whenever feasible. Failing this, we regard high C.I. readings after completion of radical treatment (allowing a three-months period to elapse in the evaluation of pre-menopausal cancer patients after radiotherapy) as suggestive of persistence of neoplastic disease, provided, of course, that no oestrogens had been administered. A low C.I. reading during the observation period after completion of treatment is regarded as a favourable prognostic omen only in cases in which pre-treatment C.I.s had been high.

It is not yet established whether our original hypothesis, that malignant tissue is capable of oestrogen production, is correct. In a few of our own cases urinary oestrogen estimations have been undertaken, and we are greatly indebted to Dr. Ian Ferguson Sommerville for kindly carrying out these investigations at the Endocrine Laboratories of the Institute of Obstetrics and Gynaecology in the Chelsea Hospital for Women. In the few patients investigated urinary oestrogen excretion was high and compared well with the high C.I. readings. However, these data are as yet incomplete and no conclusions can be drawn from them, although other authors (Young *et al.*, 1957) showed similar good correlation on a larger material.

The frequency with which a high C.I. reading is associated with malignant disease in the female genital tract is significant enough to suggest the use of it as a test for cure.

Summary and Conclusions

C.I. estimations in patients who had received radical treatment for malignant disease in the genital tract seemed to be of great diagnostic help in the recognition of failure of response or in the detection of early recurrence. Accurate forecasts, relying solely on C.I. readings, had been made in 94.8% of 165 cancer follow-up patients. Nine patients with a poor cytological prognosis and no clinical signs of recurrence are still under observation. The cytological prognosis was incorrect in eight patients with persistent or recurrent disease and low C.I. readings. The possible causes of this prognostic error are discussed.

The technique of C.I. estimation is easy and can be learned in a short time. We suggest that C.I. estimations should be included in routine cytological cancer follow-up investigations in view of the important implication of this test.

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"Most foundation trustees and executive officers find themselves sooner or later involved in a discussion of the relative merits of small versus large grants. Large grants, of course, are more spectacular and in a way more satisfying because of the splurge they make. Then, too, a large grant avoids the temptation of scattering the foundation's shots too widely, with the possibility of dissipating the effectiveness of its program. Small grants have in their favor, especially for the smaller foundations, the advantage of helping in areas not covered by the large grants—areas where a relatively small amount of money will make a larger project of greater value."—1956-57 Annual Report of the John and Mary R. Markle Foundation, 511, Fifth Avenue, New York, 17.

SYSTEMIC SCLERODERMA WITH PORTAL HYPERTENSION

BY

R. J. CALVERT, M.D., Ph.D., M.R.C.P.

B. BARLING, M.D., F.R.C.P.

M. SOPHER, M.B., M.R.C.P.

AND

M. FEIWEL, M.B., M.R.C.P.

*From the North Middlesex Hospital and
St. James' Hospital, London*

In systemic scleroderma ("progressive systemic sclerosis," Goetz, 1945), lesions of the hollow gastro-intestinal tract may occur at any site (Beigelman *et al.*, 1953; Cullinan, 1953; Leinwand *et al.*, 1954; Wiener, 1955; Piper and Helwig, 1955; Talbott and Ferrandis, 1956). Since, apart from one unelaborated report (Massimo, 1954), there appears to be no record of concurrent systemic scleroderma and portal hypertension, we describe here this association in two patients. Both had hepatic fibrosis, splenomegaly, and oesophageal varices with episodes of brisk haematemesis. One patient survived, following surgical relief of the effects of portal hypertension. The other, who had no operation on the portal system, died within one week of readmission to hospital for recurrent haematemesis.

Case 1

A housewife aged 31 was first admitted to St. James' Hospital for investigation in July, 1951. For two years she had felt increasing tightness of the fingers, which occasionally turned blue and cold. Although she had always been dark-skinned, pigmentation had increased in the past year. Her vitality, appetite, weight, mastication, and deglutition were all unimpaired. Menstruation was normal. The family, personal, and remote past histories were non-contributory.

