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Pioneering controlled trials of treatments for erysipelas and pneumonia in Glasgow, 1936–1947

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Introduction

The clinical trials of treatment with sulphonamides for erysipelas and pneumonia conducted by Thomas Anderson and colleagues in Glasgow between 1936 and 1947 are less well-known than the Medical Research Council's multi-centre trial of streptomycin for pulmonary tuberculosis reported in 1948.[1,2] The streptomycin trial is often presented as the official birth of randomised trials.[3] Although the trial report does indeed represent a methodological milestone, its iconic status has meant that important earlier controlled trials have been inappropriately overlooked.[4] Among important overlooked controlled trials, those done in the programme of trials done in Glasgow in the late 1930s and early 1940s deserve greater recognition on account of the evolution of randomised trials.

As Anderson made clear in his MD thesis, '*in each stage the allocation of the case to either method of treatment was a random one*' (p. 41).[5] This article outlines the trials of sulphonamides for erysipelas and pneumonia at Ruchill and Knightswood hospitals. In addition to use of the results published in leading British medical journals, I have drawn on information about two of the trials in Anderson's MD thesis. This was submitted to the University of Glasgow in 1944 and awarded the Bellahouston Gold Medal. It is now freely available online.[5] This article focuses on the methodology and results of the trials. A second paper will discuss their historical context in greater detail.

Background

Thomas Anderson (1904–1990) studied medicine at Glasgow University and qualified as a doctor in 1928. He worked as Deputy Physician at the Corporation of Glasgow's Ruchill Hospital from 1933 until 1941, when he was appointed as Lecturer in Infectious Diseases at the University of Glasgow and Physician Superintendent at Knightswood Hospital in 1941, where he conducted clinical trials of sulphonamides and penicillin for pneumonia. He went on to become Professor of Infectious Diseases in 1959 and was Henry Mechan Professor of Public Health from 1964 to 1971. He was also a leading member of the Royal College of Physicians and Surgeons of Glasgow.[6]

In 1951, Anderson became the first director of the newly established Brownlee Laboratory, named after John Brownlee, who studied mathematics, natural philosophy (1889) and medicine (MB 1894; MD 1897) in Glasgow. Brownlee went on to become superintendent physician at Ruchill Hospital, and was the first Director of the Medical Research Council's Statistical Department at Ruchill Hospital, which was a centre for research into the epidemiology of respiratory infections. He was made a Commander of the British Empire in 1972.

Anderson conducted several controlled clinical trials at Ruchill and Knightswood hospitals, Glasgow, in the 1930s and 1940s, partly at the instigation of William Snodgrass, assistant physician at the Western Infirmary, Glasgow. William Robertson Snodgrass (1890–1955) studied medicine at Glasgow University and gained his MB in 1913. He became a Fellow of the Royal Faculty of Physicians and Surgeons of Glasgow in 1920 and was its President between 1948 and 1950. Following medical service in World War I, he became chief medical Adviser to the Glasgow Venereal Disease service, an appointment which enabled him to carry out work for a thesis on early, latent and muco-cutaneous tertiary syphilis: for this he was awarded an MD, with honours, and a Bellahouston Gold Medal in 1935. The record of this work – 570 cases seen at the University of Glasgow Western Infirmary between 1919 and 1932 – was published in one of the Special Report Series of the Medical Research Council.[1] In addition to his University connection, Snodgrass became the first physician appointed to the Corporation of Glasgow's Southern General Hospital (formerly the Govan workhouse) in 1923.

In 1942, he was appointed consultant physician at the Western Infirmary. He was President of the Royal Faculty of Physicians and Surgeons of Glasgow from 1948 to 1950[6] (p. 246). He served as its representative on the Scottish Joint Consultants Committee (of which he was, for a time, chairman), as well as on the English Joint Consultants Committee during the negotiations on the National Health Service.[7]

Prontosil, the first specific chemical for use as a treatment for human bacterial infections, was patented by the German firm IG Farben in 1935. Derived from an aniline dye, Prontosil rapidly came to world wide attention as a miracle cure for a range of hitherto life-threatening bacterial diseases.[8] Shortly after its introduction, the active element of Prontosil – sulphanilamide, a member of the chemical class 'sulphonamide' – was isolated at the Pasteur Institute, in Paris. A range of sulpha drugs was introduced in the 1940s and 1950s and remain in use today.

