VISCERO-CUTANEOUS COLLAGENOSIS
A STUDY OF THE INTERMEDIATE FORMS OF DERMATOMYOSITIS, SCLERODERMA, AND DISSEMINATED LUPUS ERYTHEMATOSUS

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It has been known for some time that dermatomyositis and scleroderma are closely related (Freudenthal, 1940; Dowling and Freudenthal, 1938) and that intermediate forms exist between these two entities. In the present paper further material will be presented in support of this idea.

It was pointed out in a previous paper (Pagel, Woolf, and Asher, 1949) that profound visceral changes, probably ischaemic, resulting from vascular lesions, are often found in dermatomyositis simultaneously with the skin and muscle changes. In scleroderma concomitant visceral and skin lesions have long been known and extensively recorded—so much so that the demand has now been made for the abolition of the name "scleroderma" and the substitution in its place of the term "progressive diffuse sclerosis" (Goetz, 1945; Beigelman, Goldner, and Bayles, 1953), a clumsier but more precisely descriptive name. Some of the changes seen resemble those observed in disseminated lupus erythematosus. It would thus appear that overlapping features are not limited to scleroderma and dermatomyositis, but include members of the group of so-called collagen diseases. It is therefore suggested that an even more general term should be used for these overlapping syndromes, "viscero-cutaneous collagenosis."

ILLUSTRATIVE CASES

In the present paper, based on illustrative cases, the following points are discussed in detail. (1) Transition of dermatomyositis to progressive diffuse sclerosis; (2) the histological changes in nail cuticle in dermatomyositis and disseminated lupus erythematosus, and their possible diagnostic significance; (3) suprarenal changes in progressive diffuse sclerosis and dermatomyositis, suggesting nodular fibrosis developing from focal fibrinoid necrosis; (4) transitional renal and muscular changes; (5) the muscular changes in dermatomyositis compared with myositis induced experimentally with muscular extracts.

Transition of Dermatomyositis to Progressive Diffuse Sclerosis

Case 1.—The patient, a woman aged 36, was originally described as Case 3 by Pagel, Woolf, and Asher. She developed dermatomyositis 11 years before death, and five years before death both legs had to be amputated, as severe chronic and atrophic sclerodermatous lesions had rendered them ankylosed and useless. For three years after the amputations she had intermittent acute attacks of urinary infection, for which she was admitted on several occasions, responding each time to chemotherapy. Four years after operation a radiograph of the chest showed large "cysts" in the lungs. She was admitted on January 19, 1953, with a history of acute left-sided pleural effusion. She was dehydrated and drowsy and her blood pressure was 80 mm. Hg systolic. The blood urea was 163 mg. per 100 ml. Two days after admission she became cyanosed and shocked, developed rapid respirations, and died the following day.

Necropsy (No. 53/40).—The body was that of a woman looking older than her age, with scarring and pigmentation of the skin, particularly round the breasts and sites of amputation. The right lung gave a gross impression of pulmo lobatus, i.e., there were irregular deep fissures in both upper and lower lobes (Fig. 1) and on the cut surface a number of well-defined, grey, fibrosed areas, measuring about 2.5 × 1.5 cm., chiefly in the cortico-pleural, infraclavicular, and hilar areas. These contained systems of bullae up to 2 cm. in diameter (Figs. 2 and 3). The left lung was not adherent and contained one or two small, fibrous areas. Both lungs showed basal oedema and congestion. There were a few fine pericardial adhesions. The heart showed no appreciable changes.

The liver weighed 1,080 g. and was firm. The cut surface showed a fine reticular fibrosis throughout, with a loss of lobular pattern. The spleen weighed 225 g., the pulp was soft and purplish, with obscure Malpighian bodies. The kidneys were small, very irregularly scarred, with pale, mottled subcapsular surfaces, from which the capsule stripped easily. The cut surfaces showed good cortico-medullary
FIG. 1.—Case 1: "Pulmo lobatus," pleural surface of right lung.

FIG. 2.—Case 1: Cut surface of right lung, showing an infra-clavicular area of fibrosis. Inset: A similar area in the lower, more dorsal portion of the right upper lobe, with cyst formation.

FIG. 3.—Case 1: another cut surface of right lung, showing pleural thickening, including interlobar fissures and apical and cortico-pleural areas of fibrosis with cyst formation.

FIG. 4.—Case 1: histological section through lung. Fibrinoid lining of dilated alveolar ducts (arrows) (×80). Inset: close-up of fibrinoid lining (haematoxylin and eosin, ×300).

FIG. 5.—Case 1: histological section of skin. Thinning of epidermis with sub-epithelial oedema and lymphorrhagia in the cutis (haematoxylin and eosin, ×80).

FIG. 6.—Case 1: liver. Histological section showing multilobular liver cirrhosis (haematoxylin and eosin, ×80).
demarcation, but the cortical thickness was reduced to 0.5 cm. The pelves contained purulent urine. Cortical lipoid in the suprarenals was reduced.

Histology.—In the lungs, sections through the triangular fibrous foci and the multiple subpleural scars showed the uniform picture of collapse-induration with compensatory emphysema. In the fibrous tissue, curly hyperplastic elastic fibres were seen in large numbers forming plaques, chiefly subpleurally but also evenly distributed throughout the collagenous areas. Additional features were fibrinoid lining of dilated alveolar ducts (Fig. 4), collapsed bronchioli, crystalline foreign bodies with foreign-body giant cells in collapsed alveoli, and concentric intimal thickening, with elastic reduplication, of the pulmonary arterial branches.

