's disease *(1,6)* have been found inadequate to describe the problems in the management of this disease. For example, a solitary lesion of a subclavian artery with descending aorta disease is similar in type to a concomitant affection of both carotid arteries and the descending aorta but is quite different from the points of view of clinical picture and management. Similarly affections of the aortoiliac region have not hitherto been included among the clinical types of Takayasu's disease. Because of the basically diffuse nature of the disease the patients reported in this paper have been grouped according to the major site of affection which needed intervention.

## Investigations

In addition to the detailed clinical evaluation of the patients and routine laboratory investigations angiographic study of the entire aorta and all its major branches was performed as a routine. Some other special investigations such as electroencephalography (EEG), radioisotope re-

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nography, renal scanning, and renin bioassay from the renal veins and infrarenal vena cava were carried out depending on the site of affection of the disease.

Nine patients underwent immunological investigations. These included LE-cell preparations, quantitative assay of serum immunoglobulins and complement ($C_3$ and $C_4$), and study of the immunoelectrophoretic pattern of the serum proteins. A standard Mantoux test using 1 : 1000 dilution of old tuberculin was used as a marker for delayed hypersensitivity response since the test is positive in this dilution in most of the adult population of this geographical area because of the high prevalence of tuberculous infection.

Recently, after standardisation of further laboratory procedures, a few patients have been studied further. Three patients were investigated for the presence of circulating immune complex in the serum in addition to the foregoing tests. Two methods were used for the purpose—namely, the rheumatoid factor latex inhibition test *(9)* and PEG precipitation test *(10)*. In one patient it was possible to remove a portion of aorta during operation and this was then subjected to histochemical studies. In addition to the usual haematoxylin and eosin stain, these included PAS stain, elastic van Gieson stain, reticulin stain, and the peroxidase–antiperoxidase (PAP) technique for the detection of immunoglobulins in fixed paraffin sections *(11)*.

All patients were specifically screened for tuberculosis and diabetes during preoperative investigation, at the time of operative intervention by arterial-wall and lymph-node biopsy, and in the postoperative follow-up period. None had evidence of active tuberculosis or diabetes.

## Surgical aspects

### AORTIC ARCH DISEASE

The subclavian–brachial system, particularly the left subclavian artery, is often the starting point of the disease and may remain as the solitary lesion. The onset of symptoms may be rapid or may be slow enough to go unnoticed. In any case, given time, the development of collateral circulation is adequate in most patients and surgical interference is needed only if the acute ischaemia is severe enough to threaten gangrene (usually in axillary–brachial disease), chronic ischaemia is limiting function, or aneurysms have formed. Out of 14 patients seen with disease at this site only 3 needed surgery. The preferred technique is bypass or excision–replacement using the long saphenous vein, and the results have been satisfactory, without any mortality *(12)*.

Unilateral involvement of the carotid artery is also often asymptomatic since the disease is usually limited to the common carotid, leaving the bifurcation and the internal carotid free. Aorto-internal carotid bypass graft is therefore technically feasible and has been performed in bilateral disease when EEG evidence corroborated the clinical symptoms. Cerebral microembolisation in unilateral disease is possible but has not been seen so far. The situation is complicated when carotid artery disease coexists with disease in the descending aorta causing hypertension. Surgery has been performed on 3 out of 11 patients with carotid artery disease, with 1 death and 2 cures *(12)*. Facilities for better assessment of cerebral blood flow would have increased the scope of surgery in carotid artery disease.

### DESCENDING AORTA DISEASE

In descending aorta disease with hypertension and heart failure as its main presenting features surgical treatment has been used more often than in aortic arch disease *(13–15)*. The main problem has been in assessment. For example: (1) total or subtotal occlusion of the coeliac and superior mesenteric arteries at their origin or by a skip lesion may be asymptomatic and unnoticed on the angiogram but may lead to intestinal gangrene after operation owing to lowering of the driving force of aortic pressure; (2) it may be difficult to decide whether there is renal artery involvement because of distortions of the aorta in the angiogram and since the low prerenal aortic stricture may by itself produce renal ischaemia as seen in radioisotope renograms and renin assay studies; and (3) distortion or non-opacification of the distal abdominal aorta in angiograms owing to low flow may give rise to a false impression of distal extension of disease and inoperability *(14)*. In practice, surgical exploration with measurement of pressure gradients often provides the final verdict on the feasibility and technique of repair in a borderline case and an aggressive surgical approach is justified in descending aorta disease (Figs 1–3).