Examination revealed an asthenic build (weight, 7 st. 8 lb.; 48.1 kg.), melanosis mainly sparing the face and not involving the mouth, contracture of the ocular, malar, and oral regions, and moderate sclerodactyly. The respiratory and cardiovascular systems were normal. The blood pressure was 120/85 mm. Hg. The liver and spleen were enlarged, each to about 2 cm. below the costal margin. There were no relevant neurological signs. The breasts and pubic hair appeared normal but the axillary hair was scant. No cataract, calcinosis circumscripta, telangiectasia, palmar erythema, or anterior abdominal collateral venous pattern was detected.

Investigations.—Haemoglobin level, 66% (9.8 g./100 ml.); erythrocyte count, 3,600,000/c.mm.; colour index, 0.91. The leucocyte and platelet counts were normal. The bone marrow was normoblastic. The E.S.R. was 68 mm. (Westergren) in one hour. The serum sodium, potassium, calcium, chloride, and inorganic phosphate values were normal. The blood urea was 41 mg./100 ml. Although the serum-bilirubin level was normal (0.2 mg./100 ml.), the results of other conventional hepatic tests were abnormal—that is, serum proteins, 8.75 g./100 ml. (albumin 4.15 g., globulin 4.6 g.); thymol turbidity, 15 units; and serum alkaline phosphatase, 30 K.A. units/100 ml. The 17-ketosteroid excretion was low (4.4 mg. a day). A skin biopsy showed the characteristic histology of scleroderma. The radiological findings were: chest, normal; barium swallow, incorporating the Trendelenburg position, normal;

hands and feet, absorption of the distal ends of phalanges but no calcinosis. The patient was in hospital for one month.

In November, 1951, she was readmitted and given 300 mg. of cortisone on the first day, 200 mg. on the second day, and then 100 mg. daily for two weeks, followed by a week each of 75 mg. and 50 mg. daily. Related improvement was entirely subjective—namely, increased mobility of hands and face.

In April, 1952, she was again admitted because of three episodes of haematemesis in the previous 10 hours. A fourth incident occurred a few hours later. The only fresh clinical features were undue pallor and evidence of melaena from rectal examination. The haemoglobin level remained low (6.4 g./100 ml.) after the transfusion of 3 pints (1.7 litres) of blood. Next day gastroscopy revealed two large oesophageal varices but no gastric lesion.

On the third day haematemesis recurred and operation was necessary. Through a left abdomino-thoracic incision a large adherent spleen and a fine hepatic cirrhosis were seen. There was no ascites. The portal venous pressure was 390 mm. of water. After freeing the lower 5 cm. of the oesophagus and the upper end of the stomach of all vascular connexions, subcardiac porto-azygos disconnection by gastric transection (Tanner, 1950, 1954) was carried out. As the spleen was adherent it was removed to facilitate access to the cardiac region. A liver biopsy was not made. The splenic histology was identical with that of congestive splenomegaly. The patient was again in hospital for one month.

Follow-up.—There had been no recurrence of haematemesis. The hepatic enlargement and the results of hepatic tests were virtually unchanged, while no symptoms or signs attributable to the hepatic fibrosis had appeared. A post-operative barium swallow (September, 1953) showed no oesophageal varices or sclerodermatous involvement, while further barium studies showed no gastric, small-intestinal, or colonic abnormality. Nor was calcinosis apparent radiologically. The acroscleroderma, Raynaud phenomenon, and pigmentation showed no appreciable progression. The only fresh features were angular stomatitis and xerophthalmia. The former appeared in 1953 and did not respond to a course of riboflavine; the latter sign did not seem to be due to coexistent Sjögren's disease, since other features were lacking and the Schirmer test showed lacrimal secretion.

Case 2

A housewife aged 53 was referred to the North Middlesex Hospital in December, 1953. For eight months she had passed about six motions daily. The stools resembled aluminium paint (as in the "silver stool" sign of Thomas) (Ogilvie, 1955), and neither associated blood nor mucus had been observed. Spells of diarrhoea had occurred since her early twenties. Raynaud's phenomenon began when she was 20, while telangiectasia of the face had been present for about 10 years. In the previous 18 months she had received several short courses of iron intramuscularly for a rather persistent anaemia. Ulceration of the legs had occurred intermittently for one year. Her appetite was good and she had no dysphagia.