The skin from various parts of the body was markedly thinned in the epidermis with sub-epidermal oedema and conglutination of collagen. Some of the sections showed focal lymphorrhagia (Fig. 5). Irregular clumps and plaques of fragmented elastic fibres were scattered throughout the dermis, especially in the foci of conglutinated collagen.

The liver showed a multilobular portal cirrhosis with collections of lymphocytes in the perportal septa around hyperplastic bile capillaries (Fig. 6). There was a marked capsular fibrosis, containing bile capillaries. The parenchymal cells showed little change.

In the kidneys there were areas of hyalized glomeruli with some tubular atrophy and marked focal lymphocytic collections in these places. Some of the glomeruli showed partially lamellated hyaline deposits, the rest of the Malpighian corpuscles being encrusted with nummular crystalline material. There were also marked eccentric and concentric intimal thickenings of arterioles with elastic reduplication (Fig. 7). Exceptionally, a small gap in the elastica was seen (Fig. 7). Some of the atrophic and dilated tubules contained granular and homogeneous casts. One isolated but very definite area of fibrinoid necrosis was seen in the stroma between a hyalized glomerulus and some normal tubules. This area was strongly positive with the fibrin and periodic acid stains, and failed to stain with elastic-van-Gieson stain (Fig. 8).

The skeletal muscles showed (a) fibrous scars intimately woven with muscle to give an appearance of parcelling and sometimes of interruption of muscle fibres (Fig. 9A), (b) lymphorrhagia in the long axis of the muscle fibres (Fig. 9B), (c) oedema of the septa. and (d) haemorrhages.

In the oesophagus there was some thickening of the fibrous septa in the muscular layers. The thyroid showed marked thickening of the septa and some perivascular lymphocytic collections. The tonsil showed a small rim of lymphocytic tissue followed by grossly thickened and oedematous, almost hyalized, fibrous tissue. This tissue contained markedly hyalized small arteries, with an uninterrupted, somewhat thickened, internal elastic lamella.

The Diagnostic Significance of the Histological Changes in the Nail Cuticle

Case 2.—A widow, aged 55, two to three weeks before the onset of symptoms was stung by a bee on the left upper arm, which swelled up and was painful for two weeks. The main illness began six weeks before admission to hospital, when the fingers of both hands swelled up and became blue and painful on movement. There was also a dark brown swelling round the cuticles of the nails, and the pulps of the fingers were tender. Both wrists became swollen and painful at the same time. Three weeks later the ankles swelled and the thighs became painful anteriorly. A week later, pain, particularly on movement, spread to the shoulders and upper arms, but improved later. Some puffiness of the eyelids was observed on waking one week before admission, and a pleuritic pain was felt subterminally and in the left axilla. The previous history contributed nothing apart from attacks of ‘bronchial asthma.”

She was admitted to the Central Middlesex Hospital on November 24, 1953. On examination she was pale and tired-looking, with angular stomatitis. The temperature was 100.5°. Blood pressure 190/120 mm. Hg. Respiratory movements were poor, and there was some dullness of percussion at both bases. The fundi showed bilateral soft exudates. No other abnormal neurological signs were found.

The cutaneous changes were brown crusts around the cuticles of all the nails of both hands. The small joints of the hands and the wrists were stiff, the left being worse than the right. Weakness led to difficulty in sitting up. Dermatomyositis was diagnosed clinically on account of weakness and the nail changes.

Investigations showed an E.S.R. of 40 mm. in one hour. Serum proteins were 5.5 g. per 100 ml. (albumin 3.2 g., globulin 2.3 g.). The 24-hour creatine and creatine excretions were 830 mg. and 119 mg. respectively (within normal limits). The blood urea level was 28 mg. per 100 ml., and the serum potassium (two days before death) 4.5 mEq/l. (17.5 per 100 ml.). A skin and muscle biopsy of the right deltoid on December 4 showed slightly flattened papillae with oedema of the dermis. Pieces of muscle showed no inflammatory reaction or vascular changes and no evidence of dermatomyositis.

Radiography of the chest showed patchy consolidation and collapse at the right base. Three blood cultures were sterile.

Despite the negative biopsy and normal creatine metabolism, A.C.T.H. therapy was begun on December 8 with 50 mg. A.C.T.H. b.d. intramuscularly, reduced later to 20 mg. b.d. Little change was noticeable, apart from a fall in temperature to normal and changes in the radiograph suggesting pulmonary oedema. On December 20 she became much worse, with cyanosis and dyspnoea, a temperature of 100° F., and signs of left basal pneumonia. She died on December 23, 10 weeks after the onset of symptoms.
Fig. 8.—Case 1: kidney. Area of fibrinoid necrosis in the stroma (arrow) (haematoxylin and eosin, × 300). Inset: the same, stained for fibrin (P.T.A.H., × 300).

Fig. 7.—Case 1: kidney. Elastic van Gieson section, showing artery with reduplication of internal elastic. Another artery (arrow) shows a gap in the internal elastic membrane (× 80).

Fig. 9.—Case 1: skeletal muscle. A, Haematoxylin and eosin section showing fibrous scars (× 160). B, Haematoxylin and eosin section showing lymphorrhagia (× 300).
FIG. 10.—Case 2: histological section through nail bed showing intra-epidermal bulla filled with fibrin and capillary haemorrhage in the core (haematoxylin and eosin, × 160).

FIG. 11.—Case 2: nail bed. Section through intra-epidermal bulla, filled with fibrin and fibrinoid material (haematoxylin and eosin, × 300). Inset: the same. Fibrin preparation (P.T.A.H., × 300).