A long aortic bypass graft from near the arch to the lower abdominal aorta using separate exposures for the chest and abdomen with secondary grafts to the visceral branches is the preferred surgical treatment. The technique and results of surgical treatment have already been described *(14,15)*. Out of 14 patients surgical correction was possible in 9, with 2 deaths. In the 7 surviving patients the hypertension, the renal ischaemia as shown in isotope renograms, and the heart failure reverted completely to normal, and after a follow-up of 2–7 years all of them are leading a normal life without any drugs and without any reactivation of the disease.

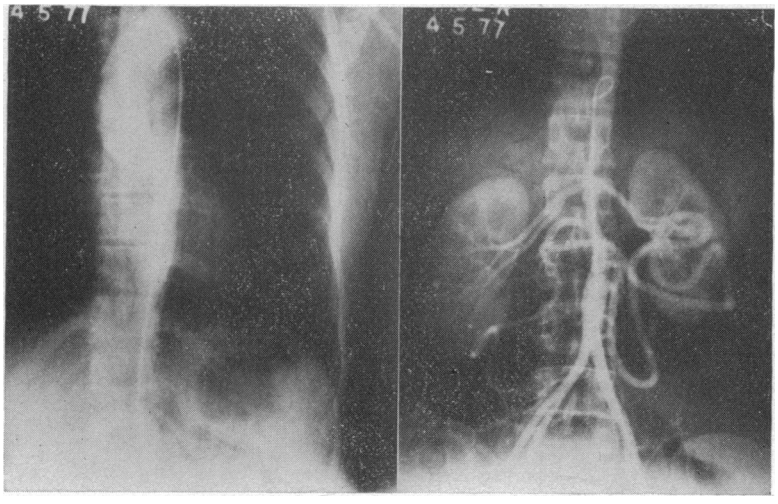

FIG. 1 *Angiogram showing diffuse narrowing of descending thoracic and upper abdominal aorta, total occlusion of coeliac and superior mesenteric arteries, which was asymptomatic, and distortion of renal arteries, whose involvement in the disease process was difficult to decide.*

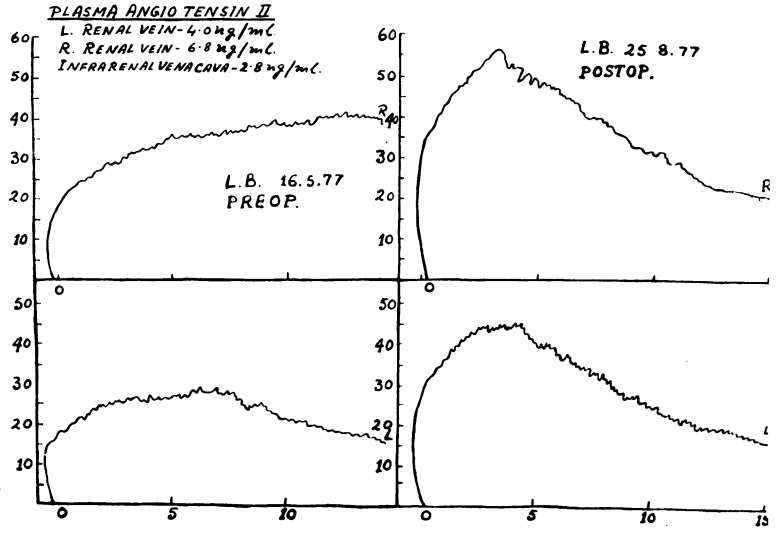


FIG. 2 *Preoperative (left) and postoperative (right) radioisotope renograms and preoperative angiotensin assays of patient in Fig. 1. The preoperative bilateral renal ischaemia was corrected following operation without any direct interference on the renal arteries. R = Right kidney. L = Left kidney. X axis is time in minutes after injection of $^{131}$I-Hippuran. Y axis is radioactivity (counts/min).*

