The Raynaud syndrome

MARTIN BIRNSTINGL
M.S., F.R.C.S.

St Bartholomew's Hospital, London, E.C.1

'Arteritis. Thank heaven I have not to express any opinion either upon its frequency, or upon the share which belongs to it in the different arterial changes, or to the part which it plays in general.'
Maurice Raynaud, 1862.

Maurice Raynaud described in his thesis '*De l'Aphxie Locale et de la Gangrène Symétrique des Extrémités*' (1862) examples of both episodic digital asphyxia and frank local gangrene, which justifies the broad pathological field covered by the present article.

Definitions

Raynaud's syndrome. The general syndrome of arterial insufficiency of the fingers, regardless of cause, and whether presenting as episodic or continuous ischaemia, digital necrosis or gangrene.

Raynaud's phenomenon. Episodic digital asphyxia, due to arterial insufficiency.

Raynaud's disease. A disorder, seen principally in young, healthy women, who show episodic digital asphyxia due to an exaggerated reaction to cold in otherwise normal digital vessels.

Introduction

Raynaud provides us with an accurate clinical description of the disease which now bears his name. 'Madame X, aged 26 years, has never been ill; but she has been the subject since childhood of an infirmity which makes her an object of curiosity to her acquaintances. Under the influence of very moderate cold, and even at the height of summer, she sees her fingers become exsanguine, completely insensible, and of a whiteish yellow colour. This phenomenon happens often without reason, lasts a variable time and terminates by a period of very painful reaction, during which the circulation is re-established little by little and returns to the normal state. Madame X has no better remedy than shaking her hands hard, or soaking them in lukewarm water. . . . This state, which I dare hardly call a disease, is local syncope in its simplest form' (1862).

Raynaud clearly recognized the vasospastic nature of this phenomenon in young, healthy women and

in a later paper (1874) he put forward 'the hypothesis of a contraction of the terminal vascular ramifications, varying from a simple diminution of calibre up to complete narrowing of the lumen of the vessel. To the total closure of the arterial and venous vessels would correspond an exsanguine and cadaveric state of the extremities . . . whilst the arterioles only being closed and the venules open, one would see a venous stasis produced by failure of vis a tergo, whence the cyanosis and livid appearance'.

Unfortunately he failed to understand the widely varying pathology of the examples he described, or that necrosis or frank gangrene can only result from actual structural obliteration of the vessels and it was left to Jonathan Hutchison (1901) to point out the many different diseases which are liable to present with digital ischaemia. Hutchison also advocated the term 'Raynaud's phenomenon' to describe the intermittent episodes and showed that these could be due either to vasospasm or organic obstruction, although even today this distinction remains difficult on clinical grounds alone.

Physiology of digital circulation

The rate of flow through any vascular bed depends upon the pressure gradient across the bed and the resistance to flow through it. The gradient, in turn, depends upon vessel length, radius and the viscosity of the blood. Variation in any of these five parameters may change the rate of blood flow; however, the local circulatory effects of digital vascular pathology are largely due to variations in digital arterial and arteriolar radius. Digital blood flow is normally concerned with temperature regulation rather than with local metabolic needs, and is remarkable both in the degree to which it is responsive to the local temperature and in the great variation of flow rates attained, which may change by as much as two hundred times (Burton, 1939). The mechanism by which local blood flow is varied is mainly in the arterioles and arteriovenous anastomoses, the latter being especially numerous in those parts of the fingers and toes—the nail beds and distal phalangeal pulps—in which flow rates alter most.

Normal control of digital blood flow is complex,

but appears to be governed by (1) central nervous influence acting mainly through sympathetic vasoconstrictor fibres and (2) local responses in the smooth muscle in the wall of the blood vessels themselves.

In true Raynaud's disease, or functional vasospasm, there is constriction of both arterioles and venules, producing the characteristic waxy appearance. Occasionally the venules and capillaries may dilate, probably through local anoxic paralysis, producing a bluish tinge. When the spasm passes off, a stage of reflex vasodilatation is produced due to local accumulation of dilator substances in the tissues.

In organic obstruction, the block is usually at the level of the digital arteries or arterioles. Quite apart from the overt reduction in digital blood flow, important passive factors contribute to the resulting ischaemia. The fall in transmural pressure in the artery beyond the block allows passive contraction of the elastic vessel wall, further decreasing flow. Moreover, this reduction in vessel radius produces a four-fold decrease in flow, according to Poiseuille's Law. Another passive factor is the apparent viscosity of the blood, which increases at low rates of blood flow. The net result of these various influences is that flow becomes dependent upon a state of unstable equilibrium, in which the intra-arterial pressure distal to the obstruction may fall beyond the 'critical closing pressure' of the vessel at this level, causing sudden standstill (Roddie and Shepherd, 1957). This is particularly likely when vasomotor tone is high, for instance during exposure to cold or when vessels are compressed by gripping with the hand, and explains the intermittency of the ischaemic episodes (Raynaud's phenomenon) in the presence of permanent organic blockage. But since the structural changes usually involve the arteries of different fingers to varying extents, it is uncommon for the ischaemia to occur symmetrically.

Effect of sympathetic denervation

The blood flow in the hand is first increased due to removal of central vasoconstrictor activity. Peak flows are reached about 2 days after sympathectomy, with increases of the order of five to twelve times resting flow. This is followed by gradual reduction in blood flow until, after a few weeks, the resting flow is close to the preoperative level (Barcroft, 1952). The decline of flow occurs irrespective of whether preganglionic or postganglionic section has been performed and is probably due to recovery of intrinsic tone in the muscle of the vessel wall. Provided sympathectomy is complete, reflex body heating or body cooling has no effect upon flow rates in the hand. However, after 1 or 2 years a vasoconstrictor response usually returns to direct cooling of the

hand, which again appears to be a property of the digital arterioles themselves.

Aetiology of Raynaud's disease

Maurice Raynaud attributed the local syncope to an exaggeration of the normal reflex response to cooling, but dominated by Claude Bernard's recent description of the sympathetic nervous system. He thought that the abnormality was central or, in his own words, due to 'increased irritability of the central parts of the cord presiding over vascular innervation' (1874). However, the fact that local syncope is usually unaccompanied by peripheral sweating and the frequency of relapse after apparently complete sympathetic denervation are against this explanation.