FIG. 12.—Case 2: nail bed. Section showing capillary thrombosis (arrows) (haematoxylin and eosin, × 300). Inset: the same, fibrin preparation (arrows) (× 300).
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**FIG. 13.**—Case 3: peripheral muscle. Waxy degeneration with syncytia and calcification (haematoxylin and eosin, × 300). Inset: close-up of calcified degenerated muscle fibres (× 700).


*Necropsy* (No. 53/561).—The body was that of a middle-aged obese woman. There were no obvious skin changes apart from some roughening and swelling of the cuticles of the finger-nails. All lobes of the lungs were consolidated, with some right basal adhesions. The heart weighed 440 g. with considerable left ventricular hypertrophy but no gross lesions. The alimentary system appeared normal. The kidneys showed a normal pattern. The thyroid weighed 90 g., with a pale, fleshy cut surface. The skeletal muscles appeared grossly normal.

*Histology.*—The skin of the nail bed showed marked subpapillary congestion, capillary haemorrhages, and oedema (Fig. 10). In one area there were deposits of fibrin (verified by phosphotungstic acid haematoxylin staining) and fibrinoid material in the tips of three dermal papillae (Fig. 11). This material lay extravascularly and was distinct from fibrin in the dermal capillaries, which showed some thrombus more proximally (Fig. 12). There was some disorganization of the basal layer of the epidermis, which gave the impression of the formation of a small “bulla” containing fibrin at the dermo-epidermal junction (Fig. 10).

In the skin of the arm the papillary body was flattened with subpapillary oedema.

There was congestion of the lung with chronic atelectasis and carnification with occasional squamous metaplasia. Collagen, but no elastic fibres, was present in the carnified areas (Weigert-Van-Gieson stain).

In the kidney a fair number of glomeruli showed fibrinoid necrosis as well as hyalinization of afferent arterioles. There was some reduplication of arteriolar internal elastic laminae.

Oedema and central cortical congestion were seen in the suprarenal, with areas of fine fat droplets in the zona fasciculata.
pectoris for six years. On examination there was
eodema of the lower parts of both legs, splinter
haemorrhages under the nails of several fingers, a
soft systolic apical murmur, and ulcers over both
heels, with small red infiltrated areas, up to 0.5 cm.
in diameter, on the sole of one foot and the tips of
two toes. There was remittent pyrexia. Oedema
developed in one arm, the lower back and thighs,
accompanied by weakness of the legs and trunk. The
knee jerks became unobtainable after three weeks.
The E.S.R. was 25 mm. in one hour. Blood platelets
were normal in number.
A biopsy of the vastus lateralis (N.H. 9/52) sent
for opinion to us showed waxy degeneration with
loss of nuclei and striation, and fine, droplet-like
calcification (Fig. 13); syncytia with more or less
muscular degeneration and collections of nuclei in
the sarcolemma (sarcoytes); lymphorrhagia in the
perivascular septa, eosinophils in the stroma, and
oedema of the perimysium. There were no appreciable
vascular changes. The patient died on June 22.

Necropsy.—Post-mortem examination showed
pallor of many skeletal muscles. There was an
ulcer in the second part of the duodenum, 1.5 cm.
in diameter, and some coronary atheroma. Pieces
of tissue were sent to us for histological examination.

Histology.—In addition to the changes seen in the
biopsy material, the vastus lateralis showed an area

Fig. 15.—Case 3: eyelid. Histological section.
Cap-like deposition of fibrin on oedematous
collagen (arrows) (haematoxylin and eosin,
× 300). Inset left: the same, fibrin stain
P.T.A.H., × 160). Inset right: combined
van Gieson and Wilder stain for argentaffine
fibres (× 1,350). Fine argentaffine fibres
preserved in oedematous areas without
collagen affinity (stained yellow).

Peripheral fatty infiltration
was found in the liver.
Sections from several areas
of the brain and from the
pituitary, thyroid, pancreas,
ovary, myocardium, tongue,
peripheral muscle, and ileum
showed no appreciable changes.

Suprarenal Changes
Case 3.—A man aged 69 was
admitted on May 31, 1952, to
another hospital complaining of
pains in the upper and lower
limbs. He had also had angina
of acute haemorrhagic infarction. In some of the veins the intima was thickened and incipient thrombosis with intramural haemorrhage (Fig. 14) was seen. One artery showed an intimal cushion, with fibrinous exudation into it.

The skin of the eyelid had a thin epidermis with a slight but definite horny layer, and oedema of the cutis with a marked "cap-like" deposition of fibrin (confirmed by fibrin stain—Fig. 15, inset A) on collagen fibres (Fig. 15).

A combined van Gieson and Wilder stain (Fig. 15, inset B) revealed argentaffine fibres throughout the yellow-staining, fibrinoid ground substance of the "caps." The "caps" are periodic acid positive.

The skin of the toe had a thin epidermis with a thick, horny layer, conspicuous oedema of the cutis, and occasional deposition of fibrin.

The suprarenals showed large, well-defined fibrous plaques up to 0.4 cm. in diameter in the stained section, replacing most of the parenchyma (Fig. 16). They did not contain amyloid, and were of collagen, fairly well vascularized. The capsule was thickened, oedematous, and hyaline. There were no appreciable vascular changes.

The tongue had a rough surface with sub-epidermal lymphocytic collections. The muscle showed slight, but definite, degenerative changes.

The aorta showed atheroma and round-celled collections round the vasa vasorum. The adventitial vessels showed concentric intimal thickening.

The liver showed some thickening of the peripheral portal septa.