Prospectively controlled trials of sulphonamides in erysipelas

> In 1936, Dr WR Snodgrass invited me to take part in testing the new drug "Prontosil Red" in human streptococcal infections. Plans were accordingly laid for its use in the treatment of erysipelas, and during the next three years further trials of drugs derived from the original one were conducted.[5] (p. (i))

In February 1936, the Medical Research Council and Therapeutic Trials Committee[9,10] accepted a request from Bayer Ltd to have its recently patented drug Prontosil tested as a treatment for streptococcal infections[8] (pp. 137–138). According to Lesch, the Therapeutic Trials Committee had already informally approved a test of Prontosil at the request of Leonard Colebrook, physician at Queen Charlotte's Hospital, London, who had obtained a quantity of Prontosil from Germany and offered to test it under the auspices of the Therapeutic Trials Committee as a treatment for puerperal sepsis. Colebrook,[11] who was keen to be the exclusive trial authority in the UK, began tests on mice, and later on a case series involving inpatients.

However, interest in Prontosil was such that by 1936 informal trials had begun in several UK locations, accompanied by reports of its use in a range of bacterial infections.[12] As Lesch has outlined, in the face of growing interest among British doctors, the Therapeutic Trials Committee felt impelled to extend the testing of Prontosil to other conditions, and to undertake trials in humans of what appeared to be a miracle treatment for bacterial infection. In March 1936, Francis Green, secretary of the Therapeutic Trials Committee, wrote to William Snodgrass in Glasgow, inviting him to take part in tests of Prontosil. Green wrote again in June 1936 inviting Snodgrass to extend testing to erysipelas, a serious, but usually not life-threatening streptococcal infection of the skin. Snodgrass asked Thomas Anderson to undertake a trial of Prontosil Red in human streptococcal infections. Anderson, who was deputy physician at Ruchill Hospital at the time, accepted the request and conducted clinical trials of Prontosil and other sulphanilamides on erysipelas, measles and pneumonia between 1936 and 1947.

The structure of the erysipelas trials

With the supplies of Prontosil made available to him, and subsequently with two new sulphonamides, Anderson undertook clinical trials to determine the effectiveness of sulphonamides as a treatment for erysipelas. It involved all patients admitted with erysipelas to Ruchill Hospital between May and June 1936 (the *BMJ* paper says May, the thesis says June) and the end of 1939[5] (p. 36). They were organised into five stages, so that different configurations of experimental and control groups could be formed. The results were reported in three papers published in leading British medical journals.[13–15]

First paper

The first paper[13] was a report of Stage 1:

> The first 161 cases were, in order of admission, allocated to three special groups. Group 1 received treatment only by ultra-violet light; Group 2 only by prontosil; Group 3 both by ultra-violet light and by prontosil. The fatality rate when 161 cases had been admitted was exceptionally low, and as two thirds of the series had received prontosil it was thought advisable to alter the proportion of cases treated with this drug. Therefore the second 151 cases were divided into three groups, of which the first two were the same as before, but the cases in the third group received treatment solely with Messrs. Burroughs Wellcome's concentrated scarlet fever antitoxin (globulin fraction).

Outcome measures were 'spread of lesion', 'duration of primary pyrexia' and 'duration of toxaemia'. The paper tabulates the four trial groups against these outcomes, and concluded that:

> the cumulative evidence indicates that those cases which received prontosil showed better results in

respect of curtailment of (i) the duration of the spread- of the local lesion; (ii) the duration of primary pyrexia; (iii) the duration of toxaemia.

Second paper

The second paper[14] was a report of Stage 2. The basic configuration of this stage was simpler, in that only two study groups were constructed:

> As in the first series of cases, ultra-violet light was used as a control method of treatment. The cases were, in the order of their admission, assigned to two treatment groups. Cases in Group 1 received treatment in the first instance only with ultraviolet light. Cases in Group 2 received treatment only with sulphanilamide. There were 270 cases in all, 135 in each group.