Sir Thomas Lewis (1930) felt that the fault lay in abnormal susceptibility of the digital arteries themselves to stimulation by local cooling. He showed that when reflex vasodilation had been produced by warming the body, vasospasm could still be produced by putting the hands in cold water. Conversely, vasospasm could not be produced by body cooling if the hands were kept warm. Whatever the explanation of Lewis's 'local fault', his theory accords with the clinical picture and explains the poor results of sympathectomy in Raynaud's disease, since the digital vessels retain their hypersensitivity to local cooling and ultimately regain their intrinsic tone. However, Raynaud was probably correct in maintaining that emotional factors play an additional part in some of these patients, since peripheral vasoconstrictor activity is undoubtedly influenced by the psyche (Fox, 1968).

Raynaud postulated that veins as well as arteries and arterioles share in the constriction, accounting for the waxy pallor, but direct evidence is lacking on this point. The accompanying numbness of the fingers is presumably caused by temporary ischaemia of sensory nerves.

Peacock (1959) has shown by plethysmography that blood flow in the hands of patients with Raynaud's disease is reduced, compared with normal controls, even under warm resting conditions. It is difficult to exclude the presence of secondary organic narrowing in such subjects. Peacock also found that the concentration of catecholamines in venous blood leaving the hands was higher in Raynaud's disease than in controls, particularly during reflex vasoconstriction. He suggested that this was due to increased production of adrenaline and noradrenaline during vasoconstriction, but unfortunately failed to exclude a more obvious cause for the observed rise in concentration, namely the reduced blood flow which he recorded. Furthermore, he did not measure the levels in the arterial inflow to the

hand. These and other criticisms throw serious doubt upon the validity of Peacock's conclusions and Kontos & Wasserman (1969) are categorical that there is 'no evidence supporting a defect in catecholamine metabolism in Raynaud's phenomenon'.

Pringle, Walder & Weaver (1965) reported the finding of increased blood viscosity in twenty-two patients with Raynaud's disease, compared with healthy controls. They correlated this with a rise in both plasma fibrinogen and red cell aggregation, but their diagnostic criteria were somewhat loose, making it impossible to exclude the effect of an underlying collagen disorder.

The precise cause of the local hypersensitivity of the minute vessels in functional vasospasm (Raynaud's disease) remains unknown.

Pathology

The term Raynaud's disease should be reserved for the type of digital asphyxia seen usually in otherwise healthy young women, and shown by Lewis to be an exaggerated reaction to cold in structurally normal vessels. But intermittent asphyxia (Raynaud's phenomenon) frequently complicates organic vascular obstruction, due to atheroma, thrombosis or embolism, in which the episodes may be identical to the vasospastic type. However, severe nutritional lesions, such as skin necrosis, atrophy or calcinosis invariably indicate the presence of organic occlusion, usually in the fingers themselves; such changes are not seen where vasospasm alone is responsible. Nevertheless difficulty arises in certain collagen disorders, notably systemic scleroderma, which may present with cold hypersensitivity several years before the other manifestations of organic disease. The symmetrical vasospasm of early scleroderma is often indistinguishable from Raynaud's disease.

Table 1 includes most of the conditions which may present with digital ischaemia.

Vasospastic ischaemia

Abnormal reactivity of digital vessels ('local fault'). The hypersensitivity may be hereditary or acquired. In Raynaud's disease the reactivity is hereditary or idiopathic, and in early Raynaud's disease the digital vessels are structurally normal; although pathological examination is rarely possible, except by skin biopsy, arteriography is normal (Lynn, Steiner & Van Wyk, 1955). In severe Raynaud's disease, concentric intimal thickening of digital arteries and arterioles is present to a greater degree than in normal warm-handed subjects of the same age, and digital artery thrombosis sometimes occurs (Figs. 1 and 2). Biopsy of digital skin is normal in early Raynaud's disease (Lewis, 1938).

Acquired reactivity probably occurs early in collagen disorders such as systemic scleroderma and

TABLE 1. Classification of digital ischaemia

Vasospastic ischaemia

1. Abnormal reactivity ('local fault'):
 - (a) Hereditary or idiopathic (Raynaud's disease)
 - (b) Acquired:
 1. Collagen disorder
 2. Cold injury
 3. Vibrating tools
2. Endocrine disorders:
 1. Hypertension
 2. Phaeochromocytoma

Organic ischaemia

1. Arterial disease:
 1. Atherosclerosis
 2. Aortic arch syndrome
 3. Thrombo-angiitis obliterans
 4. Embolism
2. Arterial compression:
 - Thoracic outlet compression
3. Collagen disorders:
 1. Systemic scleroderma. (a) Acrosclerosis; (b) diffuse scleroderma
 2. Rheumatoid arthritis
 3. Disseminated lupus erythematosus
 4. Dermatomyositis
 5. Acute nodose polyarteritis
4. Blood disorders:
 1. Cold agglutinins
 2. Thrombogenic diathesis

FIG. 1. Raynaud's disease. Arteriogram of woman aged 58. Digital arteries are fully patent throughout.

FIG. 2. Raynaud's disease. Section of digital artery. Woman aged 40. There is minimal concentric intimal thickening.

rheumatoid arthritis, in the former sometimes years before the other manifestations. But it now seems likely that the finding of Raynaud's phenomenon in collagen disorders indicates actual organic narrowing or obstruction of the digital arteries. Abnormal reactivity also develops during the post-hyperaemic stage of cold injury (e.g. frost-bite) and may persist as a late sequel, although it is again difficult to discount organic intimal thickening in such cases.

Vibrating tool disease is an environmental disorder seen in workers using pneumatic stone-cutters, metal chisels, hand grinding tools and chain saws (Jepson, 1951; Grounds, 1964). Symptoms usually appear within 1 year of starting the work and seem to be due to sensitization of the digital vessels by the vibration. Unlike idiopathic Raynaud's disease, however, the vasospastic attacks are restricted to two or three fingers of one hand, being those to which the trauma is directed. The disorder is not seen in riveters and road-drillers, since high vibration rates appear to be necessary (40–125 cycles/sec). Apart from cold hypersensitivity, which tends to remain after a change of occupation, the digital vessels show no propensity to permanent narrowing or thrombosis and nutritional lesions do not occur.

Endocrine disorders. Rare causes of digital vasospasm are essential hypertension (Pickering, 1968) and phaeochromocytoma.

