

*Ministry of Defence*

## **Synopsis of Causation**

# **Polymyositis, Dermatomyositis, Systemic Sclerosis & Systemic Vasculitis**

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## **Disclaimer**

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This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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# 1. Definition

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- 1.1. The connective tissue diseases polymyositis (PM), dermatomyositis (DM), systemic sclerosis (SSc), and systemic vasculitis (SV) are all members of the autoimmune rheumatic diseases group which also includes rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). All of these diseases can exhibit varying degrees of involvement of joints, muscles, connective tissue, skin, and blood vessels. Indeed, such is the difficulty of precise definition of each member of the group that some overlap can occur. This is particularly relevant when different studies are being examined as each set of authors may fail to define the conditions in strictly comparable ways.

## Polymyositis and dermatomyositis

- 1.2. PM and DM are considered to be subsets of the idiopathic inflammatory myopathy group of connective tissue diseases. PM is characterised by specific clinical and investigative features of muscle inflammation.
- 1.3. DM exhibits the features of PM with the addition of characteristic skin lesions.
- 1.4. The annual [incidence](#) of PM & DM is 1 per 100000 and [prevalence](#) is between 5 and 10 per 100000. The disorders occur twice as often in women than in men, especially between the ages of 15 and 44.

## Systemic sclerosis

- 1.5. SSc is included in the [scleroderma group](#) of connective tissue diseases and features skin [sclerosis](#), [Raynaud's phenomenon](#), involvement of many major organs, and the presence of specific [serological](#) abnormalities. Several different subgroups are described:
- Those with diffuse cutaneous scleroderma
  - Those with limited cutaneous scleroderma
  - Those with no scleroderma (sine scleroderma)
  - Those in overlap
- 1.6. In the overlap subgroup, features of any of the first three subgroups are present along with diagnostic criteria for other connective tissue diseases such as RA or SLE.
- 1.7. In Western Europe the annual incidence is approximately 1 per 100 000, and prevalence is approximately 10 per 100 000.

## Systemic vasculitis

- 1.8. SV consists of a group of connective tissue disorders that feature inflammation of blood vessels. Such inflammation may be secondary to infections, drugs, or other connective tissue disorders such as RA, but primary forms are recognised and can be classified by blood vessel size:

- Those involving large vessels, including giant cell arteritis (temporal arteritis), Behçet's disease and Takayasu's arteritis
- Those involving medium vessels, including polyarteritis nodosa, thromboangiitis obliterans (Buerger's disease) and Kawasaki disease
- Those involving small to medium vessels, including Wegener's granulomatosis and Churg-Strauss syndrome
- Those involving small vessels, including Henoch-Schönlein purpura and Goodpasture's disease

1.9. Only these primary forms are considered in the present account.

1.10. There are substantial variations in incidence of the conditions in different countries of the world, but in the United Kingdom annual incidence of all SV cases except giant cell arteritis is estimated to be between 10 and 50 per million. Giant cell arteritis is one of the commonest of the SV group and its incidence in Northern Europe is estimated to be between 150 and 350 per million, occurring mainly in people aged 50 or over.

## 2. Clinical features

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### Polymyositis

- 2.1 PM is an inflammatory [myopathic](#) disorder in which symmetrical [proximal](#) muscle weakness develops over several weeks or months. [Myalgia](#) and muscle tenderness may also be present. [Limb girdle](#) and [anterior](#) neck [flexors](#) are the muscles mainly affected, those involved in facial expression being spared. [Dysphagia](#) and impaired respiratory movement can sometimes feature while grip and fine movements of the hands are usually affected only in the later stages of the disease.
- 2.2 [Systemic](#) effects may include weight loss, fever, [anorexia](#), and morning stiffness.
- 2.3 [Arthralgia](#) and Raynaud's phenomenon occasionally develop and [pulmonary](#) and [cardiac](#) complications may arise during the course of the disease.
- 2.4 Laboratory testing demonstrates raised [serum](#) levels of several [skeletal muscle enzymes](#) and myositis - specific [antibodies](#) including anti-synthetase antibodies, antibodies to signal recognition particle and antibodies to Mi-2γ a nuclear helicase that may differ from person to person.
- 2.5 MRI of affected area is essential and [Electromyographic](#) examination and [biopsy](#) of proximal skeletal muscle tissue reveal characteristic changes.