In January, 1954, she was admitted for investigation of diarrhoea. Examination revealed a spare build (weight, 7 st. 12 lb.; 49.4 kg.); facial pallor; numerous telangiectatic lesions of the face and one on the tongue; tightly stretched skin over the hands, wrists, malar regions, and feet; scarred finger-tips; moderate digital clubbing but no abnormality of the respiratory system; a haemic murmur and systolic hypertension (170/90); hepatic and splenic enlargement, each to about 1 cm. below the costal margin; varicose eczema, but no oedema, of the legs.

Investigations.—Haemoglobin level 67% (9.9 g./100 ml.); erythrocyte count, 3,550,000/c.mm.; colour index, 0.93. The leucocyte and platelet counts were normal. The E.S.R. was 56 mm. (Westergren) in one hour. The serum bilirubin was

1 mg./100 ml.; serum proteins, 4.7 g./100 ml. (albumin 3 g.); thymol turbidity, 6.5 units; and serum alkaline phosphatase, 81 K.A. units/100 ml. The oral glucose-tolerance test showed a "flat" curve (fasting value of 68 mg./100 ml. and successive half-hourly levels of 120, 115, 104, and 78 mg./100 ml.). Stool examination showed occult blood in each of three specimens but no organism of the *Salmonella* or *Shigella* group was isolated.

Chest x-ray examination showed left ventricular enlargement and clear lung fields. Barium studies disclosed loss of colonic haustrations and redundancy in the sigmoid segment as the only abnormalities. Oesophagoscopy down to the level of the gastric mucosa revealed no abnormality.

Exploratory laparotomy was undertaken to exclude a colonic neoplasm. The liver was found to be granular but not nodular. The spleen was firm and enlarged to 9 in. (23 cm.) in its long axis. A few ounces of ascitic fluid was present. The mesenteries of the small and large bowel contained haemorrhagic lymph nodes. The colon was dilated but not hypertrophied, and showed a general milky opacity and a complete loss of haustrations. The stomach, gall-bladder, small bowel, and appendix all appeared to be normal.

Biopsies of the liver and of a haemorrhagic lymph node were taken. The hepatic histology showed a distinct cirrhosis with hyperplasia and much round-cell infiltration. The lymph node revealed "sinus catarrh."

Frequently loose stools persisted. The patient was in hospital for three months.

In September, 1954, she was readmitted because of haematemesis. On admission the haemoglobin level was 3 g./100 ml., so blood transfusion was promptly begun. Pronounced shock, moderate oedema, and slight icterus were the only fresh clinical findings. After transfusion of 6 pints (3.4 litres) of blood the haemoglobin level was 5.9 g./100 ml.

The results of hepatic tests showed as the main changes a raised serum bilirubin level (2.1 mg./100 ml.) and lowered serum alkaline phosphatase (57 K.A. units/100 ml.). A barium swallow revealed a marked diminution and peristalsis, with dilatation but no constriction of the oesophagus. A barium meal with follow-through showed no gastric or duodenal lesion but many dilated coils and a few areas of constriction in the small intestine, where the mucosal pattern, especially of the jejunum, was coarse. A daily dose of 100 mg. of cortisone for two months produced no improvement in the acroscleroderma or in the colitis, and "moon-ing" of the face appeared. This treatment was therefore suspended for three weeks, then a daily dose of 50 mg. was given for one month. The supportive treatment was a high-calorie, high-vitamin, low-residue, low-salt diet; mistura kaolini et morphini; daily retention enemas of 0.5% tannic acid; and intramuscular injections of iron. However, on discharge from hospital after a stay of five months the only evidence of improvement was the disappearance of icterus and a haemoglobin level of 70% (10.4 g./100 ml.).

The patient was readmitted in July, 1955, on account of recurrent melaena. Her haemoglobin level had fallen to 5.5 g./100 ml., and 7 pints (4 litres) of blood was transfused. Impaired biliary excretion was revealed by intravenous cholangiogram, in which biligradin produced no outline of the hepatic ducts or gall-bladder. A fat-absorption test gave a value of only 70%, which was in keeping with the earlier demonstration of a "flat" glucose-tolerance curve. Steatorrhoea was also separately confirmed by a faecal fat value of 41.2 g./100 g. of dried stool. No special treatment was prescribed for the steatorrhoea. On discharge from hospital after a stay of 11 weeks the haemoglobin level was 60% (8.9 g./100 ml.).