Organic ischaemia

Atherosclerosis is uncommon in the proximal limb arteries, but thrombosis in the digital arteries is a frequent cause of ischaemia in middle-aged men. This condition, which Jepson (1951) called 'digital artery disease', causes segmental occlusion in the arteries, usually in the proximal part of the fingers and also in the palmar and metacarpal arteries (Figs. 3 and 4). The onset may be simultaneous in several fingers of one or both hands, especially the ring, middle or index, but the thumb is rarely affected. When the resulting ischaemia remains mild the patient begins to complain of Raynaud's phenomenon in the affected fingers; but the suddenness of the occlusion frequently results in severe ischaemia and painful dry necrosis of part of the digital pulp close to the nail (Fig. 5). Histological section of the occluded segments show thrombosis, generally without obvious mural disease, and the unaffected arteries are usually wide in calibre. A collateral circulation develops in the soft tissues around the blocks, together with narrow recanalized channels

FIG. 3. Digital artery thrombosis (atherosclerosis). Man aged 54. Segmental blocks in palmar arch and many digital arteries.

FIG. 4. Digital artery thrombosis (atherosclerosis). Man aged 42. The artery is blocked by organized thrombus, with scanty recanalized channels.

FIG. 5. Digital artery thrombosis. Man aged 56. The fingers healed after upper thoracic sympathectomy and have been symptom-free during 13 years.

through the thrombosed segments (Birnstingl, 1967). The cause of the disorder probably lies in a transient thrombotic tendency in the constituents of the blood, rather than any local abnormality in the vessels themselves. Co-existing coronary artery disease is common.

Aortic arch syndrome is a rare condition in which the origins of the innominate, subclavian or carotid arteries become obstructed, producing Raynaud's phenomenon with forearm 'claudication' and sometimes blindness. This 'pulseless disease' (Takayasu's syndrome) is commoner in middle-aged women and can result from a variety of pathological processes, including giant-cell arteritis, rheumatoid arthritis and occasionally atherosclerosis.

Thrombo-angietis obliterans involves the lower limbs to a greater extent than the upper, but the radial, ulnar and occasionally the digital arteries may be affected. The patient is almost invariably a heavy-smoking male and migratory thrombophlebitis is common. Histology shows thrombosis at various stages of development, usually with marked fibroblastic and endothelial cell proliferation. Some infiltration of the wall of the vessel with lymphocytes

and polymorphs is usual and recanalization is a prominent feature, but it is doubtful if any histologic features differentiate the disorder from atherosclerosis. Nevertheless, Buerger's disease presents a clear-cut clinico-pathological syndrome. Since histological material is seldom available, apart from amputations for gangrene, little is known of the early structural changes in this disease.

Arterial embolism in the upper limb may occur with mitral stenosis, toxic goitre, myocardial infarction or bacterial endocarditis. The embolus usually impacts in the axillary artery or brachial bifurcation. Gradual recovery over 1–3 days is the usual sequel as the collateral circulation opens up, but the degree of ischaemia is influenced by previous sub-clinical embolism and by the cardiac status at the time of the incident.

Ischaemia of the hand due to embolism often arises in relation to fusiform aneurysm of the subclavian artery, associated with a cervical rib. The aneurysm is a post-stenotic dilatation immediately lateral to the constriction produced by the rib, and platelet thrombi on the interior of the sac provide the source of the emboli (Figs. 6 and 7). Thrombosis of such an aneurysm occasionally causes serious ischaemia, because of previous embolic obstruction in the distal vessels (Wickham & Martin, 1962; Eastcott, 1962).

FIG. 6(a). Cervical rib with post-stenotic dilatation of subclavian artery containing mural thrombus.

FIG. 6(b). More distal view of same arteriogram showing site of impaction of embolus in brachial artery.

Arterial compression. *Thoracic outlet compression* of the subclavian artery may be due to the following: cervical rib; rudimentary first thoracic rib; costoclavicular compression; scalenus anterior muscle; and pectoralis minor during hyperabduction of the arm. Pressure by a cervical rib or its bony anterior end is the commonest of these; the rest are certainly rare, although all can produce a post-stenotic dilatation of the artery, with liability to thrombo-

embolic complications particularly during a thrombotic phase due to changes in the constituents of the blood. In milder cases, the compression can produce Raynaud's phenomenon or forearm 'claudication'. These vascular symptoms rarely arise on both sides and it is unusual for neurological and vascular compression to co-exist in the same patient, since whenever a rib is long enough to displace the artery the brachial plexus is usually prefixed and out of the way (Ross, 1959).

It is important to remember that only about 10% of patients with a cervical rib develop vascular symptoms and that Raynaud's disease, itself common, may occur in a patient who happens to possess a symptomless rib abnormality (Rob & Standeven, 1958).

Carpal tunnel syndrome. Compression of the median nerve under the flexor retinaculum is a common cause of pain in the lateral part of the hand and forearm. Paraesthesiae in the thumb and index finger and exacerbation of the pain in the early hours of the morning are characteristic features. A few of these patients develop Raynaud's phenomenon in the affected hand, usually because of a collagen disorder underlying both conditions (Linschoten, Peterson & Juergens, 1967).

Collagen disorders

Both Sokoloff, Willens & Bunim (1951) and Bywaters (1949) have clearly described the changes which occur in blood vessels in rheumatoid arthritis. Involvement of small arteries, particularly the digital arteries, is now known to be frequent in this disease and closely associated with nodules and serological changes. Widespread vascular changes also accompany systemic scleroderma, in addition to the better known hyperplasia of collagen fibres in skin and viscera and the inflammatory changes. The Raynaud's phenomenon seen in the collagen disorders is the result of these lesions, rather than the more theoretical arteriospastic hypersensitivity which has been invoked in the past.

The vascular lesions accompanying the collagen disorders are significant both from their associated symptoms and because they provide clues to the immunological pathogenesis of these diseases (Rodnan, 1963). There is evidence that during anaphylaxis, antigen-antibody precipitation takes place within the blood vessels. It seems likely that the localization of the consequent intimal thickening of thrombosis to the digital arteries is due to their particular contractility, rather than to other factors such as their liability to trauma, the proximity of joint lesions, or compression by surrounding connective tissue changes.

The principal pathological features of some individual collagen disorders are as follows:

Systemic scleroderma (progressive systemic sclerosis)

A disorder of connective tissue with characteristic changes in the skin (scleroderma), synovium and certain viscera. Tuffanelli & Winkelmann (1961) have subdivided the disease into two types: (1) acrosclerosis and (2) diffuse scleroderma, but the boundary is indistinct. Visceral changes occur in both types, which probably represent the extremes of a wide spectrum of clinical behaviour.

The classical skin changes are inelasticity, oedema, patchy pigmentation or depigmentation, accompanied by dermal atrophy and marked collagenosis. The initially oedematous skin later becomes smooth, waxy and bound down to the underlying structures and the face becomes drawn, pinched and expressionless, with narrowing of the mouth.