**Progressive Diffuse Sclerosis with Focal Fibrinoid Necrosis in the Suprarenals**

**Case 4.**—A woman aged 50 was admitted complaining of blueness, coldness, and pain in the feet and hands, progressing for the past 20 years. For six years she had suffered from arthritis. Examination showed an emaciated woman, with atrophic, shiny skin over the whole body, erythematous blots on the face, and cyanosis of fingers and toes, with incipient gangrene and ulceration of the fingers. She also had signs of congestive heart failure, in which she died.

**Necropsy (46/270).**—The tonsils were dark red, ulcerated, and necrotic. There were some light pleural adhesions. The lungs had the consistency of consolidation in the lower lobe, but the cut surface showed no actual consolidation, only many haemorrhagic areas up to 2 x 2 cm. in diameter. The appearances resembled those of "rheumatic" lung. The pulmonary arteries appeared normal. The heart showed mitral stenosis with mural thrombus in the apical portion of the interventricular septum. There was also a haemorrhagic area in the posterior part of the septum, 3 x 1 cm. in diameter. The lower parts of the oesophagus and cardia were almost black and oedematous. The kidneys showed a regular granulation, with many sub- and intra-capsular haemorrhages. The cut surface showed a variegated picture of small haemorrhages and yellow flecks.

**Histology.**—The papillae of the skin of the chest wall were flattened, with marked oedema of the cutis beneath.

In the kidney there were some small cortical infarcts with central haemorrhages and intra- and extra-tubular collections of lymphocytes. The intima of medium-sized arteries was thickened concentrically. Some glomeruli showed thrombosis of afferent vessels and others fibrinoid necrosis of capillaries of the tuft (Fig. 17A and B), the latter change being rarer. Elastic stains showed that in some arterioles...
there were gaps in the elastic laminae similar to those seen in the kidney of Case 1 (Fig. 17C).

The tonsils showed sub-epithelial areas of fibrinoid necrosis around congested capillaries, in which the blood appeared to be static (Fig. 18A).

In the suprarenal there were ill-defined foci of fibrinoid necrosis scattered through the cortex (Fig. 18B). A few lymphorrhages were present.

In the tongue there was an oedematous conglutination of the connective tissue between the papillae and the muscle with lymphocytes. In addition, hemorrhages were seen round post-capillary veins. The oesophagus showed a picture similar to that in the tongue. The myocardium showed sub-endocardial haemorrhagic infarction. In the lungs there was intra-alveolar oedema and an exudate of lymphocytes into the bronchi. The liver showed severe passive congestion and the spleen marked oedema.

**Transitional Renal and Muscular Changes**

**Case 5.**—A man aged 46 was well until the onset of rheumatoid arthritis in the feet, shoulders, and knees in 1950. Butazolidin, begun in October, 1953, relieved most of his symptoms. He developed clinical signs of lesions of the fifth, ninth, and tenth cranial nerves on the right side in January, 1954. The spleen became palpable. Investigations revealed a blood pressure of 190/100 mm. Hg with papilloedema and retinal exudates. The urine contained protein. The globulin content of the blood was 6.12 g. per 100 ml., albumin 2.88 g. per 100 ml., zinc sulphate turbidity 42 units per 100 ml., and a blood urea level (terminally) of 240 mg. per 100 ml.

(One month before the blood urea had been 32 mg.

per 100 ml.) The blood showed a leucocytosis of 18,000 per c.mm. with 67% neutrophils. The maximum erythrocyte sedimentation rate was 105 mm. in one hour. Bone marrow biopsy showed one doubtful lupus erythematosus cell. The clinical diagnosis was considered to lie between acute disseminated lupus erythematosus and polyarteritis nodosa. The patient died in uraemia within two weeks of admission.

**Necropsy** (54/204).—The body was that of a well-nourished man. The brain appeared normal externally. The lungs showed some grey hepatization, and there was some fibrous pleurisy. The heart showed hypertrophy of the left ventricular wall. The caecum showed a small mucosal slough. The kidneys weighed 215 (right) and 275 (left) g. respectively. The capsules stripped easily, leaving smooth surfaces showing occasional petechiae and some yellowish flecks. The cut surface was of brownish red, and the corticomedullary pattern was almost completely lost, without focal infiltrations or haemorrhages and without arterial prominence. The pancreas weighed 160 g. and had a firm nodular consistency. Two areas of necrosis were present, the larger, measuring 3 × 2 × 0.5 cm., being in the head; it was sharply defined, with a yellowish homogeneous surface and an adjacent area of haemorrhagic necrosis which seemed grossly to contain a thrombosed artery. The smaller infarct measured 1.5 × 1 × 1 cm. and was situated at the junction of the left and middle thirds; it showed a similar cut surface, without haemorrhage. There was no adjacent fat necrosis. The skeletal muscles and other major viscera showed no gross abnormalities.
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**Histology.**—In the glomeruli the most striking change was a focal fibrinoid necrosis of the tufts, with occasional “wire-loop” formations due to picking out of the basement membranes. Proliferative glomerulitis and capsulitis were not seen. There were a few hyalinized glomeruli. The tubules showed patchy necrosis, often severe and hyaline in appearance, occasionally with a collection of neutrophils. The lumina contained casts which were often brightly eosinophilic and positive for fibrin (P.T.A.H. staining). The vessels showed various lesions, the most conspicuous change being a fibrinoid necrosis of afferent glomerular and larger arterioles, with which a thrombosis was sometimes associated. In the periphery extensive hyaline and thrombotic lesions were often associated with subcapsular acute infarcts. The larger arteries showed hyperplastic intimal and medial sclerosis. There was moderate interstitial oedema with occasional lymphocytic collections. Staining for amyloid was negative.