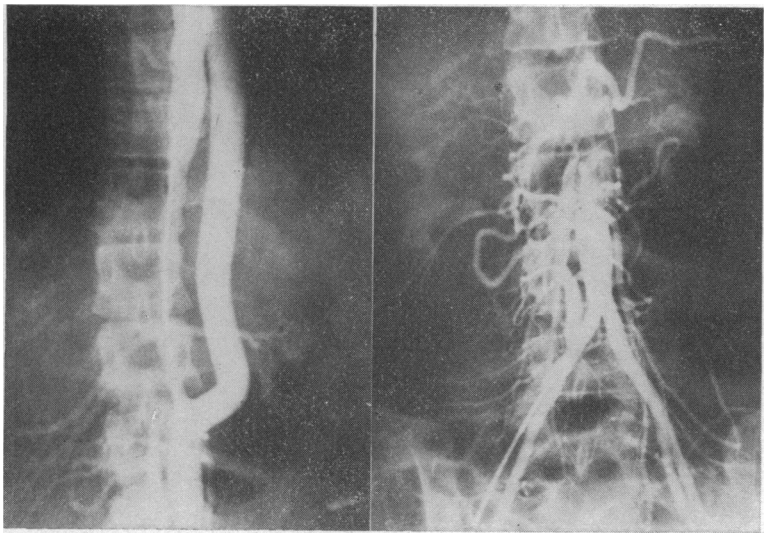

FIG. 3 *Postoperative angiogram of patient in Fig. 1 showing the main aortic bypass (left) providing adequate retrograde renal perfusion and the revascularised superior mesenteric artery from the right common iliac artery (right) filling the coeliac axis through collaterals.*

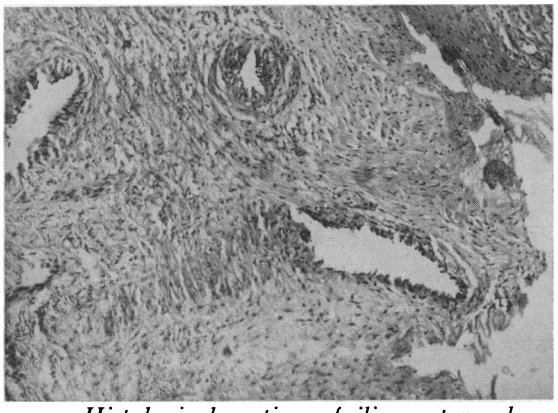

FIG. 4 *Histological section of iliac artery showing grossly thickened infolded intima with inflammatory collagen tissue and dilated vasa vasorum. Haematoxylin and eosin, ×67.*

In childhood descending aorta disease commonly presents with heart failure, and an aortaplasty procedure has been devised since the child is likely to outgrow a long bypass graft *(15)*. Essentially the technique consists in heparinising the patient and using intraluminal polyvinyl chloride tubing inserted through the longitudinal aortotomy incision to act as a shunt while a long piece of preclotted Dacron (polyethelene terephthalate) fabric is sutured as an onlay patch to enlarge the entire length of the diseased segment of aorta. It has been seen that postponement of operation exposes the children with significant stenosis of the aorta, as shown by measurement of pressure gradients and renal blood flow, to the risk of increasing heart failure and sudden death *(15)*.

AORTOILIAC DISEASE

Involvement of the lower abdominal aorta and its bifurcation in Takayasu's disease is doubted by many *(1,6)* in spite of its earlier description *(3)*. However, in our experience, in 6 cases of aortoiliac obstruction subjected to operative treatment the appearance of the arteries at operation and their histological picture (Fig. 4) were the same as in Takayasu's disease. One of these patients, aged 19 years, was female and the rest were male non-smokers aged between 19 and 40. This is in contrast to the female predominance of the disease at other sites. One of the male patients had had a previous operation for subclavian–brachial disease (Fig. 5). Three out of these 6 patients presented with symptoms of subacute onset caused by thrombus formation in the diseased segment of the artery. Early gangrene of the great toe which was present in 2 patients was probably due to distal embolisation from such thrombus because the distal arterial tree was otherwise normal.

