The Paper that most influenced my practice

Carol Black
The Patient

1970

- Age 26 years  Female
- Admitted via A&E Bristol Royal Infirmary
- Raynauds
- Lethargy
- Aches and pains in joints
- Puffy hands
- Painless swelling of lower extremities
- Pigmentation of skin
- 2 weeks of increasing breathlessness
O/E

- Distressed breathless
- Pulse 84  BP 190/110
- Skin pigmented, oedematous shiny and thick over hands, arms and legs
- Creps at base of lungs
- Heart enlarged to the left
- Urine – proteinuria, granular casts
- BUN 129 mg %
- X-ray – large heart, lung infiltrates

⚠ Diagnosis - Scleroderma Renal Crisis

- Clinical course
  - Increasing renal failure
  - Convulsions
  - Rapid decline
  - Death by 14th day of admission
Renal Involvement in Progressive Systemic Sclerosis (Generalized Scleroderma)*

Gerald P. Rodnan, m.d., † George E. Schreiner, m.d. and Roger L. Black, m.d.

Pittsburgh, Pennsylvania


“We have observed the development of rapidly fatal renal insufficiency and malignant hypertension in seven patients with progressive systemic sclerosis. The clinical and pathogenic features of these cases are here recorded”
## Composition of patient group with progressive systemic sclerosis and renal involvement

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>Duration</th>
<th>Organ involvement</th>
<th>Previous Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.F.</td>
<td>66/M</td>
<td>3.5 months</td>
<td>Skin, oesophagus muscle, kidney</td>
<td>Adrenal cortical extract</td>
</tr>
<tr>
<td>V.M.</td>
<td>44/F</td>
<td>8 months</td>
<td>Skin, oesophagus muscle, lung, kidney</td>
<td>ACTH, hydrocortisone, cortisone</td>
</tr>
<tr>
<td>M.B.</td>
<td>26/F</td>
<td>3 years</td>
<td>Skin, lung, heart kidney</td>
<td>Adrenal cortical extract, thyroid extract</td>
</tr>
<tr>
<td>G.D.</td>
<td>50/M</td>
<td>2 years</td>
<td>Skin, heart, kidney</td>
<td>Phenylbutazone</td>
</tr>
<tr>
<td>J.H.</td>
<td>45/F</td>
<td>1 year</td>
<td>Skin, heart, oesophagus kidney</td>
<td>hydrocortisone, cortisone</td>
</tr>
<tr>
<td>A.C.</td>
<td>47/F</td>
<td>2 years</td>
<td>Skin, heart, kidney</td>
<td>Cortisone</td>
</tr>
<tr>
<td>J.P.</td>
<td>43/F</td>
<td>1 year</td>
<td>Skin, heart, kidney</td>
<td>Cortisone</td>
</tr>
</tbody>
</table>
Clinical features of patient group with progressive systemic sclerosis and renal involvement

<table>
<thead>
<tr>
<th>Case</th>
<th>DTI (weeks)</th>
<th>Blood Pressure</th>
<th>Urinary Protein</th>
<th>BUN/NPN (mg, %)</th>
<th>Anti-hypertensive Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.F.</td>
<td>1</td>
<td>210/110</td>
<td>2</td>
<td>180 NPN</td>
<td>----</td>
</tr>
<tr>
<td>V.M.</td>
<td>1</td>
<td>132/74</td>
<td>0</td>
<td>41 BUN</td>
<td>----</td>
</tr>
<tr>
<td>M.B.</td>
<td>2 1/2</td>
<td>250/140</td>
<td>4</td>
<td>141 BUN</td>
<td>Hydralazine, Alkavervir</td>
</tr>
<tr>
<td>G.D.</td>
<td>3 1/2</td>
<td>220/120</td>
<td>1-3</td>
<td>105 BUN</td>
<td>Cryptenamine, pentolinium, alkavervir</td>
</tr>
<tr>
<td>J.H.</td>
<td>3-4</td>
<td>180/110</td>
<td>1-3</td>
<td>167 BUN</td>
<td>Pentolinium, Hydralazine</td>
</tr>
<tr>
<td>A.C.</td>
<td>4</td>
<td>170/1102</td>
<td>2-4</td>
<td>211 NPN</td>
<td>Haemodialysis</td>
</tr>
<tr>
<td>J.P.</td>
<td>3</td>
<td>160/98</td>
<td>1</td>
<td>260 NPN</td>
<td>Haemodialysis</td>
</tr>
</tbody>
</table>
Gerald Paul Rodnan 1927-1983

Developed the skin thickness scoring system
Described:
- Renal involvement in a series of SSc patients
- Acroosteolysis in a series of SSc patients
- Tendon friction rub

Identified reduced DLCO as the first physiologic abnormality in ILD
First:
- noted the association of pulmonary arterial hypertension with limited cutaneous SSc (CREST syndrome)
- used the term “systemic sclerosis sine scleroderma”
- used the term “eosinophilic fasciitis”.

Motivated development of preliminary classification criteria for SSc
Through his writings and lectures, stimulated investigators in many countries to study scleroderma

“The memory of this great physician, who declared war against scleroderma, will last for many generations of dermatologists and rheumatologists.

Jablonska, Int.J. Derm. 1984
Brief outline history of scleroderma

• Hippocrates and Galen described possible cases of scleroderma

• First convincing case published by Curzio (Italy) 1753
  Treatment: “…warm milk, vapor baths, bleeding and small doses of quicksilver. After 11 months the patient’s skin had become perfectly soft and flexible.” A cure !?