The patient was again admitted in September, 1955, because of recurrent haematemesis and melaena. Icterus and oedema were minimal. There was no ascites. Her haemoglobin value was 30% (4.5 g./100 ml.), but rose to 43% after the prompt transfusion of 3 pints (1.7 litres) of blood.

Numerous investigations, some merely repetitive, were made. For convenience, only a few of these are mentioned. Blood investigation showed no L.E. cells, a negative Coombs test, and a normal red-cell osmotic fragility curve. The blood-urea level was 33 mg./100 ml. Hepatic tests showed: serum bilirubin, 2.2 mg./100 ml.; prothrombin index, even without parenteral vitamin K administration, 100%; thymol turbidity, 15 units; serum alkaline phosphatase, 70 K.A. units. The electrocardiogram was consistent with myocardial involvement. X-ray examination of the hands showed speckled calcinosis and distal erosion of the terminal phalanges as in the Thibierge-Weissenbach syndrome. A barium swallow revealed no oesophageal varices, but the oesophagus showed absence of peristalsis, slight general dilatation, and an irregularity of the lower end, which was interpreted as a sequel to oesophagitis, since considerable oesophageal reflux occurred in recumbency. The barium-meal pattern was still normal. During the barium enema it was observed that the colon was dilated, toneless, and almost devoid of haustrations. After evacuation, following complete colonic filling, no area of normal mucosal pattern could be demonstrated, the colonic wall appearing fluffy as in colitis. Further study of the colonic mucosa by sigmoidoscopy showed that the sigmoid segment was red and granular, and bled readily, but no discrete ulceration could be demonstrated.

On April 18, 1956, the patient was discharged with a fairly stable haemoglobin level of 60% (8.9 g./100 ml.). Despite weekly injections of iron intramuscularly the blood film still showed signs of a marked iron deficiency.

In May, 1956, the patient was admitted to the Whittington Hospital following a further haematemesis and the continued passage of loose blood-stained motions. The haemoglobin value was 20% (3 g./100 ml.) and the blood pressure 80/40 mm. Hg. Clinical improvement followed the transfusion of 5 pints (2.8 litres) of blood. Her haemoglobin level was 57% (8.4 g./100 ml.), but the blood urea had risen to 75 mg./100 ml. A few days later, icterus deepened and she lapsed into fatal coma.

Post-mortem Findings

Examination showed a waxy pale woman, 5 ft. 6 in. (167.5 cm.) in height. The skin of the hands, wrists, neck, and ankles was thickened. Many transfusion scars were seen. She had congestion of the brain and meninges, the lungs were grossly oedematous. The heart was enlarged to the left, its valves were healthy, and the coronary arteries were patent, but the myocardium was extremely pale and soft. The lower oesophagus was dilated and showed several varices. The stomach was dilated and grossly deformed by adhesions to the liver. The intestines were oedematous and, like the stomach, contained blood. The liver (weight, 1,575 g.) showed a fine cirrhosis with a smooth capsular surface and varying degrees of nodularity. The sectioned liver tissue appeared pale and bile-stained. The spleen (weight, 49.5 g.) was firm and enlarged. The gall-bladder appeared healthy and there was no cholelithiasis or other abnormality in the extrahepatic biliary tract to explain the greatly elevated alkaline phosphatase level. The generative organs and renal tract were healthy, apart from pallor of the kidneys.

Death was ascribed to melaena from oesophageal varices with hepatic cirrhosis (non-alcoholic) and scleroderma.

Histology.—A virtually complete histological study, designed to ascertain evidence of systemic sclerosis, especially in unusual sites, proved remarkably uninformative. Sections prepared from both lobes of the liver showed, with some surprise, that the degree of the basic hepatic fibrosis was neither uniform nor intense, in contrast to the marked fibrosis which usually underlies hepatic portal fibrosis with fatal oesophageal haemorrhage. Unfortunately, a detailed examination of the portal system was not undertaken in search of an extrahepatic contribution to the advanced portal hypertension. The splenic histology conformed to that of hepatolienal fibrosis (Banti's syndrome).