### Dermatomyositis

- 2.6 DM findings are the same as those in polymyositis with the addition of a number of distinctive skin features that can sometimes precede the muscular changes by several months.
- 2.7 The development of a scaly, [erythematous](#) eruption over the knuckles (Gottron's sign) is [pathognomonic](#) and similar lesions (Gottron's papules) may arise on other [extensor surfaces](#) including the elbows and knees. Other characteristic lesions include scalp involvement and calcification of the skin.
- 2.8 Erythema over the shoulders and upper chest and back forming "V" shapes (shawl sign) is common as is erythema on the face and hands.
- 2.9 Eyelids may show a heliotrope rash accompanied by [oedema](#), and the photosensitive [malar](#) rash typical of SLE may also occur.
- 2.10 The roughened and cracked skin and dark lines across the [lateral](#) and [palmar aspects](#) of the fingers (so called, mechanic's hands) may feature.

### Systemic sclerosis

- 2.11 Most cases of SSc present with Raynaud's phenomenon and other features can arise at any time within the ensuing two years.
- 2.12 Fever is uncommon but malaise, fatigue and weight loss are likely.

- 2.13 The dermatological features vary according to the subgroup diagnosed.
- 2.14 Those with [diffuse](#) cutaneous scleroderma exhibit skin thickening on the trunk, face, and proximal and [distal](#) extremities.
- 2.14.1. Those with limited cutaneous scleroderma are characterised by skin thickening only on the face and neck and sites distal to the elbow and knee.
- 2.15 The sine scleroderma subgroup manifests no clinically detectable skin abnormalities.
- 2.16 Progression of the [dermatological](#) features can vary widely in different cases, ranging from rapid development of widespread skin thickening within a few months to very slow change over several years. As skin thickening worsens, movements become increasingly impaired, being especially disabling in the hands.
- 2.17 Finger and hand swelling, arthralgia, muscle pain and morning stiffness are common, and muscle weakness can vary substantially from case to case.
- 2.18 Involvement of the [gastrointestinal](#) system can give rise to a wide range of problems including difficulty with chewing or swallowing, abdominal distension, diarrhoea, constipation, and incontinence.
- 2.19 Effects on pulmonary tissues can cause obstructive airways disease and [pleural](#) abnormalities.
- 2.20 Cardiac complications can cause a variety of problems including [arrhythmias](#) and heart failure.
- 2.21 Impaired [renal](#) function may occur, with risk of [hypertensive](#) crises, and may go on to renal failure.
- 2.22 A number of other effects may develop including dry eyes, dry [mucous membranes](#), impaired sexual performance, and psychological difficulties.
- 2.23 Nearly all SSc patients carry specific [autoantibodies](#) and many develop [antinuclear](#) antibodies along with a variety of other serological features.
- 2.24 Beyond the initial five years, constitutional symptoms usually settle, skin and muscle problems often progress no further, and while internal disease may continue to worsen, involvement of new organs becomes less likely.

### **Systemic vasculitis**

- 2.25 Most diseases in the SV group cause fever, weight loss, malaise, arthralgias and arthritis. Other symptoms and signs are typical of subgroups defined by vessel size.
- 2.26 Large vessel disease patients may exhibit limb [claudication](#), absence of pulses, asymmetric blood pressures, and [bruits](#) and Xray examination may show dilatation of the [aorta](#).
- 2.27 Features of medium vessel disease include skin nodules, ulcers, and [gangrene](#) of fingers and toes.
- 2.28 Small vessel disease may lead to [purpura](#), splinter haemorrhages, [urticaria](#), [alveolar](#) haemorrhages, [glomerulonephritis](#), and eye inflammation such as [uveitis](#) and [scleritis](#).

- 2.29 However, overlap of subgroup features commonly occurs.
- 2.30 Antibodies of various types characterise different diseases within the SV group, antineutrophil cytoplasmic antibody (ANCA) being particularly useful in diagnosis.