However, in place of Prontosil Red, its active ingredient – sulphanilamide – was used: '*the preparation used was that marketed under the trade name of "streptocide" by Messrs. Evans Sons Lescher and Webb Ltd.*' A secondary aim of Stage 2 was to investigate the optimal dosage of Streptocide; during this stage the initial dosage of Streptocide was either 1, 2 or 3 g. The paper concluded:

> Sulphanilamide is of benefit in securing curtailment of (i) the duration of the spread of the lesion; (ii) the duration of primary pyrexia; (iii) the duration of toxaemia.

In contrast to the first paper, the second paper reported a statistical calculation, namely the standard error of the difference between the two groups. It reported that the difference between spread and fever was statistically significant, but was not for toxaemia. The paper concluded:

> An effective method of treatment is to give 1 gramme of sulphanilamide by mouth at four-hourly intervals until the cessation of primary pyrexia, and thereafter 0.75 gramme by mouth thrice daily until final cure is determined.

Third paper

The third paper[15] is a report of the two trials which formed Stage 3 of the overall trial programme: Prontosil vs. Proseptasine, and Prontosil vs. Streptocide. In both trials, the doses of drugs were varied to provide information about appropriate dosage (Figure 1).[15]

Figure 1. Schedule for paper 3 of the Ruchill erysipelas trial.[15]

Part I : 122 Cases.—There were four treatment groups:

A. Benzylsulphanilamide, 1 gramme four-hourly.
B. Benzylsulphanilamide, 2 grammes four-hourly.
C. Sulphanilamide, 1 gramme four-hourly.
D. Sulphanilamide, 2 grammes four-hourly.

For each group fifteen male patients and fifteen female patients were gathered—the cases being allocated strictly in order of admission. (In each ward, male and female, one extra case was taken on at the end of the investigation and was retained in the series.)

These cases were admitted during the months of November and December, 1937, and early in January, 1938.

Part II : 120 Cases.—There were four treatment groups:

A. Sulphamido-chrysoidine, 1 gramme four-hourly.
B. Sulphamido-chrysoidine, 2 grammes four-hourly.
C. Sulphanilamide, 0.5 gramme four-hourly.
D. Sulphanilamide, 0.75 gramme four-hourly.

Again each group comprised fifteen male patients and fifteen female patients taken in rotation according to the order of admission. These cases were admitted during the months of January, February, and March, 1938.

Its purpose was to test the effectiveness of May and Baker's new sulphonamide, Proseptasine, and to establish the minimum effective dose of sulphonamide, because side effects had been common in the Stage 2 trials:

> Toxic symptoms in [the] second series, in which large doses of sulphanilamide were used, were common, amounting to 35.5 per cent. in 270 cases. Cyanosis was the most frequent manifestation and occurred in 29.6 per cent. of cases. It was considered, therefore, that further work was necessary in an attempt to settle a minimum adequate dosage, for the incidence of cyanosis rapidly increased with an increase in dosage.

The results reported in the paper found that Proseptasine was not as effective as either Prontosil or Streptocide, and that lower doses of Streptocide were just as effective as Prontosil. Discounting Proseptasine, the paper concluded:

> We are, however, of the opinion, from the above figures, that the choice of drug to be employed can be left to individual preference. The method of administration to an adult patient should be: (i) Sulphamidochrysoidine: 1.5 grammes every four hours-that is, 9 grammes a day until cure is established; thereafter 1 gramme three times daily for a further period of fourteen days. (ii) Sulphanilamide: 1 gramme every four hours – that is, 6 grammes a day until cure is established; thereafter 1 gramme three times daily for a further period of fourteen days.

Methodological aspects of the erysipelas trials

The main methodological point of note in the erysipelas trials is the use of alternate allocation, a technique which is, in principle, a good 'randomiser'.[16] It was used by Anderson as a means of constructing comparison groups in which factors affecting outcome were distributed unbiasedly. Anderson was certainly not the first trialist to use alternate allocation;[4,17] what his papers show is that by 1936/1937 alternate allocation to create comparable comparison groups could be employed and reported without controversy.

A reading of Anderson's thesis alongside the published papers on erysipelas adds a range of detail to the published results and, above all, gives a strong impression of the logic with which the trials were undertaken and the rigour with which there were conducted. This logic is based on clinical rather than academic or mathematical considerations, and sets out the rationale for sample size, method of allocation, and application of statistics.