An increase in collagen content is also seen in the synovia and in the viscera, producing atony and lack of peristalsis in the oesophagus and ureter, whilst blood vessels in the heart, lung and kidney show intimal hyperplasia and focal infarcts. The afferent arterioles and glomerular tufts of the kidney may show fibrinoid necrosis.

Acrosclerosis and the 'CRST syndrome'. Acrosclerosis is the commonest form of systemic scleroderma. It is usually seen in women and is characterized by Raynaud's phenomenon and sclerosis of the fingers. Raynaud described a common late appearance: 'On the pulp of all the digits a great number of small, white, depressed, very hard cicatrices is seen, which are, so to speak, the stigmata left after the malady'. He goes on to describe 'the formation of veritable sloughs, especially on the little finger. But that which strikes one most is the slender form which the ends of the digits take, the hardness of their tissue, and their shrivelled aspect' (1862). The changes may later involve the forearms, face, upper part of the trunk and the feet. Pigmentation, telangiectases, ulceration, and subcutaneous calcification (hyperdermolithiasis) may occur (Fig. 7). Gastrointestinal and other visceral involvement is common and the course is very chronic. The association of calcinosis and scleroderma was recognized by Thibierge & Weissenbach in 1911; it is a late sequel.

In a study of 727 patients with systemic scleroderma, Tuffanelli & Winkelmann (1961), found that more than 90% showed 'vasospastic changes' in the extremities; Raynaud's phenomenon heralded the onset of the disease in 48%, often preceding the onset of the other changes by many years.

Johnston, Summerly & Birnstingl (1965) investigated seventy-five patients after sympathectomy for

FIG. 7. Acrosclerosis. Subcutaneous digital calcification in woman aged 52 with facial scleroderma and telangiectases.

what was originally thought to be functional vasospasm (Raynaud's disease). Prolonged follow-up revealed that 19% had developed clinical evidence of systemic scleroderma.

Winterbauer (1964), whilst still a medical student, gave an excellent account of the telangiectasia which may accompany acrosclerosis, and which may be so obvious as to mimic the hereditary haemorrhagic condition. Winterbauer proposed the term 'CRST syndrome', to include the calcification, Raynaud's phenomenon, sclerodactyly and telangiectasia. He emphasized the benign prognosis of this variant.

Diffuse scleroderma is characterized by generalized cutaneous sclerosis, beginning on the face, neck and upper trunk and usually sparing the extremities. Visceral involvement is often severe, but the changes are similar to those found in acrosclerosis, and the prognosis is poor, some patients dying within 1 year. Nevertheless, the 10-year survival in the 727 patients studied by Tuffanelli & Winkelmann was 59%, although they failed to separate the much commoner, benign acrosclerosis cases from those with the so-called diffuse disorder.

Disseminated lupus erythematosus is also commonest in women and characterized by widespread

necrosis of small arteries and arterioles. About 50% of those affected die within 3 years of onset of the symptoms. Of 520 patients reviewed by Tufanelli & Dubois (1964), 18% presented Raynaud's phenomenon, but it rarely preceded the other manifestations. Digital necrosis or gangrene may occur (Fig. 8)

FIG. 8. Disseminated lupus erythematosus. Digital lesions in woman aged 33.

but involve the toes more often than the fingers. Polyarthritides, leucopenia, raised gamma globulin and a positive LE cell phenomenon are pathognomonic. Renal biopsy, when obtainable, shows 'wire loop' lesions in the glomeruli. The fibrinoid change in the renal arterioles has been shown to have a preferential concentration of gamma globulin, rather than the fibrinogen found in systemic sclerosis and hypertension (Vazquez & Dixon, 1958).

Dermatomyositis. A rare condition of children and young adults. Raynaud's phenomenon is common, accompanied by fever, dermatitis and a myopathy.

Acute nodose polyarteritis (periarteritis). This presents only rarely with digital ischaemia, but has protean manifestations. The lesion is a widespread, focal inflammatory infiltration involving all the coats of small muscular arteries and arterioles, leading to thrombosis or aneurysm formation (microaneurysms). It is a type of diffuse hypersensitivity angiitis.

Rheumatoid arthritis. The vascular lesions of rheumatoid arthritis have been documented by

Bywaters & Scott (1963). They present clinically as skin nodules and Raynaud's phenomenon and can be demonstrated by brachial arteriography (Laws, Lillie & Scott, 1963). There is a close correlation with a positive differential agglutinating titre (DAT) and with the finding of skin nodules. The term 'rheumatoid arteritis' has been applied, but the vascular changes are the result of the basic immunological disturbance.

The vasculitis seems to have no bearing upon prognosis, apart from the rare occurrence of digital gangrene (Bywaters, 1957).

There is a slight but inconstant tendency for the digital arterial lesions to occur in relation to phalangeal joint lesions.

Blood disorders

Raynaud's phenomenon or even gangrene may accompany high titres of cold agglutinins in the serum and appears to be due to temporary plugging of minute vessels by masses of agglutinated red cells (Nelson & Marshall, 1953; Olesen, 1967). At temperatures between 34 and 24°C the cold agglutinins adsorb onto the red cells, producing a reversible agglutination, but subsequent haemolysis of the agglutinated cells may lead to paroxysmal cold haemoglobinuria and haemolytic anaemia.

Another rare cause of digital ischaemia is the presence of cryoglobulins in the blood, which undergo cold precipitation within the vessels. The abnormal globulin is usually secondary to a malignant reticulosis, but an idiopathic type has been described (Ritmann & Levin, 1961).

The rarity of these conditions does not justify routine screening for cold agglutinins and cryoglobulins in patients presenting with Raynaud's phenomenon unless haemoglobinuria, purpura, anaemia, lymphadenopathy or other bizarre features are discovered.

Digital necrosis may occur in the presence of previously unrecognized malignant disease, the discovery of which it may precede by months or even years (Hawley, Johnston & Rankin, 1967). It is the result of digital artery thrombosis, presumably due to transient thrombogenic changes in blood platelets or clotting factors. Similar digital thrombosis, without co-existent malignant disease, occur in middle-aged men, described above under the heading 'organic ischaemia'. But its precise causation is unclear and if the evidence is accepted that the common white plaque of atherosclerosis arises by organization of a thrombus, changes in the constituents of the blood seem likely (Rokitansky, 1852; Duguid, 1949; Haust, More & Movat, 1959). I have recently seen four young women with digital artery thrombosis and local gangrene as a complication of oral contraceptives, and further reports can be anticipated.