Large areas of recent infarction, with peripheral neutrophil reaction, were seen in the pancreas. There were areas of haemorrhage with necrosed vessels, one of which contained thrombus. Arteritis was not seen. Many vessels showed hypertensive changes.

Some of the sections of peripheral muscle showed degeneration and fragmentation of muscle fibres, with cellular ingestion of fragments in the sarcolemmal tubes. There was a general increase of sarcolemmal nuclei and also some focal lymphorrhages with a few plasma cells.

Fibrinous pleurisy, with an organizing oedema and incipient bronchopneumonia in the parenchyma, was found. Many siderophores were present in the alveoli.

The caecum showed an infarcted mucosa associated with thrombosed vessels. Serosal vessels showed very severe intimal sclerosis.

Sections of the bone marrow, liver, spleen, thyroid, small intestine, suprarenal gland, and retina showed...
no significant changes apart from those of hypertension. The Gasserian ganglia showed focal demyelination.

**Dermatomyositic Changes Resembling Experimental Findings**

Case 6.—A woman aged 37 was admitted to another hospital with an obscure pyrexia, thought to be due to pneumonia. Soon after admission solid subcutaneous oedema of the arms and thighs was noted. A clinical diagnosis of dermatomyositis was made and cortisone was given, with rapid improvement. A biopsy of the skin and biceps was sent to us for opinion.

**Histology.**—The sections showed a variety of characteristic changes.

The sarcolemmal tubes were filled with fairly large polygonal cells with somewhat hyperchromatic, round, elliptic, or spindly nuclei. These cells had engulfed or clustered round fragments of necrotic muscle (Fig. 19A). Sometimes they seemed to lie in deep lacunae or else form round muscle bundles (Fig. 19B). Besides these there were peripheral remnants of muscle tissue adherent to the sarcolemmal wall, leaving a central space ("pseudo-vessels").

Synctia, mostly forming seans along degenerating muscle fibres, were found.

Polymorphs, including a few eosinophils, formed micro-abscesses replacing parts of muscle bundles within the confines of the sarcolemma (Fig. 19C).

The stroma, which contained a few plasma cells, some capillary haemorrhages, a few polymorphs, and somewhat juicy fibroblasts (Fig. 19D), was thickened and oedematous.

The papillary body, with marked oedema of the cutis, was flattened.

**CLINICAL AND HISTOLOGICAL CONCLUSIONS**

**Diagnosis**

Looking back at the descriptions of these cases, the first point to be discussed is diagnosis.

In Case 1 the patient, developing dermatomyositis 11 years before death, died of a disease which accords with the descriptions of generalized scleroderma or progressive diffuse sclerosis.

In Case 2 the diagnosis was doubtful. The clinical picture could equally well have fitted a case of acute disseminated lupus erythematosus, a rash often being absent in this condition. Clinically the parallel is close; in both disseminated erythematous and dermatomyositis there is fever, muscular weakness, oedema of the eyelids, and lesions around the cuticles of the nails. Pleurisy is perhaps more in favour of lupus erythematosus, while the absence of anaemia and leucopenia and the normal serum proteins are against it. It is unfortunate that lupus erythematosus cells were not searched for.

In Cases 3 and 6 the clinical diagnosis was consistent with subacute dermatomyositis, which was confirmed by biopsy.

Case 4 was clinically one of scleroderma.

In Case 5 the clinical diagnosis of polyarteritis nodosa was not borne out by the histological findings. These included "wire loop" glomeruli and capillary and arteriolar thromboses in the kidney, changes suggestive of disseminated lupus erythematosus. It should be added that a doubtful lupus erythematosus cell was found in the bone marrow, but lupus erythematosus cells have been observed by Cohen (1954) in rheumatoid arthritis and can therefore not be considered diagnostic. Finally, the striking reversal of the albumin: globulin ratio, such as in this case, is not normally seen in polyarteritis nodosa, and supports the diagnosis of disseminated lupus erythematosus.

**Histology of the Affected Organs**

**Lungs.**—These were affected principally in Case 1. According to Ellman and Cudkowicz (1954) and Evans and Parker (1954) the pulmonary changes recorded in scleroderma are diffuse fibrosis, fine nodulation, cyst formation, and pleural fibrosis. Getzowa (1945), who gives a detailed description of these changes, shows a photograph of the cystic lesions, resembling a "honeycomb" lung. Other authors lay stress on the diffuse fibrosis without macroscopic changes (Weiss, Stead, Warren, and Bailey, 1943). The appearance of the right lung in the present case differs considerably from those already described—a picture of thick, fibrous bands with large fibrous plaques obliterating most of the parenchyma. Histologically, the striking feature is the presence of much elastic tissue in the fibrous areas, in contrast to Getzowa's cases, in which elastic fibres had disappeared from the fibrous areas, indicating a probable sequence of collapse followed by fibrosis. The small cysts are produced by a compensatory emphysema. The fibrinoid lining of the alveoli was described by Getzowa and resembles that seen sometimes in the so-called rheumatic lung (Hadfield, 1938). It has been pointed out since that these membranes are not specific of rheumatic aetiology. We observed several classical examples in cases with acute terminal circulatory failure, e.g., after thoracoplasty. Nevertheless, the frequency of such changes in acute rheumatic diseases, especially when combining with organizing changes ("Masson's
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Kidney.—The main question in respect of this organ is the incidence and specificity of arteriolar fibrinoid necrosis in scleroderma, as described by Moore and Sheehan (1952), of “wire loop” glomeruli in disseminated lupus erythematosus, as described by Klemperer, Pollack, and Baehr (1941), and of gaps in the elastic lamellae as seen in burnout polyarteritis nodosa (Pagel, 1951).