First, from his detailed account of the natural history of erysipelas in Glasgow, Anderson concluded that a large sample was needed in order to include young and old of both sexes and different severities of erysipelas. Second, again from the natural history of erysipelas, the most appropriate outcome measure was not mortality, which was relatively rare. Instead, Anderson considered the following to be appropriate outcome measures: the duration of spread, pyrexia and toxaemia. All of these, he recognised, were biometric characteristics that could be measured, but because they will fluctuate naturally, statistical analysis would be required. In addition to descriptive statistics, Anderson used chi-squared and standard error of difference tests, only some of which were reported in the published papers. Third, since the effectiveness of a chemotherapeutic agent was dependent on a range of factors associated with a patient's constitution, it was necessary to allocate patients to treatment and control groups in an unbiased way to achieve groups similar in constitutional factors that might otherwise mask treatment differences. Accordingly, Anderson recruited all patients entering Ruchill Hospital over several years, and allocated them in an alternating pattern – which he regarded as 'random' – to treatment and control groups:

> At the beginning of each stage of the experiment a large card was hung in the ward, divided into parallel columns according to the number of methods of treatment under test. When the diagnosis of erysipelas was confirmed cases were entered in the different treatment columns strictly in the order of their admission to hospital. **The particular method of treatment which they received was, therefore, left entirely to chance**.[5] [my emphasis] (p. 38)

The trials were organised into five stages (Figure 2). The first published paper[13] is a report of Stage 1; the second[14] is a report of Stage 2; the third[15] corresponds to Stage 3. Stage 4, involving a placebo, and Stage 5, a comparison of two sulphonamides – Bayer's Prontosil Red (sulphonamido-chrysomidine) and Roussel's recently issued Rubiazol (carboxy-sulphonamide-chrysomidine) – were not reported in the published literature.

The phasing of the erysipelas trials was intended to deal with a rapidly evolving number of sulphonamides coming onto the market and the concomitant uncertainty about optimal dosage and toxicity. The published results succeeded in this aim by demonstrating the efficacy of Prontosil and newer sulpha drugs, at the same time providing a practical guide to dosage schedules and information about side effects. In his thesis, Anderson was able to analyse the results of the trials as chemotherapy vs. ultraviolet light. Analysed in this way, there could be little doubt as to the value of sulphonamides, as Figure 3 shows.

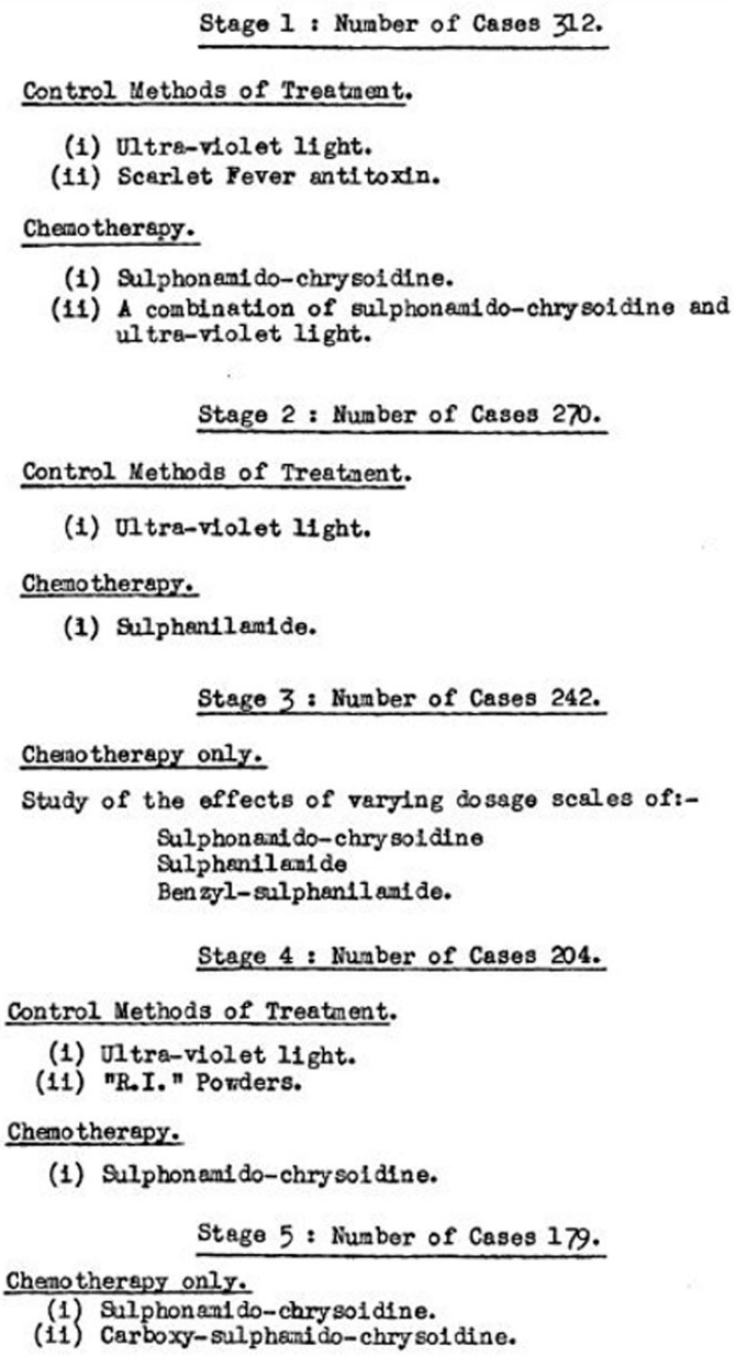
Other points of note reported from Anderson's thesis:

- A comparison of Prontosil with a placebo ('RI powders') and ultraviolet light (Stage 5 of the trial) found that there was some value in ultraviolet light[5] (p. 76).
- An analysis of the impact of the introduction of sulphonamides on mortality from erysipelas showed a dramatic effect after the introduction of Prontosil in 1935 (Figure 4).
- The analysis was done on an intention-to-treat basis[5] (p. 44).
- For ethical reasons (i.e. because it was increasingly clear that sulphonamide was effective), all cases aged under five admitted after August 1937 were treated with sulphonamide and analysed separately[5] (p. 38).

From erysipelas to pneumonia trials, via a prospectively controlled trial of prophylactic sulphanilamide in measles

An epidemic of measles in the winter of 1937–1938 enabled Anderson to undertake a trial of prophylactic

Figure 2. The stages of the erysipelas trials at Ruchill Hospital, 1936–1939 (p. 37).[5]



Stage 1 : Number of Cases 312.

Control Methods of Treatment.

(i) Ultra-violet light.
(ii) Scarlet Fever antitoxin.

Chemotherapy.

(i) Sulphonamido-chrysoidine.
(ii) A combination of sulphonamido-chrysoidine and ultra-violet light.

Stage 2 : Number of Cases 270.

Control Methods of Treatment.

(i) Ultra-violet light.

Chemotherapy.

(i) Sulphanilamide.

Stage 3 : Number of Cases 242.

Chemotherapy only.

Study of the effects of varying dosage scales of:-

Sulphonamido-chrysoidine
Sulphanilamide
Benzyl-sulphanilamide.

Stage 4 : Number of Cases 204.

Control Methods of Treatment.

(i) Ultra-violet light.
(ii) "R.I." Powders.

Chemotherapy.

(i) Sulphonamido-chrysoidine.

Stage 5 : Number of Cases 179.

Chemotherapy only.

(i) Sulphonamido-chrysoidine.
(ii) Carboxy-sulphamido-chrysoidine.

Burroughs Wellcome sulphonamide (made available through the Medical Research Council's Therapeutic Trials Committee) in measles. A total of 125 cases admitted to hospital were allocated alternately, in order of admission, either to 'the usual nursing and expectant medical treatment' or to sulphanilamide. There were 15 cases of complications usually associated with streptococcal infections (tonsillitis, adenitis and otitis media) in the control group compared with only three such cases ($p = 0.01$) among those who had received prophylactic sulphanilamide.[18] As he stated in his thesis[5] (p. 124), this finding was the gateway to

Figure 3. Consolidated results, erysipelas trials (Anderson,[5] p. 46, 58).

TABLE 9.

Duration, in Days, of the Presence of the three main Factors of Assessment.

(i) Duration, in days, of spread of erysipelas.

Days	0	1	2	3	4	5	6	7	Over 7	Total
Chemo-therapy	161 (3)	120 (5)	25 (0)	5 (1)	1 (0)	0	0	0	0	312 (9)
U.V. Light	97 (1)	68 (3)	53 (2)	42 (1)	23 (1)	14 (0)	4 (0)	4 (2)	1 (0)	306 (10)

(ii) Duration, in days, of Primary Pyrexia.