The usual surgical treatment is bypass grafting, endarterectomy, or excision–replacement, depending on the extent of the disease. In the only female patient in this series reconstructive surgery was not possible because at operation there was active disease with stenosis of the entire abdominal aorta extending to the bifurcation of the common femoral artery on the left side. Lumbar sympathectomy was performed and the patient improved so much with medical treat-

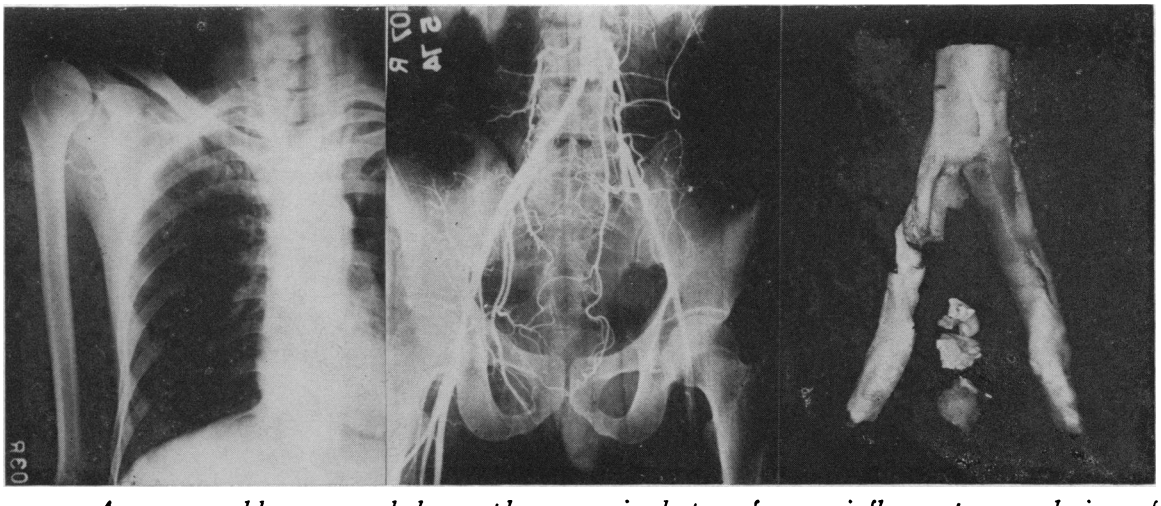

FIG. 5 *A 35-year old man needed a saphenous vein bypass for an inflammatory occlusion of right axillary artery (left). Six months later he came with aortoiliac disease and lower limb ischaemia (centre) which was treated by bilateral aortoiliac endarterectomy. The endarterectomy specimen (right) showed the same histological picture as in Fig. 4.*

ment that the plan for a later axillofemoral bypass was abandoned. All the other patients had successful surgical reconstruction.

On follow-up one patient had a late occlusion of the unilateral Dacron bypass graft, probably due to the habitual adoption of a squatting posture since the lower anastomosis was just behind the inguinal ligament. In such a situation we would now prefer an endarterectomy. No further operative intervention was, however, needed since the patient did not have a recurrence of symptoms in spite of an occluded graft. Another patient had a recurrence 2 years later with inflammatory occlusion of the popliteal artery and distal gangrene, and it would be controversial to label him as a case of Takayasu's disease. The controversy can be extended further by asking whether inflammatory occlusive diseases of the large arteries can be divided into different diseases merely by their different sites of affection and slightly altered sex predilection.

## Immunological aspects

The findings of immunological investigations carried out on the first 9 patients were that LE-cell preparations were negative in all cases, the Mantoux test was negative in 55%, a high serum IgG level was found in 55%, with normal values for other immunoglobulins, and low values for serum complement C3 and C4 were found in all (Fig. 6). The same findings were