• Scleroderma first established as a clinical entity, and called ‘sclerodermie’ by Gintrac 1847

• Goetz (1945) described systemic disease: “.. obviously the term Scleroderma should be abandoned.”
• Moore and Sheehan (1952) described the “Scleroderma kidney”
• Osler 1894 “.. patients are apt to succumb to pulmonary complaints or to nephritis.”

The modern history of Scleroderma starts around 1945, only 65 years ago.
My first contact with a patient suffering from this disease was in 1957 when I was an intern at the Philadelphia General Hospital.

I was astonished that no single reference in the Medical Library covered the systemic manifestations in sufficient detail, and realized that many areas needed more thorough clinical and pathologic study.

My purpose in writing this book is to fill the void that I found as an intern. I hope that the reader will share my belief that a famous aphorism might be rephrased:

‘To know scleroderma is to know medicine.’
Advance in Scleroderma

1960

- Ideas on linked pathogenesis
- First reports of defined autoantibodies
- Vascular disease hypothesis
- First animal model for Scleroderma
- Collagen accumulation in Fibroblasts
- Appreciation of cellular and humoral factors
- Classification criteria published
- Exposure to environmental agents suggested
- Early studies on epidemiology and genetics (MHC)
- Microchimerism?
- Candidate gene approaches
- Detailed studies of disease pathogenesis
- New pathogenic autoantibodies
- Gene expression profiling and GWAS

Landmarks in Scleroderma Research

- 2000:49
- 2006:101
- 2009:215

ACR Scleroderma Abstracts Accepted

Papers

- 1960-1970: 1615
- 1980-1990: 3448
- 1990-2000: 4207
- 2000-2009: 5561
Major areas of progress

- **Clinical expertise**: numbers of health professionals
- **Centres**: consortia, national and international bodies; EUSTAR, SCTC
- **Classification**: risk stratification, assessment
- **Collaborations**: with other specialties, and basic scientists
- **Integrated holistic care**: teams, nurses
- **Patient organisations**: number increasing, breadth and depth enlarging
- **Research**: basic, translational, clinical
- **Treatment**: for some aspects of SSc
- **International meetings**: Research
Unravelling Disease Development

Initiation and Susceptibility
- Genetics, injury, environment

Inflammation and Autoimmunity
- Activation of host defence mechanisms

Damage to Blood Vessels
- Poor blood supply, Reduce oxygen and poor nutrition of tissues

Aberrant Cell Communication
- Activation of fibroblasts
  - Increased deposition of scar tissue
  - Tissue contraction and Fibrosis

Abnormal Tissue Repair with increased Scarring

FIBROSIS of Vital Organs
Mouse models at the Royal Free Hospital

Increasing knowledge of its pathogenesis from human and animal studies

Skin, pulmonary, liver

The Tight skin mice

Dysregulated TGFβ

Surgical-induced Fibrosis Kidney

Chemically-induced

Over-expression CTGF

Skin

Lung
Clinical Progress – Vascular Disease?

- Acute Hypertensive Renal Crisis

- Pulmonary hypertension

- Raynaud’s

- Ulcers

- Telangectasia
Scleroderma renal crisis

- Rapidly progressive renal impairment
- New onset accelerated phase hypertension
  - Headaches
  - Visual disturbances
  - Encephalopathy with seizures
  - flash pulmonary oedema
  - fevers / malaise
  - pericardial effusion
- +/- MAHA
- Hyper-reninaemia
- In an American cohort, 1 year survival improved from 15% to 76% with ACE inhibitors (Steen et al, 1990)
- Early diagnosis and expert renal units are critical

Grade IV retinopathy

Schistocytes - MAHA
Patient involvement

Education from specialist nurses

Warning card

Regular blood pressure monitoring

Advice line available
Algorithm for management of SSc renal crisis

Follow up:
Renal function improvement may continue for up to 24 months after renal crisis

Antihypertensive requirements often fall

Other aspects of disease may improve

Occult cardiac disease may manifest

Education, BP monitoring, avoid precipitants
ACEI (or ARB)
Close observation renal function, check for MAHA and end-organ disease

Hospital admission increase ACEI/ARB, additional oral antihypertensive
?prostacyclin infusion, close monitoring, renal support

Post-transplant surveillance

SSc stage and subset

BP elevated

Renal impairment

Renal failure

Recovery

Long term renal replacement

Transplant
Scleroderma renal crisis (SRC) at the Royal Free Hospital

- 110 patients with hypertensive SRC identified 1990-2005
- Mean age 50.7 years
- 79% female
- Duration of disease
  - 22% had SRC as presenting feature of SSc
  - 66% within 1 year of presentation with SSc
- Subset
  - 22% lcSSc (1.9% of those under follow-up)
  - 78% dcSSc (16% of those under follow-up)
- Serology
  - 50% RNA polymerase antibodies (odds ratio 11)
  - 2% ACA (odds ratio 0.05)
- 59% received steroid in 1 month prior to SRC
- Mean GFR prior to SRC 77 ml/min

Renal recovery after SRC

- 42% long term dialysis
- 24% dialysis and recovery
- 34% no dialysis

- Recovery occurs up to 2 years after SRC
- eGFR improves for at least 4 years

Penn et al. QJM (2007)
Survival for SRC stratified by renal outcome

- Survival at:
  - 1 year = 82%
  - 3 years = 71%
  - 10 years = 47%

- Poorer prognosis in males

“May the struggle continue until this most obstinate disease is made to give up its secrets”

Gerald Rodnan, 1979