## 3. Aetiology

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### Polymyositis and dermatomyositis

- 3.1. PM and DM are considered to be [autoimmune](#) diseases due to their association with a number of other recognised autoimmune diseases and to the presence of significant amounts of circulating antibodies. They are thought to arise in genetically susceptible individuals exposed to environmental factors.

#### Genetic susceptibility

- 3.2. These very uncommon diseases can occur in more than one family member,<sup>1,2</sup> and a number of studies have shown an association between certain types of PM and DM and the presence of particular genes in the affected individuals. Human leukocyte antigen (HLA) genes on [chromosome](#) 6 are amongst those involved.<sup>3,4,5</sup> It is likely that [genotype](#) has a role in aetiology but its relative importance is not clear.

#### Environmental factors

##### Infections

- 3.3. A number of studies have demonstrated clear [temporal](#) associations between certain infectious agents and the occurrence of PM and DM but the number of cases is small and cause and effect relationships have not been firmly established.
- 3.4. Associations with parvovirus B19, coxsackie B, hepatitis C, human immunodeficiency virus (HIV) and enteroviruses have been found.<sup>6,7,8,9,10,11</sup>
- 3.5. Associations have also been found with the protozoan parasite *Toxoplasmosis gondii* and the roundworm *Trichinella pseudospiralis*, and features of DM have been reported in cases of Lyme disease, caused by the tick-borne parasite *Borrelia burgdorferi*.<sup>12,13,14,15,16</sup>
- 3.6. The significance of these associations remains uncertain.

##### Trauma

- 3.7. There is no evidence linking physical trauma to the onset of PM or DM.

##### Drugs

- 3.8. A substantial variety of drugs have been implicated in triggering PM and DM,<sup>17</sup> statins<sup>18</sup> and proton pump inhibitors<sup>19</sup> being among them, but the reports have been mainly of individual cases and the significance of the association remains unclear. The use of high activity antiretroviral therapy, which can improve survival rates in HIV cases, is reported to be associated with myopathies including PM.<sup>20</sup> Whether the association is with the drugs used or with the underlying condition is uncertain.

##### Other causes

- 3.9. Reports of medical implants, occupational exposures, and ultraviolet radiation being

implicated in the aetiology of PM & DM lack convincing confirmatory evidence.

## **Systemic sclerosis**

3.10 The detection of activated immune cells and disease-specific antibodies in SSc cases confirms the autoimmune nature of the disease. However, the role of genetic and environmental factors in its aetiology is still not well defined.

### **Genetic susceptibility**

3.11 The suspicion that genetic susceptibility has a role in this disease, as in some other connective tissue diseases, has not yet been convincingly confirmed although familial clustering has been observed and HLA genes have been associated with specific autoantibodies.<sup>21,22,23,24,25,26</sup>

### **Infections and vaccines**

3.12 Parvovirus B19 and cytomegalovirus have been implicated in SSc aetiology but associations are weak.<sup>27,28</sup> Various other infectious agents including insect-borne parasites such as *Borrelia burgdorferi* have been linked with SSc but evidence of a cause and effect relationship is lacking. Suspicion of vaccine involvement in triggering SSc is not supported by evidence.

### **Occupational exposure**

3.13 A number of case-control studies have raised the possibility that SSc may be associated with prolonged occupational exposure to various substances including crystalline silica (a mineral frequently found in sand, rock, and soil), trichlorethylene, chlorinated solvents, welding fumes, and some other solvents.<sup>29,30,31,32,33</sup> However, the studies vary in their conclusions, numbers are small and no cause and effect relationship has been established.

### **Other causes**

3.14 Concern has been raised that silicone breast implants might be implicated in the aetiology of SSc<sup>34</sup> but the evidence is unconvincing.<sup>35,36,37</sup> A few cases of SSc developing after physical trauma have been reported but there is no evidence of trauma having a causative role.<sup>38,39</sup>

## **Systemic vasculitis**

3.15 The aetiology of SV diseases is uncertain, with variation in emphasis of reported factors in different conditions within the group. Genetic factors and environmental triggers appear to be involved, but the sparse evidence varies from one SV disease to another.