Days	0	1	2	3	4	5	6	7	Over 7	Total
Chemo-therapy	19 (0)	127 (3)	109 (4)	34 (2)	12 (0)	8 (0)	3 (0)	0	0	312 (9)
U.V. Light	29 (0)	58 (1)	64 (0)	42 (2)	42 (3)	20 (0)	25 (1)	11 (1)	15 (2)	306 (10)

(iii) Duration, in days, of Evidence of Toxaemia.

Days	0	1	2	3	4	5	6	7	Over 7	Total
Chemo-therapy	13 (0)	47 (2)	110 (2)	81 (2)	34 (1)	17 (1)	7 (1)	2 (0)	1 (0)	312 (9)
U.V. Light	18 (0)	35 (1)	65 (0)	54 (1)	46 (1)	36 (2)	20 (1)	17 (1)	15 (3)	306 (10)

Note: In each of the three tables the figures in brackets represent the duration of the particular factor of assessment in those patients who died.

TABLE 15.

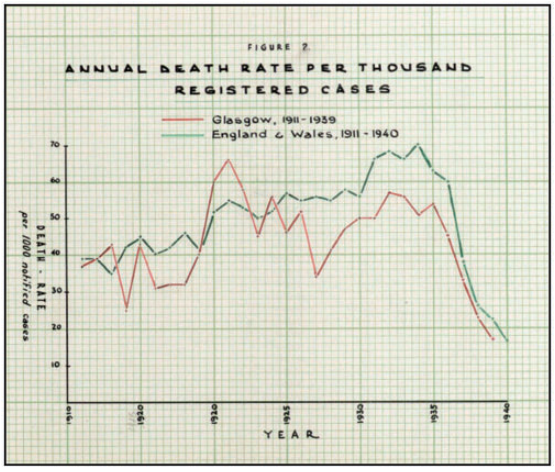
Summary of Results.

Comparison of Chemotherapy and Ultra-Violet Light.

Factor of Assessment	Chemo-therapy (per cent.)	Ultra-violet Light. (per cent.)	Difference (S.E.D.)
1. Ceased spread after 24 hours in hospital	90.1	54	10.9
2. Apyrexial after 48 hours in hospital	81.7	49.4	9.0
3. Toxaemia absent after 72 hours in hospital	80.7	55.4	7.0
4. Complicated Case Rate (true infective complications)	11.6	18.3	2.4
5. Nephritis	-	2.6	2.9
6. Relapse Rate	3.2	6.9	2.1
7. Fatality Rate	2.9	3.3	-
8. Average Days Residence	15.34	17.16	-
Total number of Cases	312	306	

(In the last column is shown for each factor of assessment the ratio of the percentage difference to the Standard Error of the Difference (S.E.D.)).

Figure 4. Annual death rate from erysipelas in Glasgow and England and Wales (Anderson,[5] p. 91).



The Ruchill Hospital pneumonia trial: methodology

The second volume of Anderson's thesis is a report of the trials of treatment for pneumonia. The main treatment evaluated was sulphapyridine (M&B 693); a small trial of sulphapyridine combined with serum was also reported.

The clinical trial of sulphanilamide was based on a case series of 501 cases of pneumonia admitted to Ruchill Hospital between 1939 and 1940, all treated with sulphapyridine:

> The experiment was begun in January 1939 and continued until I left the hospital in December 1940. It includes practically all notified cases of primary pneumonia admitted to the hospital above the age of eleven years, in whom the notified diagnosis was confirmed.[5] (p. 138)

The results in the 1939–1940 case series were compared with 498 cases under Anderson's management between 1931 and 1934, receiving the care available at that time.