Clinical diagnosis

Presenting symptoms. Raynaud's phenomenon, whether due to vasospasm or organic change, is brought on by cooling of the hands or occasionally by emotion. There is numbness and tingling of the fingers, which become waxy white or slightly cyanosed. As the episode passes off, often accelerated by rubbing or shaking the fingers, they become more cyanosed and later suffused and this stage may be painful. Raynaud's disease is about ten times commoner in women and strikingly symmetrical, the thumbs being spared. Where the phenomenon is secondary to organic disease, the distribution varies amongst the fingers, although in digital thrombosis it is not uncommon for the same one or two fingers on both hands to be involved. When there is blockage of a proximal artery, as in subclavian compression, all the fingers of one hand may develop intermittent ischaemia.

The diagnosis of Raynaud's disease usually presents no difficulty, but systemic scleroderma may start with the same symmetrical distribution. Raynaud's phenomenon in childhood is occasionally a manifestation of acute rheumatism due to hypersensitivity to the β -haemolytic *Streptococcus*.

Trophic lesions. The presence of terminal ulceration or patches of dry pulp necrosis on the fingers indicates severe local ischaemia and is evidence that there is structural obliteration of the feeding arteries. In Raynaud's disease, where the condition is one of uncomplicated vasospasm, ischaemic digital necrosis does not occur, although these patients are often susceptible to pyogenic or monilial paronychia infections. The commonest cause of local digital necrosis in men is digital artery thrombosis, whilst in women it suggests a collagen disorder. More severe necrosis amounting to gangrene is also seen in thrombo-angiitis obliterans, ergot poisoning, disseminated lupus erythematosus and thrombo-embolic complications of cervical rib. Gangrene in childhood raises a wide differential diagnosis (Lowenthal, 1967).

Atrophy of the terminal digital pulp, producing a 'sharpened' effect, and trophic changes in the nails indicate long-standing ischaemia, often seen in systemic scleroderma. In this disease, absorption of almost the entire distal phalanges may occur, so that the deformed, claw-like nails come to overhang the stunted pulps of the fingers. Other features suggesting scleroderma are subcutaneous calcification in the pulp and telangiectases on the face and lips. Loss of pulp may also accompany atherosclerotic digital thrombosis, following separation of the necrotic eschars.

History

In Raynaud's disease the patient is usually a young woman complaining of coldness of the fingers for as long as she can remember, with a worsening between 18 and 25. Later onset suggests the presence of collagen disease, and although some menopausal women develop a functional vasospastic disorder, symptoms arising for the first time at this age are more in favour of organic disease. A few patients presenting Raynaud's phenomenon in the early twenties, develop stigmata of collagen disorder a few years later. There seems no infallible way of predicting this outcome.

Sudden onset of severe ischaemia in a few fingers of a middle-aged manual worker is a common presentation of atherosclerotic digital thrombosis. The usual combination is asymmetrical Raynaud's phenomenon with painful necrosis of the terminal pulps. A similar event in a young woman suggests lupus erythematosus, idiosyncrasy to contraceptive pills or very occasionally ergotism. A history of migratory thrombo-phlebitis suggests thrombo-angiitis obliterans, particularly if the patient is a heavy-smoking male. Careful questioning is necessary for any associated symptoms, since a history of joint swelling may indicate rheumatoid disease or disseminated lupus, whilst dysphagia and other intestinal symptoms are typical of systemic scleroderma. The patient's occupation will be important in vibrating tool disease.

Examination

A careful look at the patient's face may help to exclude established systemic scleroderma, in which the appearance is unmistakable, with a small, tight mouth and inelastic, slightly oedematous skin on the face and neck. Polygonal telangiectases on the lips and buccal mucosa may also be present. The hands must be examined for similar telangiectases and for the presence of trophic lesions. Skin colour is noted, and the hands are elevated above the patient's head to observe whether postural colour change occurs: in the ischaemic hand associated with subclavian arterial obstruction, marked pallor is produced.

The arterial pulses are next compared. Congenital absence of the ulnar pulse is relatively common, so that tests to demonstrate the patency of this vessel are of doubtful significance. In the aortic arch syndrome and after embolism, the axillary, brachial or radial pulses are often lost. The supraclavicular region should be examined for aneurysm or a palpable cervical rib; the effect of bracing back the shoulders and of hyperabduction of the arms should also be noted. These manoeuvres sometimes obliterate the pulses of normal subjects and do not necessarily indicate the source of the symptoms. The diagnosis of embolism requires the identification of

a source, such as atrial fibrillation, myocardial infarction or cervical rib; proximal atherosclerotic plaques or aneurysms are occasionally responsible.

Finally, auscultation with a stethoscope over the subclavian artery above or below the clavicle may reveal a murmur, indicating turbulent flow produced by stenosis or compression. When thoracic outlet compression is suspected, this test should be tried with the shoulders in various positions. Differences in blood pressure in the two arms are an occasional indication of main vessel obstruction.

Reactive hyperaemia, after occlusion of the circulation for 3–5 min with a cuff, gives useful clinical evidence of maximal blood flow in the various fingers. This reflex is independent of nervous connexions with the central and sympathetic systems, being due to local chemical and physical changes.

Radiology

Cervical rib is easily recognized in the chest X-ray, but subclavian compression occasionally occurs without bony abnormality (costo-clavicular compression and scalenus anterior syndrome).

Plain X-rays of the hands may help to exclude rheumatoid arthritis. Calcification in the pulp compartments of the fingers (hypodermolithiasis) is pathognomonic of systemic scleroderma, most often seen in acrosclerosis and the CRST syndrome, in which radiological changes in the viscera may be minimal.

Barium studies reveal characteristic changes in established diffuse scleroderma, due to interference with smooth muscle contractility. During examination of the oesophagus in the supine position, there is absence of peristalsis and pouch-like dilatation is seen. Radiological changes may precede the development of dysphagia and the barium swallow is probably the most convenient way to demonstrate changes, but there are similar abnormalities in the small intestine, colon and upper urinary tract. Tuffanelli & Winkelmann (1961) found oesophageal changes in 67% of 481 patients studied radiologically.

Arteriography can give valuable information, but has the obvious limitation that the demonstration of a blocked artery does not indicate what caused it. The most useful techniques are brachial arteriography, for the demonstration of the digital and hand vessels and retrograde arch aortography, to show the origin of the trunks to the head and neck and demonstrate the subclavian arteries. Direct puncture of the subclavian or axillary are occasionally useful.