Discussion

There are many *a priori* reasons, mainly indirect causations, for predicting a fair incidence of hepatic fibrosis in patients with systemic scleroderma. The hepatic mesenchymal tissue would be expected to share in the polyfibrotic process of this collagen disease. Surprisingly, however, the extensive literature on scleroderma (Rothman and Walker, 1949; Leinwand *et al.*, 1954; Wiener, 1955; Talbott and Ferrandis, 1956) provides no definitive indication of the incidence and nature of associated hepatic fibrosis of the direct, the indirect, or the fortuitous type. Reliance for a preliminary impression therefore rests on the fragmentary published clinical, histological, radiological, and biochemical evidence.

Clinical and Histological

Leinwand *et al.* (1954), in a study of 150 patients with scleroderma, clearly stated that none of their 12 cases coming to necropsy showed hepatic changes, nor were there any contrary reports. Calkins and Bauer (1955) make no mention of hepatic changes in patients with scleroderma in their discussion on the protean manifestations of connective-tissue diseases. In contrast, both Weiner (1955) and Talbott and Ferrandis (1956) merely note that hepatic changes have been observed; while Cullinan (1953), in presenting his observations on 14 cases of diffuse scleroderma, considered that there were hints of involvement of other viscera such as the liver and spleen.

Sporadic accounts of hepatic involvement in systemic scleroderma have appeared in the literature. Goetz (1945) described the clinical and post-mortem observations on an emaciated middle-aged woman with visceral scleroderma. The hepatic histology showed biliary cirrhosis without any detectable abnormality of the biliary tract or pancreas. Although Gil (1951) found hepatomegaly in two out of eight patients with visceral scleroderma, both had concurrent signs of congestive cardiac failure to explain the enlargement. Beigelman *et al.* (1953) recorded five fatalities among 15 cases of diffuse scleroderma; in two of these five there was definite fibrosis histologically. However, both patients had congestive cardiac failure, confirmed at necropsy. The necropsy findings in 31 patients with progressive systemic sclerosis were described by Piper and Helwig (1955), who contended that the liver usually showed passive hyperaemia as the sole distinctive feature. However, they referred without detail to a solitary instance of portal cirrhosis and to three examples of focal hepatic necrosis. Similarly, Harvey and Bordley (1955) described areas of hepatic necrosis in a jaundiced patient with progressive scleroderma who came to necropsy. They attributed the jaundice to congestion of the liver plus anoxia from pulmonary fibrosis and pneumonia.

Radiological and Biochemical

Boyd *et al.* (1954) reviewed the radiological observations on 63 patients with generalized scleroderma, and noted that hepatic or splenic enlargement was evident in 13 out of 24 patients so investigated. They considered that this hepatomegaly might be due to congestive cardiac failure.

There is no convincing biochemical evidence of impaired hepatic function in the scant relevant literature. The evidence is confusing rather than conflicting. For clarity, it is emphasized that a selectively deranged protein metabolism is not uncommon in patients with systemic scleroderma. In this respect the results of the serum lability tests, protein fractionation, and electrophoresis indicate the appropriate quantitative and/or qualitative deviations. The common electrophoretic pattern of the serum proteins is a moderate but significant decrease in albumin and a marked increase in the gamma-globulin fraction (Walker and Benditt, 1948), whereas the total serum protein concentration is often normal. Beigelman *et al.* (1953) found hyperglobulinaemia with a reverse albumin/globulin ratio in 5 out of 10 patients. Leinwand *et al.* (1954) recorded that the results for the cephalin-cholesterol flocculation test were positive in 10 out of 12 patients and for the thymol turbidity test were

abnormal in 8 out of 13 patients. However, the bromsulphthalein excretion and the percentage of esterified serum cholesterol were normal. Since these two tests are more specific, the possibility of misinterpretation of deranged protein metabolism as evidence of liver disease rather than as an integral feature of systemic scleroderma needs no emphasis.