The “scleroderma” change was absent in Case 1, present in Cases 2 and 4. Whereas Case 1, in spite of its absence, was a typical example of diffuse scleroderma (“visceral sclerosis”), Case 2, in which it was present, was not. The “L.E.D.” change was found only in Case 5 only, in which it was established that the diagnosis of disseminated lupus erythematosus, against the clinical diagnosis of polyarteritis nodosa, as it can for practical purposes be considered characteristic of disseminated lupus erythematosus (Allen, 1951).

The “polyarteritis nodosa” change occurred in Cases 1 and 4, which were both of scleroderma.

Two other less characteristic vascular changes were capillary and arteriolar thromboses, as seen in Case 5.

Of non-vascular kidney changes, the area of fibrinoid necrosis in the stroma is of interest, for such extravascular renal foci do not seem to have been observed previously in scleroderma, although they are well recognized in the skin (see Case 3).”

Liver and Pancreas.—The liver was grossly changed in Case 1 only (a case of scleroderma). Beerman (1948) remarks that little has appeared in the recent literature on hepatic involvement in scleroderma. This remark still holds good. Brock (1934) noted in his Case 4 an increase of periportal connective tissue. Perdomo de Fernández, Ravera, and Piovan (1951) performed a liver biopsy on a man aged 43 with scleroderma, whose liver was palpable two fingerbreadths below the costal margin. He comments that few cases of scleroderma have hepatic symptoms and that the abdomen is often difficult to palpate because of the rigidity of the wall. Histological examination showed foci of sclerosis consisting of whorls of collagen fibres showing some hyaline degeneration. There were also some collections of round cells and fibroblasts. Both lesions were accompanied by discrete hepatocellular degenerative lesions—fatty changes, with bile pigment deposits. Harvier and Bonduelle’s case (1947), a woman aged 43, showed radiologically calcification of the hepatic capsule. Biopsy was not performed. Goetz describes the “deposition of a peculiar amorphous material in a cirrhotic liver of an unusual type,” but gives no further details of these cases. Beigelman et al. (1953) describe centrilobular hepatic fibrosis in their Case 9. The findings in the present case seem to correspond fairly closely with those of Perdomo de Fernández et al., the portal changes being more advanced with little parenchymal damage. In Harvier and Bonduelle’s case there was probably a similar capsular fibrosis, in which calcium deposits had been laid down. It seems then that the tendency to fibrosis extends to the portal tract and capsule of the liver in some cases.

The pancreas was involved in Case 5, in which there was evidence of malignant hypertension. Pancreatic necrosis due to arterial thrombosis in malignant hypertension has been reported (Pagel and Woolf, 1948) and we have also seen recanalized thrombosis without necrosis of the pancreas in a case of malignant hypertension. The lesion in the caecum in the present case was probably of a similar nature.

Skin.—Lesions of scleroderma were found in Case 1 (scleroderma), in Case 2 (a transitional case between dermatomyositis and disseminated lupus erythematosus), in Case 3 (dermatomyositis), and in Case 4 (dermatomyositis). Nail bed changes were seen in Case 2 (transitional between dermatomyositis and disseminated lupus erythematosus).

Lesions of the nail cuticles in dermatomyositis are well recognized (Keil, 1942) and may be an early symptom. Searching through the cases referred to by Keil and through subsequent literature, we have been unable to find any account of the histological appearance of these lesions and so are unable to compare our own findings with any

Fig. 20.—Case 2A: naked-eye appearances of nail bed changes in lupus erythematosus disseminatus. Splinter haemorrhages in nails, in addition to multiple petechiae, swelling, and blisters of nail cuticulae.
The necrosis. Fibrinoid seems (1935) quitous hallmark we found no but particular Lever, 1949). of result combination of lupus the of bacterial thrombotic micro-angiopathy as seen picture of 4--ysts Baehr, Klemperer, and Schifrin, 1936) or in subacute bacterial endocarditis (Pagel, 1949) and thrombotic micro-angiopathy (Symmers, 1952), or else that of extravascular fibrinoid necrosis as seen in collagen disease (disseminated lupus erythematosusdermatomyositis). In polyarteritis nodosa, the classical collagen disease of blood vessels, no evidence of primary thrombosis can be found and sub-endothelial hyaline deposition, said to precede acrothrombosis (Gore, 1950), differs from the early polyarteritis changes (Pagel, 1951).

Thrombosis observed in the same area is not incidental, however. This is shown by its occurrence in a similar setting in the skin changes of disseminated lupus erythematosus. As an example the case may be briefly described of a man aged 62 years (Case 2A) who died after a five months' illness suggestive of disseminated lupus erythematosus — erythematous rash, joint pains, and progressive loss of weight.

No lupus erythematosus cells were found in the bone marrow and a skin biopsy was not helpful. Terminally the rash became bullous and there were swelling, cyanosis, and epidermolysis of the nail folds (Fig. 20). There was no response to treatment with A.C.T.H. and cortisone. The post-mortem examination (P.M. 54/265) showed grossly only a basal bronchopneumonia and a diffusent splenic pulp. Significant histological changes were restricted to the skin and nail fold, and were similar at both sites. The epidermis was flattened and atrophic, more so in the skin than in the nail fold, with liquefaction degeneration of the basal layer (Fig. 21). The corium was markedly oedematous with capillary congestion. Some of the dilated capillaries contained fibrin thrombi (Fig. 21). Small haemorrhages had occurred in some of the papillae. In addition, there was fibrinoid degeneration in the deeper corium. There was a moderate lympho...
VISCERO-CUTANEOUS COLLAGENOSIS

**Fig. 22.**—Rabbit muscle. Intramuscular injection of 0.1 ml. of a specific anti-muscular anti-serum. Three aspects of the histological changes, experimental anaphylactic myositis (Kallós and Pagel, unpublished). Fragments of muscle surrounded by "sarcocytes." Top left, × 50. Top right, × 200. Bottom, × 300.

cytic infiltration of the corium, sometimes localized round the appendages.