Raynaud's disease. The digital arteries are patent and appear normal on arteriography. Anatomical abnormalities are common in the hand and may lead

to misinterpretation. Examples include absence of the ulnar artery, the palmar arches and the lateral digital artery of the index.

Thoracic outlet compression. In patients with thrombo-embolism associated with cervical rib, the site of impaction of emboli is readily demonstrated (Fig. 6). These are usually multiple. A subclavian aneurysm can sometimes be shown.

Arterial thrombosis. Arteriography reveals the extent and distribution of the blockage accurately, but it does not indicate its aetiology. Identical arteriographic pictures may be obtained in atherosclerosis, thrombo-angiitis obliterans and the collagen disorders, and rarely as a complication of longstanding Raynaud's disease. In digital artery thrombosis, whatever the cause, segmental blocks are usually multiple, lying opposite the proximal phalanges. A tuft of minute collateral vessels is visible in good quality films, but occlusion should not be diagnosed unless opaque medium is seen in the arteries distal to the block and in the digital pulp. The arteriogram may give an indication of the extent of the digital collateral circulation.

Collagen disorders. Arteriography is of little use in the early diagnosis of collagen disorders, although patients with systemic scleroderma may show a peculiar susceptibility to vasospasm, the vessels contracting down to fine threads during the investigation. The digital thrombosis, seen in both systemic scleroderma and rheumatoid arthritis, has no specific arteriographic features, although the blocks are often sited in relation to the peri-articular swellings. Occlusions also occur in patients with nodose polyarteritis, said to be accompanied by an irregular network of abnormal collaterals in the hand (Laws *et al.*, 1963).

Laboratory tests

Haemoglobin, white cell and platelet counts, blood smear examination and erythrocyte sedimentation rate should always be obtained. A moderate elevation of ESR is common in collagen disorders, whilst very rapid sedimentation may indicate the presence of haemagglutination. Screening tests for cold agglutination and the presence of cryoglobulins are occasionally needed. When digital artery thrombosis or digital gangrene is present, smears should be examined for the LE cell phenomenon, bearing in mind that a negative result does not exclude disseminated LE and that the test may need to be repeated. Examination for differential sheep cell agglutinins (DAT) and a latex test should be done where collagen disorder is suspected. Anti-

streptolysin-0 titre should be estimated when acute rheumatism is a possibility and when Raynaud's phenomenon is encountered in infancy. Serological tests for syphilis are occasionally needed.

Treatment

Raynaud's disease

Results of sympathectomy in functional vasospasm of the upper limbs are disappointing, mainly due to the high local reactivity of the hand blood vessels and the early return of autonomous vascular tone. Relapse after sympathectomy is liable at any time during the first 5 years after operation (Felder *et al.*, 1949; Jepson, 1951; Johnston *et al.*, 1965). By the end of 5 years only about two-thirds of patients operated for Raynaud's disease are left with improvement in their symptoms. The remaining one-third are found to have reverted to their original state, with the added disadvantage that their hands are uncomfortably dry as the result of sudomotor denervation. The main causes of relapse are as follows:

Persistence of the 'local fault'. Although sympathectomy causes an initial twelve-fold increase in hand blood flows in patients with Raynaud's disease, the vasodilation almost disappears in the weeks following operation. Cold hypersensitivity can be demonstrated within a few days of operation (Lewis, 1938; Hyndman & Wolkin, 1942). As Lewis maintained, the response to local cooling predominates in Raynaud's disease over the neurogenic vasoconstrictor pathway. This hypersensitivity persists after sympathectomy, although partly offset by abolition of reflex vasoconstriction, which keeps the fingers warmer and consequently helps to prevent the cold stimulus.

Re-innervation of sympathetic effectors. This accounts for a few relapses which may be (1) early, due to incomplete sympathetic denervation, or (2) late, due to the development of alternative anatomical pathways—particularly along the vertebral bodies (Boyd, 1957)—or to collateral axonal sprouting (Murray & Thompson, 1957). Re-innervation is diagnosed when reflex heating can be shown to produce an increase in finger blood flow or evidence of sweating in the hand.

Incorrect initial diagnosis. A few patients sympathectomized for what appears to be Raynaud's disease later develop florid systemic scleroderma, and the 'relapse' is then due to progression of the collagen disorder. This occurred in 19% of a group of seventy-five patients with Raynaud's disease (Johnston *et al.*, 1965). There appears to be no

certain way of diagnosing systemic scleroderma in its early stages.

Medical treatment of functional vasospasm is equally unsatisfactory because cold vasoconstriction overrides the vasodilator influence of the drugs. The best cure is to avoid local cooling or seek a warmer climate. However, several lines of empirical treatment may be tried.

Reassurance is important. As Raynaud remarked 'this strange disease, so striking in appearance, is far from having the seriousness to which one is at first glance led'. Nevertheless, the clinician may have to eat his words several years later, since about 20% of these patients develop overt evidence of collagen disorder.

General metabolic stimulation. Thyroxine must be given when there is evidence of hypothyroidism, but sometimes benefits euthyroid patients. There seems no sound reason for giving tri-iodothyronine instead of thyroxine.

Adrenergic blockade. Reserpine 0.25 mg twice daily acts partly by depressing the vasoconstrictor outflow centrally and partly by generalized depletion of catecholamine, both in the wall of blood vessels and elsewhere in the body (Kontos & Wasserman, 1969). It may be combined with thyroxine. Guaneethidine 10–50 mg each morning has a postganglionic blocking effect as well as depleting catechol amines.

Other vasodilator drugs. In general these are of little value in Raynaud's disease but phenoxybenzamine (alpha-adrenergic blocker) 10–20 mg three times daily, nicotinic alcohol (smooth muscle relaxant) 25–50 mg three times daily or thymoxamine hydrochloride (alpha-adrenergic blocker) 40 mg three times daily and tolazoline hydrochloride (alpha-adrenergic blocker and vascular smooth muscle relaxant) 25–50 mg three times daily have their advocates.

Organic ischaemia

Preliminary sympathetic nerve block is valueless in predicting the outcome of surgical sympathectomy, because results depend as much upon growth of collateral vessels as on any immediate vasodilatation in the skin. Furthermore, the test cannot indicate the likelihood of later relapse, dependent on recovery of intrinsic vascular tone and progression of the original disease. Selection for sympathectomy must therefore be made on clinical grounds alone.