Anderson regarded the concurrent, no-selection approach as an ideal, but this did not preclude him from seeing value in other approaches. This was partly because there was no gold standard way to conduct a clinical trial in the 1930s. It was also partly because, as Anderson argues in the extended quotation below, in some situations there were limits to the efficacy of alternate allocation as a mechanism to balance all the relevant variables and reduce confounding by extraneous risk factors when sample

further trials: first a very small case series, which produced inconclusive findings; then, an unpublished assessment of sulphanilamide for pneumonia using historical controls at Ruchill Hospital; then, prospectively controlled alternate allocation trials comparing sulphanilamide and penicillin for pneumonia at Knightswood Hospital, published in the *Lancet* and the *British Medical Journal*.[19,20]

sizes are modest. His observation prefigured those of other writers.[21] Anderson also considered that there might be some clinical knowledge to be gained from case studies:

> The report of the investigation of erysipelas has already shown the great value of a concurrent control by the administration of chemotherapeutic drugs only to alternate cases. In erysipelas, such a method was effective because the variable factors between different patients were relatively few so that in a reasonably large sample they could be presumed to balance. Further, the turnover of cases was more rapid, and their clinical supervision much easier than was possible with cases of pneumonia. The typing of the pneumococcus alone entailed additional work which consumed a large amount of time, so that over a year it was unlikely that more than 200 cases could be undertaken, then the type incidence alone was taken into effect in such a relatively small series of cases **it was at once obvious that the comparison of two groups (treated and untreated) of about 100 cases might well produce evidence at once unconvincing and uninformative.** [my emphasis] In these circumstances, therefore, I decided that two considerations should be borne in mind:
>
> Previous experience had shown that although variations in the fatality rates occurred, they were sufficiently small to allow of comparison of two groups of cases of the same type. In other words, the cases collected in the earlier period (1931–1934) would serve as a useful yardstick to assess the value of chemotherapy. Study of the fatality rates in the City of Glasgow over a period of years did not support a view that the disease was lessening in its severity.
>
> **One of the first necessities quite apart from any new method of treatment was to obtain as quickly as possible in a series of British cases, type-specific fatality rates for the different types, more especially for those types previously classed as 'Group IV', for the individual members of which no British figures existed** [my emphasis]. It was, therefore, decided that in a disease like pneumonia (bearing in mind the main factors already discussed) the best method of investigation was to treat, in as nearly a similar manner as possible, a series of cases in which the type of infecting pneumococcus and the incidence of bacteriaemia were known and to produce fatality rates specific for age, type, and bacteriaemia.
>
> In this way, if the treatment were unsuccessful, a body of evidence upon the behaviour of pneumonia would be amassed which would be of value in later studies. If, on the other hand, the treatment were successful, knowledge would be acquired of its relative efficacy at different ages and on the different type infections: and from a study of any failures future investigations might be planned.[5] (pp. 131–133)

Pneumonia trial: results

Anderson's analysis in Chapter 4 of Volume 2 of his thesis consists of three parts:

- Analysis of the 1939 cohort, to investigate the effectiveness of sulphapyridine on different types of pneumonia.
- Comparison of outcomes between cohorts, taking into account the similarities and differences between the 1931 and 1939 cohorts.
- Analysis of a sub-trial of sulphapyridine combined with serum.

The 1939–1940 series of 501 cases resulted in 71 deaths; the lowest rate of mortality was seen in Type I pneumococcus infections; the highest in Type III[5] (p. 174). A chi-squared test showed these differences to be statistically significant. Further analysis showed that age, presence of bacteraemia and duration of illness before admission to hospital were all associated with fatal outcome, though Anderson considered these factors likely to be connected.

The analysis goes on to compare the 1939–1940 results with the earlier case series of 498 cases from 1931 to 1934. Of this, Anderson says:

> It has already been explained that during 1931–34 I investigated the types of pneumococci responsible for 498 cases of pneumonia. Although **due regard must be given to the dangers which are associated with the comparison of two series of cases investigated at entirely different periods,** it is submitted that there is some value in discussing them; for all of these cases have one set of circumstances in common: **they were all examined in one hospital by one observer.**[5] [my emphasis] (p. 206)

Anderson's analysis begins by observing that the overall difference in mortality between the two series was not statistically significant[5] (Table 46, p. 206). He then examines the differences in the two cohorts in order to explain the apparent lack of effectiveness of sulphanilamide. Noting age and type differences between the two series, Anderson[5] tries to correct for them, concluding that, for younger patients with either Type I or II pneumonia, sulphapyridine is effective (Table 50, p. 214):

> The comparison made between the two groups of cases of pneumonia due to Types I, II, and III