These changes are fairly characteristic of acute lupus erythematosus, in which we would like to include capillary thrombosis, although Klemperer *et al.* (1941) on the basis of a much more extensive material considered thrombosis to be uncommon in this disease. We regard the thrombosis to be independent of vascular damage, which was absent in the walls of thrombosed vessels.

It should be mentioned, however, that it is the combination of capillary thrombosis and fibrinoid necrosis rather than their occurrence singly which seems to be characteristic. For, in one of three control nail beds selected from random post-mortem material (Nos. 54/182, 54/183, 54/184), a case of coronary thrombosis in a male aged 74, a small fresh, fibrin thrombus was seen in an intrapapillary vessel, whereas no appreciable changes were seen in the two other control cases.

In connexion with the aortothrombosis and capillary haemorrhages seen in the present case, it should be noted that, according to Keil, gross haemorrhages may occur in the nail beds in disseminated lupus erythematosus, and splinter haemorrhages in the nail beds are a feature of dermatomyositis.

A feature worthy of comment is the fibrinoid "caps" lining bundles of collagen fibres in the eyelid. A combined van Gieson-Wilder stain shows that the "caps" consist not of fibrin alone but of a non-collagen ground substance in which argentaffine fibres are present. It is tempting to assume that this ground substance was originally collagen in a state of fibrinoid degeneration, and to compare the presence of argentaffine fibres with that typically observed in rheumatic and para-rheumatic conditions (Klinge, 1933; Pagel, 1951).

**Muscle.**—Muscle changes were absent in Cases 2 (transitional case) and 4 (scleroderma).

Of the others, Case 5 (disseminated lupus erythematosus) showed myositis changes which will be discussed in the final comment. In connexion with this case, it should be remembered that lesions of striped muscle are not uncommon in rheumatoid arthritis (Cruickshank, 1952).

The classical myositis changes were seen in Cases 1, 3, and 6. The changes in Case 6 indicate acute episodes superimposed on a more protracted.
though extensive, destruction of muscle. The acute changes are shown by micro-abscesses replacing parts of necrotic muscle bundles and by the perimysial haemorrhages. Chronic changes are shown by extensive collections of cells engulfing small fragments of necrotic muscle within the confines of the sarcolemmal tubes. The first impression is of inflammatory cells in vessels, but a closer study soon shows that the spaces are really sarcolemmal tubes, partly empty, partly filled with special cells, namely the sarcoytes described by Glücksmann (1934) in the metamorphosis of amphibia. These cells should be regarded as the associates, or perhaps the precursors, of the syncytia, the well-known products of muscular regeneration. Apart from the polymorphs, the inflammatory cells, notably plasma cells and macrophages, are rare though present here and there in the stroma. These pictures invite a comparison with the experimental findings by Kallós and Pagel (1937) produced by injecting a muscular antiserum into rabbit muscle. Here, too, fragments of muscle, often within the sarcolemma tubes, were found. These formed, together with distinctly eosinophilic sarcoytes, small granulomata and syncytia comparable to those seen in the present case (Fig. 22).

Suprarenals and Tonsils.—The extensive focal fibrosis of the suprarenal cortex seen in Case 3 seems to be a noteworthy feature. From the soft, oedematous nature of the fibrous tissue we would suggest that the change is related to the disease and is not accidental or congenital. In view of the suprarenal changes found in Case 4—foci of fibrinoid necrosis—it is not unlikely that the focal fibrosis represents the terminal stages of such necrotic foci. In Case 4 areas of focal fibrinoid necrosis were also found in the tonsil.

DISCUSSION

It can be seen from the discussion of the cases that the differential diagnosis of dermatomyositis, progressive diffuse sclerosis, and disseminated lupus erythematosus can be a matter of the utmost difficulty. Case 3 is the most straightforward and one can with fair confidence diagnose it as a subacute dermatomyositis, both clinically and histologically. With Case 1, however, we encounter difficulty. Are we to call it chronic dermatomyositis with visceral changes or progressive diffuse sclerosis supervening upon a former attack of dermatomyositis? The continuity of the disease since the original onset 11 years before death would favour the former diagnosis, but the visceral lesions were certainly those of a progressive diffuse sclerosis. Nor is histology helpful. Brock states that the late stages of the two diseases can be distinguished because in dermatomyositis, "inflammatory infiltrations and a variety of degenerations of the parenchyma of muscles are outstanding features to the end." From his description, it seems he is referring to the round-celled infiltrations of muscle now known as "lymphorrhagia." They are also now known to be non-specific (Cruickshank, 1952; Russell, 1953). Feuer- dental (1940) was able to demonstrate lymphorrhages in muscle in a case of scleroderma and concluded that "the histological changes in skin and muscle in generalized scleroderma and dermatomyositis show no essential difference." With this latter view we agree. We also feel that either chronic dermatomyositis has the visceral lesions of progressive diffuse sclerosis or that dermatomyositis merges imperceptibly into it. We therefore conclude that Case 1 is an instance of dermatomyositis terminating in progressive sclerosis.