### **Genetic susceptibility**

3.16 Links with many of the SV diseases and certain HLA genes have been reported and are well established in Behçet's disease and giant cell arteritis.<sup>40,41,42</sup> However the precise role of genetic factors in the aetiology of the SV diseases is complex and incompletely understood.

### **Environmental factors**

3.17 A number of environmental factors have been implicated as risk factors for certain SV conditions, infections, smoking, drugs, and silica being those most commonly reported.

## **Infections**

- 3.18 The infections associated with diseases in the SV group include hepatitis B and polyarteritis nodosa,<sup>43,44,45</sup> hepatitis C and cryoglobulinaemic vasculitis,<sup>43,44,45,46,47</sup> and *Staphylococcus aureus* and Wegener's granulomatosis<sup>48,49</sup> These associations are well established although whether they indicate cause and effect has not been clearly defined. Also, cases of each of these three SV diseases can occur without evidence of the associated infection having been present.
- 3.19 Several other SV diseases have been linked with bacterial and viral infections but the links are not so clearly established.

## **Smoking**

- 3.20 A very large proportion of people with thromboangiitis obliterans (Buerger's disease) are smokers and it is considered likely that tobacco smoking plays a role in the onset of that disease.<sup>50,51,52</sup> The place of smoking in the aetiology of other SV diseases is not clear.

## **Drugs**

- 3.21 A large number of drugs have been reported to be associated with SV cases, but the evidence for a causal relationship is lacking.<sup>33</sup>

## **Silica**

- 3.22 Prolonged occupational exposure to silica (a mineral frequently found in sand, rock, and soil) has been reported to be associated with some of the SV diseases, but firm evidence of a triggering role is not available.<sup>49,53</sup>

## **Trauma**

- 3.23 There is no evidence that physical trauma contributes to the aetiology of SV.

## 4. Prognosis

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### Polymyositis and dermatomyositis

- 4.1. Although few cases of PM or DM are completely cured, the [five-year survival rate](#) is now over 80%.
- 4.2. Adverse prognostic factors include severe myositis, pulmonary or cardiac involvement, dysphagia, associated malignancy and the detection of certain myositis-specific antibodies.

### Systemic sclerosis

- 4.3. There are wide variations in the estimates of five-year survival, being in the range of 35-75%. Mortality risk remains increased for up to 15 years after onset.
- 4.4. Adverse prognostic factors include the extent of skin involvement, the presence of pulmonary, cardiac, or renal complications, greater age at onset and the detection of particular types of autoantibodies. Improved techniques of early diagnosis and management of systemic complications have improved the outlook for SSc patients in recent years.

### Systemic vasculitis

- 4.5. In some of the diseases within this group, but not all, the five-year survival rate is now over 80%. The prognosis is related mainly to the severity of systemic complications.
- 4.6. In thromboangiitis obliterans in particular, the length of smoking history and its intensity are important indicators of prognosis and stopping smoking can have a valuable effect on improving outcome.

Improvements in the outlook for connective tissue disease patients are likely to continue as further advances in understanding the underlying [pathogenic mechanisms](#) are made and better methods of treatment emerge.

## 5. Summary

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- 5.1. The autoimmune rheumatic diseases consist of a substantial number of connective tissue disorders that, along with rheumatoid arthritis and systemic lupus erythematosus, include the idiopathic inflammatory myopathies polymyositis (PM) and dermatomyositis (DM) and conditions within the systemic sclerosis (SSc) and systemic vasculitis (SV) groups.
- 5.2. PM is typified by muscle pain and tenderness in varying muscle groups, systemic involvement, and specific investigative findings.
- 5.3. DM exhibits the characteristics of PM with the addition of a number of distinctive skin features.
- 5.4. Patients with a disease of the SSc group develop Raynaud's phenomenon, varying degrees and distribution of skin thickening, and specific autoantibodies.
- 5.5. The SV diseases, classified by vessel size, can cause a variety of problems according to the particular condition involved.
- 5.6. In all of the conditions described in this account genetic factors probably have an aetiological role but the mechanisms involved remain undefined and the importance of the genetic factors is not thought to be uniform throughout the group.
- 5.7. Some environmental factors may have a triggering effect but, while many associations between different factors and particular diseases described in this account have been reported, their significance is not well established (except perhaps in the case of smoking and thromboangiitis obliterans). Relevant environmental factors include bacterial, viral, and parasitic infections, drugs, and exposure to silica and various toxins.
- 5.8. The outlook for patients varies according to the condition involved and the severity of its systemic effects but the prognosis of these diseases has improved in recent years with advances in treatment.