> pneumococci, one of which received expectant treatment in 1931–34 and the other sulphapyridine in 1939–40 shows that in the latter period the fatality rates of Type I and II infections have fallen to a half of the former figures. There is a more striking reduction in Type II infections in patients under the age of 40 years than in those above this age. Finally, it has been found that cases in the later period are admitted on average almost one day later than those in the earlier period. Despite this the total duration of fever has been reduced from 7.7 days to 6.5 days.[5] (p. 221)

The final part of the results concerns the addition of serum treatment:

> An analysis of 33 cases of pneumonia due to Type II pneumococcus, to whom a combination of sulphapyridine and type-specific rabbit serum was administered, indicates that in respect of the fatality rates (specific for age and the presence of bacteriaemia), the duration in days of primary pyrexia and the occurrence of complications, the results showed no improvement over those obtained with sulphapyridine alone.[5] (p. 226)

Prospective trials of pneumonia treatment at Knightswood Hospital

At the end of World War II, Anderson took up a post at the Knightswood Fever Hospital, where he undertook two further trials of treatment for pneumonia. The purpose of the first trial is clearly stated in the Introduction:

> Although the general success of properly applied sulphonamide chemotherapy in pneumonia is now well established, there is no doubt that there are patients in the older age-groups who show a poor response to chemotherapy, even in adequate dosage; and, further, that complicating factors are often present in such patients which may make therapy hazardous and difficult to control. The pneumococcus, which is the responsible aetiological agent in a high proportion of pneumonias, is susceptible to the action of penicillin (Fleming 1929). It accordingly becomes necessary to find, first, if penicillin is effective in the treatment of human pneumonia, and second, whether it possesses any advantages over the earlier method of treatment.[19]

In view of the effectiveness of sulphonamides in patients aged under 35 years, 126 men over the age of 35 years suffering from pneumonia (there was no explanation of why women were excluded) were allocated alternately either to sulphathiazole or to penicillin. The principal conclusion was that the drugs were of equivalent effectiveness. Notice was drawn to three cases: '*We regarded these 3 as the most serious cases in the series, and we believe that the treatment with penicillin was instrumental in saving their lives*'.[19]

The second trial was a comparison of different routes of administering penicillin. A comparative study[19] of the efficacy of the sulphonamides and penicillin in the treatment of pneumonia showed that there was little to choose between the two methods. Although certain advantages could be claimed for penicillin on account of its lack of toxicity, its use had one great drawback, especially for the general practitioner – the need for repeated intramuscular injections.[20]

The trial involved all male patients admitted to Knightswood Hospital with confirmed pneumonia during the winter of 1946–1947. Patients were allocated alternately either to receive intramuscular penicillin or to oral penicillin. The results were comparable:

> From the results recorded it is clear that the oral administration of penicillin is a satisfactory method of treatment for pneumonia. Our experience would suggest that treatment should start with a daily oral dosage equal to four times that required by the intramuscular route.[20]

Conclusion

> The discovery of any new method of treatment raises problems of wide variety, often, it might seem, unrelated to the original discovery. The clinician's part is the most clearly defined: he must apply the new remedies to the disease in men. In addition, but of equal importance, he should try to assess their real value and measure their limitations[5] (p. (i)).

The high degree of integration of clinical, epidemiological and mathematical thinking evident in the clinical trials undertaken in Glasgow in the 1930s and 1940s by Thomas Anderson and colleagues suggests they deserve wider recognition as precursors to the randomised controlled trial of streptomycin for tuberculosis.[1] If all patients in a consecutive series are entered in a clinical trial, then strict alternate allocation will result in comparable comparison groups. As Anderson[5] understood it, the purpose of alternate allocation was to allow chance to randomly balance variables across trial groups (p. 38, 41). More generally, Anderson's thesis demonstrates the sophistication of his thinking about clinical trial design including: concurrent controls; quantified

outcome measures; statistical testing; intention-to-treat analysis and placebos. Of note, his rationale for trial construction comes as much from clinical medicine – from an appreciation of the natural history of disease – as it does from statistical theory. Even the arguments informing the decision *not* to randomise – as in the Ruchill Hospital pneumonia trial – adds to the sense of his high degree of understanding of trial methodology tempered by a clinical perspective. How such sophisticated trials came about in a second-tier hospital in 1930s Glasgow will be the subject of a second paper.

Declarations

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