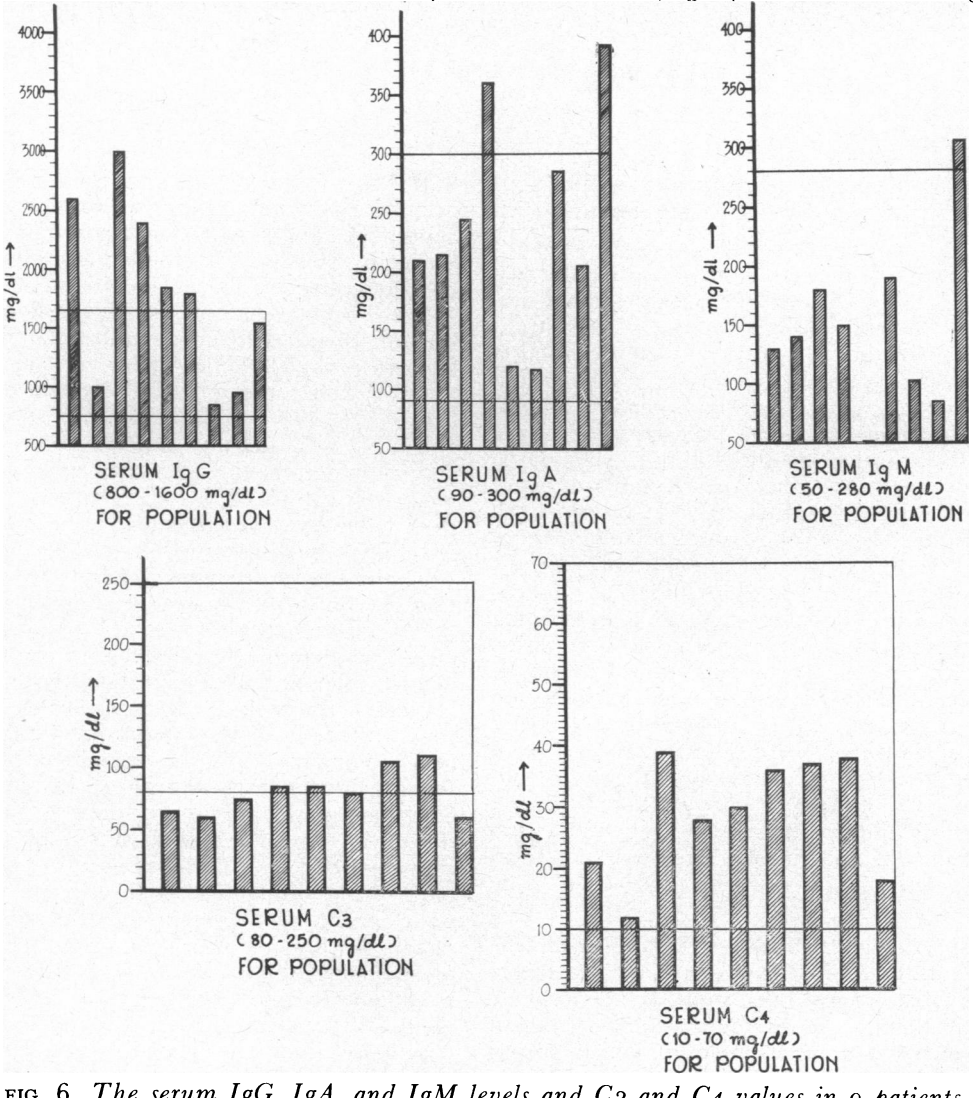


FIG. 6 *The serum IgG, IgA, and IgM levels and C3 and C4 values in 9 patients with Takayasu's disease, with normal range for population.*