## **6. Related Synopses**

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Rheumatoid Arthritis and Systemic Lupus Erythematosus

## 7. Glossary

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alveolar	Pertaining to the microscopic air spaces in the lungs.
anorexia	Lack of appetite for food.
anterior	Nearer the front.
antibodies	A large variety of protein molecules produced as part of the body's immune defence.
antinuclear	Pertaining to reaction with the nucleus, the body within a cell that contains the chromosomes.
aorta	Large artery arising from the heart.
arthralgia	Joint pain.
arrhythmias	Abnormal rhythms of the heart.
autoantibodies	Antibodies formed in response to, and reacting against, elements of the individual's own normal body constituents.
autoimmune	Pertaining to the process by which tissues are attacked by the body's own immune system.
biopsy	A procedure that involves obtaining a tissue specimen.
bruit	An abnormal sound heard over a blood vessel.
cardiac	Pertaining to the heart.
chromosome	One of the self-replicating genetic structures within each cell of body tissues.
claudication	Limb pain brought on by muscle use, reflecting restriction in blood flow.
dermatological	Pertaining to the skin.
diffuse	Widely distributed.

distal	Further from the point of attachment to the body.
dysphagia	Difficulty in swallowing.
electromyographic	Pertaining to a test of muscle response to nerve stimulation.
enzymes	Molecules that stimulate biochemical reactions within the body.
erythematous	Pertaining to erythema (redness of the skin).
extensor surface	That aspect of a limb underlain by muscles which extend, or straighten the limb.
five-year survival rate	The proportion of patients that survive for five years beyond the date of diagnosis.
flexors	Muscles that flex, or bend the limb.
gangrene	Death of tissue, usually associated with loss of blood supply and followed by bacterial invasion and putrefaction.
gastrointestinal	Pertaining to the digestive system.
genotype	The genetic constitution of an organism or cell.
glomerulonephritis	A type of inflammation of the kidneys.
hypertensive	Pertaining to high blood pressure.
incidence	The rate of new occurrence in the population being studied.
lateral	Outer; i.e. away from the midline.
limb girdle	The muscles around the area of attachment of the limb to the trunk.
malar	Pertaining to the part of the cheek bone below the eye.
mucous membranes	The lubricated inner linings of the mouth and other body passages.
myalgia	Muscle pain.
myopathic	Pertaining to muscle disease.

oedema	An abnormal build up of fluid between tissue cells in the body.
palmar aspect	Pertaining to the surface corresponding to the palm of the hand.
pathogenic mechanism	The method by which a disease is caused.
pathognomonic	Specially characteristic of a disease.
pleural	Pertaining to the smooth lining between the outer surface of the lung and the chest wall.
prevalence	The proportion of individuals in a population having a disease.
proximal	Nearer the point of attachment to the body.
pulmonary	Pertaining to the lungs.
purpura	A rash consisting of small areas of bleeding into the skin.
Raynaud's phenomenon	Intermittent attacks of markedly reduced blood supply to the fingers or toes.
renal	Pertaining to the kidney.
scleritis	Inflammation of the white area of the eyeball.
scleroderma group	Diseases characterised by abnormal hardening of skin tissues.
sclerosis	Abnormal hardening of skin tissues.
serological	Pertaining to the detection of antibodies in the serum.
serum	Fluid surrounding blood cells.
skeletal muscle	The type of muscle that provides movement of bony structures.
systemic	Affecting the body as a whole.
temporal	Pertaining to time.
urticaria	An allergic skin reaction, characterised by irregular, elevated patches and itching.
uveitis	Inflammation of the middle layer of the

eyeball.

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