The hepatic fibrosis observed at operation in our first patient defies ready explanation, since there was no evidence of malnutrition, previous hepatic or biliary disease, generalized passive venous congestion, small intestinal defect, or ulcerative colitis. Though not subject to proof, it may be a direct manifestation of the viscerosclerodermatous process. Massimo (1954) seems to have been the first clear advocate of this view. He pointed out that both the liver and the spleen are rich in mesenchymal tissue, and he claimed priority in reporting hepatosplenomegaly in association with scleroderma. In his patient, a 54-year-old woman, splenectomy was performed and a histological diagnosis of fibroadenoma of Banti's type was established. This same histological pattern of what we prefer to call congestive splenomegaly was confirmed in both of our patients. By contrast, Massimo made no mention of portal hypertension, the theme of our communication. The importance of the prompt recognition of this vascular complication, which has not hitherto received special attention, is self-evident.

Eventual hepatic fibrosis is a recognized sequel to congestive hepatomegaly from cardiac and pulmonary scleroderma and might also be expected to occur in some patients with sclerodermatous haemorrhagic colitis, especially if there were concomitant steatorrhoea as exemplified in our second patient. Her "silver stool" was regarded as a product of these abnormalities. It is, however, equally admitted that the hepatic fibrosis and its complications in our two patients might be independent of the sclerodermatous process.

Finally, we suggest that the possibility of the presence of oesophageal varices, as witnessed in both our patients, should be entertained during the standard radiological studies of visceral scleroderma.

Summary

Two illustrative cases, both in women, of scleroderma and hepatic fibrosis are fully reported. In each patient the salient feature was portal hypertension, including oesophageal varices, which led to recurrent haematemesis, an aspect apparently not previously described.

The first patient survived a palliative subcardiac portocaval anastomosis and remained well five years later, with no subsequent haematemesis. The second patient, whose illness was further complicated by a combination of sclerodermatous haemorrhagic colitis and steatorrhoea to produce the "silver stool" sign, was treated conservatively for repetitive haematemesis. After prolonged invalidism she died in coma, as a result of haemorrhage from an oesophageal varix, some 20 months after her first haematemesis.

The scant literature on hepatic fibrosis in systemic scleroderma is reviewed and the causation of such hepatic lesions is briefly discussed in relation to the observations on our two patients.

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GANGRENE OF THE LEGS IN DISSEMINATED LUPUS ERYTHEMATOSUS

BY

E. C. B. KEAT, M.C., M.D., M.R.C.P.

Consultant Physician, Brighton, Lewes, and Mid-Sussex
Group of Hospitals

AND

J. H. SHORE, M.D.

Lecturer in Morbid Anatomy, Charing Cross
Hospital Medical School

Disseminated lupus erythematosus has been recognized as a generalized disease since Kaposi drew attention to the systemic manifestations of lupus erythematosus in 1872 and Osler's later description in 1895. The clinical syndrome of facial erythema in the classical butterfly distribution, arthritis, involvement of serous membranes, lymphadenopathy, leucopenia, and fever are now well known, but we have been unable to find a record of any case in which gangrene of the legs was due to involvement of large arteries in this disease.

Case Report

A girl aged 14 was admitted to hospital in September, 1953, having developed an erythematous, itchy eruption on the face and hands in July, and for the past month had noticed pain in the left calf on walking, severe enough to make her stop. Four days before admission she awoke to find her left foot cold and numb, becoming painful, and later swollen. There was no relevant history apart from chilblains.

On examination her temperature was 101° F. (38.3° C.) and pulse 120. There was erythema of the face and bridge of the nose in a butterfly distribution, with a shiny erythema at the bases of the finger-nails. The left foot was cold and swollen. The calf muscles were firm and tender. Femoral arterial pulses were present and equal, and both popliteal arteries were easily palpable. The dorsalis pedis and the posterior tibial arteries could not be felt on the left side. Joint sense of the left big toe was diminished and there was some loss of light touch sensation. The urine was free from albumin. The erythrocyte sedimentation rate was 82 mm. (Westergren) in one hour. Other systems were normal. The haemoglobin was 84%, colour index 1. There was a moderate leucocytosis, with 83% polymorphs. L.E. cells were present.