Table 2 shows the final diagnosis and result of sympathectomy in a series of forty-three patients with organic digital artery disease. The criteria for inclusion in this series were severe ischaemia (necrosis

TABLE 2. Results of sympathectomy in organic digital ischaemia (forty-three patients; follow-up 2-25 years)

Final diagnosis	Males		Females	
	No. of cases	No. improved after sympathectomy	No. of cases	No. improved after sympathectomy
Atherosclerosis	19	16 (84%)	4	1
Systemic scleroderma	3	1	3	1
Acrosclerosis	—	—	12	5
Other	—	—	2	—
Total	22	17 (77%)	21	7 (33%)

or gangrene) or arteriographic evidence of digital artery occlusion (Birnstingl, 1967).

It can be seen that the late results are largely dependent upon the underlying pathology. Thus in nineteen men with atherosclerosis (thrombosis of digital arteries) sixteen improved although most had necrosis prior to the operation. Digital artery thrombosis seldom progresses, once the patient has recovered from the initial episode. On the other hand fifteen of twenty-one women had a collagen disorder, reflected in an overall improvement rate of 33%. Nevertheless the operation seemed justifiable in women when they had active pulp ulceration, since five out of nine showed no further nutritional lesions, although ischaemic symptoms continued.

Methods of treatment which have been insufficiently tried are the use of *low-molecular weight dextran* (10% Rheomacrodex) by Holti (1965) and of *hyperbaric oxygen* (Copeman, Ashfield & Dowling, 1967). In patients with systemic scleroderma, improvement has been claimed for several weeks after treatment by either method.

Technique of upper thoracic sympathectomy. The operation can be performed by any one of three alternative routes: (1) anterior supraclavicular, (2) posterior and (3) axillary transthoracic (Atkins, 1954). Resection of the second and third thoracic ganglia provides a sympathectomized hand without a Horner's syndrome. There is no clinical difference between preganglionic sympathectomy and (post-ganglionic) ganglionectomy and Baddeley (1965) found no improvement in results after an extended intrathoracic procedure.

Operation for thoracic outlet compression. Where there is evidence of compression of the subclavian artery, and particularly when this is complicated by aneurysm or embolism, operation should be undertaken. Through a supraclavicular approach, the scalenus anterior is divided, and this step may allow the artery to bulge forward sufficiently to relieve the symptoms. Where a cervical rib is found, it is usually preferable to remove most of this together with its periosteum using rongeurs. The rib must

be resected back as far as the costo-transverse joint, taking great care to avoid injury to the first thoracic root of the brachial plexus. The rib having been removed, a sympathectomy can be done if ischaemic symptoms are severe enough. Where a substantial aneurysm is present, it should be replaced or repaired with Dacron fabric or cephalic vein. Distal embolism requires the use of a Fogarty embolectomy catheter.

A few authors have advised resection of the first rib for the relief of thoracic outlet compression, amongst them Roos (1966) who advocates a trans-axillary approach. However, in the absence of clear evidence of aneurysm or thrombo-embolism, it is doubtful if these patients need operation.

Conclusions

1. In Raynaud's syndrome, whether presenting as episodic ischaemia or frank finger-pulp necrosis, it is essential to separate patients with organic digital artery disease from those with vasospasm. This has been greatly helped by brachial arteriography.

2. Severe nutritional lesions invariably indicate organic occlusion, which is also likely when ischaemic symptoms show an asymmetrical distribution and when there is evidence of arterial disease in other parts of the body.

3. The prevalence of organic vascular lesions in all forms of collagen disorder and their demonstration, in particular, in systemic scleroderma and rheumatoid arthritis is closely related to their immunological character. It is necessary constantly to be aware of these disorders masquerading in various guises, from mild Raynaud's phenomenon to actual digital gangrene.

4. The natural reactivity and autonomous tone of the digital vessels makes it difficult to secure permanent vasodilatation and largely explains the poor results of both sympathectomy and vasodilator therapy in Raynaud's phenomenon, whatever its cause. But the initial effect of sympathetic denervation may be sufficient to secure healing of nutritional lesions. The operation should therefore only be advised when these are present.

5. The results of treatment in digital ischaemia

depend largely upon the underlying pathology and emphasize the importance of accurate diagnosis.