Where then does Case 2 stand diagnostically? Clinically it appeared to be a case of dermatomyositis, but no muscular changes were found either during life or after death when the only relevant change was in the nail bed. Reports in the literature indicate the difficulties of other authors (Bradley, Drake, and Mack, 1951; Madden, 1950). Out of 21 biopsies in Madden's cases of disseminated lupus erythematosus, six showed nodular myositis. Fifty per cent. of them showed lupus erythematosus cells in marrow examination. He concluded that the "muscle changes in dermatomyositis and disseminated lupus erythematosus are not specific" and even discourages muscle biopsy as a major procedure for a very ill patient, recommending rather the examination for lupus erythematosus cells, despite the low incidence of positive results in the latter investigation. Histological evidence of the non-specific character of the muscular changes in dermatomyositis had already been adduced by Pagel et al. (1949). Degos, Garnier, Darnis, and Vissian (1949) described a case of subacute lupus erythematosus with dermatomyositis. Of Spühler and Morandi's (1949) two cases, the first showed diffuse scleroderma with Raynaud's syndrome, clinical dermatomyositis, and a Libman-Sacks endocarditis. They concluded that disseminated lupus erythematosus, dermatomyositis, and scleroderma are differing forms of reaction to a non-specific infection. In Klein's (1953) case of acute dermatomyositis the muscle biopsy (reported by us) was negative, but this was not considered to exclude dermatomyositis. The case bore a close resemblance clinically to
our Case 2, but showed no cuticular changes and had an erythematous rash. Retrospectively it is difficult to exclude also the possibility of an acute disseminated lupus erythematosus in Klein's case, which responded to cortisone. Later the patient developed a condition resembling rheumatoid arthritis. We suggest therefore that our Case 2 combines clinical features of dermatomyositis with histological features of progressive diffuse sclerosis and disseminated lupus erythematosus.

Case 5 illustrates a further aspect of the clinical diagnostic difficulty. Polyarteritis nodosa was considered here because the one possible lupus erythematosus cell seen was thought to be a "tart" cell rather than a true lupus erythematosus cell (the ingested nuclear fragment was sharply defined and retained a recognizable chromatin pattern) and was therefore disregarded. As the "tart" cell is supposed to be a precursor of the lupus erythematosus cell and as neither of these cells occurs in polyarteritis nodosa, this disregard seems to have been unjustified. The histological findings quite definitely excluded polyarteritis nodosa. Many of the changes found, necrotizing arteriolitis, capillary thrombosis, pancreatic necrosis, and myositis, are also found in other syndromes, and we are left with the distinctive "wire-loop" phenomenon. This case had features in common with progressive diffuse sclerosis, dermatomyositis, and disseminated lupus erythematosus.

Case 6 shows that dermatomyositis is primarily a degenerative and not an inflammatory lesion of muscle. The majority of the cells seen are young myogenic elements, probably sarcolemma cells, which engulf and cluster around fragments of necrotic muscle. They seem to be related to the syncytia seen in a similar site, at or lining, the sarcolemma and fragments of necrotic muscle. Inflammatory cells are secondary invaders; in the present case, polymorphs, including some eosinophils, form an addition somewhat unusual in dermatomyositis, whereas plasma cells, a conspicuous feature in some cases, are very scarce. Lymphocytes commonly seen in the form of "lymphorrhagia" are also scanty.

In none of these cases were the haematoxophil bodies said to be characteristic of disseminated lupus erythematosus (Klemperer, Gueft, Lee, Leuchtenberger, and Pollister, 1950) found. They were, however, present in a case previously reported by Pagel (1951, Fig. 7). The latter case showed a clinical picture of polyarteritis nodosa with consistently high eosinophilia, polynuiritis, and fleeting pulmonary infiltrations. An excised skin nodule showed extensive deposition of granules with intense affinity for haematoxylin—the picture of haematoxophil bodies. An additional feature was the distinct foreign-body reaction of tuberculoid type which they elicited. This observation of haematoxophil bodies in a case of polyarteritis nodosa confirms the findings of Worken and Pearson (1953) that these bodies need not be invariably associated with disseminated lupus erythematosus.

The distinctive features of the present series are summarized in Table I.

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
</tr>
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<tr>
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<td>+</td>
<td>0</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Muscle changes resembling experimental myositis</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Skin changes resembling dermatomyositis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Skin changes resembling scleroderma</td>
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<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
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<td>+</td>
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<tr>
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<td>0</td>
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<td></td>
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</tbody>
</table>

It would appear, then, from the increasing number of reports in the literature and from our own experience, that the clear-cut diagnosis of diseases of the collagen group (notably acute dermatomyositis and disseminated lupus erythematosus) is becoming progressively undermined, from both the clinical and histological points of view.

**SUMMARY**

The clinical and histological features of dermatomyositis, progressive diffuse sclerosis, and disseminated lupus erythematosus may overlap sufficiently to render differential diagnosis impossible in some cases. We suggest that such intermediate forms be grouped under the name of "viscero-cutaneous collagenosis."

From the material presented, the view that dermatomyositis and scleroderma are stages of the same disease is confirmed.

The changes in the nail fold, clinically regarded as characteristic of disseminated lupus erythematosus and dermatomyositis, are a clearly recognizable histological entity, consisting of patchy extravascular fibrinoid necrosis associated with capillary thrombosis—an unusual combination of collagen disease and acronecrosis.
One of the cases of dermatomyositis presented shows muscular changes strikingly similar to those reproduced experimentally by means of an antimuscular serum.

Focal necrosis and focal fibrosis in the suprarenal are thought to represent the early and end stages of a process which can be associated with dermatomyositis.

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REFERENCES