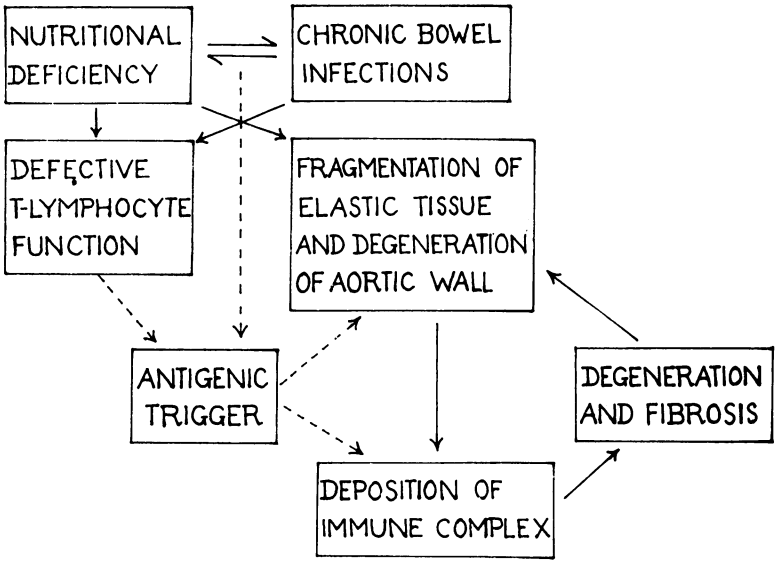


FIG. 7 *A hypothesis for the pathogenesis of Takayasu's disease.*

observed in 3 patients subsequently studied, but in all these the tests for circulating immune complex in serum were negative.

The sections of aorta stained with haematoxylin and eosin showed the well-described appearance of total disorganisation of the structure of the aortic wall with complete destruction of the elastic lamina, gross fibrosis of the media and adventitia with focal and general round-cell infiltration and gross thickening, fibrosis, and vascularisation of the intima. The same findings were also noted in the dilated vasa vasorum in the adventitia. PAS staining of the same section showed pinkish-blue colouring of the background matrix of the intima, suggesting the histochemical presence of mucopolysaccharide elements. Elastic van Gieson stain showed total destruction of the elastic lamina in both the aorta and its vasa vasorum and reticulin stain showed marked proliferation and formation of reticulin in all the layers, including the intima. PAP stain for IgG showed diffuse staining of the extracellular ground substance of the intima. PAP stain for IgM and IgA showed some staining in the junctional area of the media and intima and around focal aggregations of inflammatory cells in the adventitia.

It is difficult to draw conclusions from the histochemical observations alone until a larger number of cases have been studied, but probably the PAP stains for immunoglobulins suggest deposition of immune complexes, which is corroborated by the depleted serum complement. The probable deposition of IgA and IgM in the region of the elastic lamina suggests the possibility of an antigen of intestinal origin as the original antigenic trigger to start a chain reaction. A complement-binding immune complex forms in addition to a reactive humoral response by B-lymphocytes on a background of defective T-lymphocyte function which may be caused by nutritional deficiencies and intercurrent infections *(16–19)*. The original antigenic trigger to start the process may be any one of a number of different possibilities. In some studies *(5,20,21)* antiaorta antibodies have been demonstrated in serum without any depletion of complement C3 and CH50. There are others who have failed to demonstrate such antibodies *(22)*.

In an earlier communication on the subject *(14)* the higher frequency of lesions in the portions of aorta which are in close proximity to the drainage pathway of the intestinal lymphatics was mentioned to indicate a possible aetiological role of parasitic infestations of the intestines. Takayasu's disease occurs predominantly among the low-income groups who very commonly suffer from chronic bowel infections in this part of the world. Recently, circulating immune complexes have been found in the serum of patients with intestinal amoebiasis showing extraintestinal symptoms of arthropathy *(23)* and also in a group of children with established protein energy malnutrition *(24)*. It has also been shown in experiments on monkeys that nutritional deficiencies cause fragmentation and degeneration of the elastic tissue of the aortic media *(25)*. Based on these observations and the data obtained in this study a possible hypothesis for the pathogenesis of Takayasu's disease is diagrammatically depicted in Figure 7.

## Conclusions

The surgical treatment of Takayasu's disease has been complicated by the extensive nature of the lesions, lack of accurate knowledge regarding the preferred sites and extent of the lesions, presence of skip lesions, and chances of reactivation. On the other hand the patients are young, with an otherwise normal vascular system beyond the diseased area. Previously published reports *(4)* expressing reservations about the efficacy of surgical treatment do not seem justified. Careful assessment of each patient as to his residual disability after conservative treatment and the haemodynamic status will make surgical treatment safe and rewarding for a large number of patients. Immunological investigations indicate the possibility of a mechanism involving immune complex formation on a background of defective T-lymphocyte function in Takayasu's disease. Whereas the original antigenic trigger could be any one of a number of different possibilities, parasitic infestation and chronic infection in the intestines along with protein energy malnutrition may be possible aetiological factors.

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