References

- ATKINS, H.B. (1954) Sympathectomy by axillary approach. *Lancet*, **i**, 538.
- BADDELEY, R.M. (1965) The place of upper dorsal sympathectomy in the treatment of primary Raynaud's disease. *British Journal of Surgery*, **52**, 426.
- BARCROFT, H. (1952) Problems of sympathetic innervation and denervation. *British Medical Bulletin*, **8**, 839.
- BIRNSTINGL, M. (1967) Results of sympathectomy in digital artery disease. *British Medical Journal*, **2**, 601.
- BOYD, J.D. (1957) Intermediate sympathetic ganglia. *British Medical Bulletin*, **13**, 207.
- BURTON, A.C. (1939) The range and variability of the blood flow in the human finger and the vasomotor regulation of body temperature. *American Journal of Physiology*, **137**, 437.
- BYWATERS, E.G.L. (1949) Variant of rheumatoid arthritis characterized by recurrent digital pad nodules and palmar fasciitis, closely resembling palindromic rheumatism. *Annals of the Rheumatic Diseases*, **8**, 1.
- BYWATERS, E.G.L. (1957b) Peripheral vascular obstruction in rheumatoid arthritis and its relation to other vascular lesions. *Annals of the Rheumatic Diseases*, **16**, 84.
- BYWATERS, E.G.L. & SCOTT, J.T. (1963) The natural history of vascular lesions in rheumatoid arthritis. *Journal of Chronic Diseases*, **16**, 905.
- COPEMAN, P.W.M., ASHFIELD, R. & DOWLING, G.B. (1967) Raynaud's phenomenon in scleroderma treated with hyperbaric oxygen. *Proceedings of the Royal Society of Medicine*, **60**, 1268.
- DUGUID, J.B. (1949) The pathogenesis of arteriosclerosis. *Lancet*, **ii**, 925.
- EASTCOTT, H.H.G. (1962) Reconstruction of the subclavian artery for complications of cervical rib and thoracic outlet syndrome. *Lancet*, **ii**, 1243.
- FELDER, D.A., SIMEONE, F.A., LINTON, R.R. & WELCH, C.E. (1949) Evaluation of sympathetic neurectomy in Raynaud's disease. *Surgery*, **26**, 1014.
- FOX, R.H. (1968) Effects of cold on the extremities. *Proceedings of the Royal Society of Medicine*, **61**, 785.
- GROUND, M.D. (1964) Raynaud's phenomenon in users of chain saws. *Medical Journal of Australia*, **1**, 270.
- HAUST, M.D., MORE, R.H. & MOVAT, H.Z. (1959) The mechanism of fibrosis in arteriosclerosis. *American Journal of Pathology*, **35**, 265.
- HAWLEY, P.R., JOHNSTON, A.W. & RANKIN, J.T. (1967) Association between digital ischaemia and malignant disease. *British Medical Journal*, **3**, 208.
- HOLTI, G. (1965) The effect of intermittent low molecular weight dextran infusions upon the digital circulation in systemic sclerosis. *British Journal of Dermatology*, **77**, 560.
- HUTCHISON, J. (1901) Raynaud's phenomenon. *Medical Press and Circular*, **72**, 403.
- HYNDMAN, O.R. & WOLKIN, J. (1942) Raynaud's disease. A review of its mechanism, with evidence that it is primarily a vascular disease. *American Heart Journal*, **23**, 535.
- JEPSON, R.P. (1951) Raynaud's phenomenon: a review of the clinical problem. *Annals of the Royal College of Surgeons*, **9**, 35.
- JOHNSTON, E.N.M., SUMMERLY, R. & BIRNSTINGL, M. (1965) Prognosis in Raynaud's phenomenon after sympathectomy. *British Medical Journal*, **1**, 962.
- KONTOS, H.A. & WASSERMAN, A.J. (1969) Effect of reserpine in Raynaud's phenomenon. *Circulation*, **39**, 259.
- LAW, J.W., LILLIE, J.G. & SCOTT, J.T. (1963) Arteriographic appearances in rheumatoid arthritis and other disorders. *British Journal of Radiology*, **36**, 477.
- LEWIS, T. (1930) Observations upon the reactions of the vessels of the human skin to cold. *Heart*, **15**, 177.
- LEWIS, T. (1938) The pathological changes in the arteries supplying the fingers in warm-handed people and in cases of so-called Raynaud's disease. *Clinical Science*, **3**, 287.
- LINSCHIED, R.L., PETERSON, L.F.A. & JUERGENSEN, J.L. (1967) Carpal tunnel syndrome associated with vasospasm. *Journal of Bone and Joint Surgery*, **49A**, 1141.
- LOWENTHAL, M.N. (1967) Peripheral gangrene in infancy and childhood. *British Medical Journal*, **2**, 700.
- LYNN, R.B., STEINER, R.E. & VAN WYK, F.A.K. (1955) Arteriographic appearances of the digital arteries of the hands in Raynaud's disease. *Lancet*, **i**, 471.
- MURRAY, J.G. & THOMPSON, J.W. (1957) Collateral sprouting in response to injury to the autonomic nervous system and its consequences. *British Medical Bulletin*, **13**, 213.
- NELSON, M.G. & MARSHALL, R.J. (1953) The syndrome of high titre cold agglutination. *British Medical Journal*, **2**, 214.
- OLESEN, H. (1967) The cold agglutinin syndrome. *Danish Medical Bulletin*, **14**, 138.
- PEACOCK, J.H. (1959) Peripheral venous blood concentrations of epinephrine and nor-epinephrine in primary Raynaud's disease. *Circulation Research*, **7**, 821.
- PICKERING, G. (1968) *High Blood Pressure*, 2nd edn, p. 195. Churchill, London.
- PRINGLE, R., WALDER, D.N. & WEAVER, J.P. (1965) Blood viscosity and Raynaud's phenomenon. *Circulation*, **39**, 259.
- RAYNAUD, M. (1862) *De l'Asphyxie et de la Gangrène Symétrique des Extrémités*. Rignoux, Paris.
- RAYNAUD, M. (1888) *On Local Asphyxia and Symmetrical Gangrene of the Extremities* (1862), and *New Researches on the Nature and Treatment of Local Asphyxia of the Extremities* (1874) (Translated by Thomas Barlow). New Sydenham Society, London.
- RIITMAN, S.E. & LEVIN, W.D. (1961) Cryopathies: a review. *Archives of Internal Medicine*, **107**, 754.
- ROB, C.G. & STANDEVEN, A. (1958) Arterial occlusion complicating thoracic outlet compression syndrome. *British Medical Journal*, **2**, 709.
- RODDIE, I.C. & SHEPHERD, J.T. (1957) Evidence for critical closure of digital resistance vessels with reduced transmural pressure and passive dilatation with increased venous pressure. *Journal of Physiology*, **136**, 498.
- RODNAN, G.P. (1963) A review of recent observations and current theories on the aetiology and pathogenesis of progressive systemic sclerosis (diffuse scleroderma). *Journal of Chronic Diseases*, **16**, 929.
- ROKITANSKY, C. (1852) *A Manual of Pathological Anatomy*, translated by G. E. Day. The Sydenham Society, London.
- ROOS, D.B. (1966) Transaxillary approach for first rib resection to relieve thoracic outlet syndrome. *Annals of Surgery*, **163**, 354.
- ROSS, J.P. (1959) The vascular complications of cervical rib. *Annals of Surgery*, **150**, 340.
- SOKOLOFF, L., WILLENS, S.L. & BUNIM, J.J. (1951) Arteritis of striated muscle and rheumatoid arthritis. *American Journal of Pathology*, **27**, 157.
- THIBIERGE, G. & WEISSENBACH, R.-J. (1911) Concrétions calcaires souscutanées et sclérodémie. *Annales de dermatologie et de syphiligraphie*, **42**, 129.
- TUFFANELLI, D.L. & DUBOIS, E.L. (1964) Cutaneous manifestations of systemic lupus erythematosus. *Archives of Dermatology*, **90**, 377.
- TUFFANELLI, D.L. & WINKELMANN, R.K. (1961) Systemic scleroderma: a clinical study of 727 cases. *Archives of Dermatology*, **34**, 359.
- VAZQUEZ, J.J. & DIXON, F.J. (1958) Immunohistochemical analysis of lesions associated with 'fibrinoid change'. *Archives of Pathology*, **66**, 504.

WICKHAM, J.E.A. & MARTIN, P. (1962) Aneurysm of the subclavian artery in association with cervical abnormality. *British Journal of Surgery*, **50**, 205.

WINTERBAUER, R.H. (1964) Multiple telangiectasia, Ray-

naud's phenomenon, sclerodactyly and subcutaneous calcification: a syndrome mimicking hereditary haemorrhagic telangiectasia. *Bulletin of Johns Hopkins Hospital*, **114**, 361.