Leukaemia and aplastic anaemia in patients irradiated for ankylosing spondylitis

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MEDICAL RESEARCH COUNCIL SPECIAL REPORT SERIES

No. 295

LEUKAEMIA
AND APLASTIC ANAEMIA
IN PATIENTS IRRADIATED
FOR ANKYLOSING SPONDYLITIS

W. M. COURT-BROWN, O.B.E., M.B., B.Sc., F.F.R.
and R. DOLL, O.B.E., M.D., F.R.C.P.

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PREFACE

The increase in the number of deaths from leukaemia has been one of the striking features of the national vital statistics over the last thirty years, and in December 1954, the Medical Research Council convened a conference under the chairmanship of Professor L. J. Wits to consider its possible causes. Factors such as the increasing use of new kinds of drugs, changes in diet, and the influence of infections were reviewed; but discussion centred mainly on the effects of ionizing radiations, since reports of increased mortality from leukaemia in Nagasaki and Hiroshima after the atomic explosions of 1945, as well as results obtained from experimental studies on animals, had produced convincing evidence that such radiations could induce the disease. Following the conference, a Working Party on leukaemia research was formed, and an investigation was sponsored into the reported increased incidence of leukaemia among patients given X-ray treatment for ankylosing spondylitis, to which attention had been directed by a preliminary memorandum from Professor B. W. Windeyer and Dr. W. M. Court-Brown. In June 1955, an account of this investigation, published by Dr. Court-Brown and Dr. J. D. Abbott, confirmed that such patients did in fact show a somewhat increased mortality from leukaemia.

Meanwhile, in March 1955, the Medical Research Council had been requested to appoint a committee to report to Parliament on the hazards to man of nuclear and allied radiations. One of the main questions which the Committee had to consider concerned the long-term effects of small doses of radiation, but very little evidence was available to enable them to assess this risk. Accordingly, Dr. Court-Brown and Dr. Richard Doll were asked to undertake, as a matter of urgency, a more extensive investigation of patients with ankylosing spondylitis who had been treated with X-rays, to assess the death rate among them from leukaemia and aplastic anaemia, and to attempt to determine the relationship between the doses of radiation given and the subsequent incidence of these diseases.

The extended survey began in August 1955, and was completed within nine months. In that period the records of over 13,000 patients distributed among 81 radiotherapy centres were investigated, the patients followed up, physical investigations on the estimation of the actual radiation received by the bone marrow carried out, and assessments made of the doses received by each patient over the period of survival, which in some cases extended up to 20 years. That this exacting programme was carried out in so short a time reflects the highest credit on the many members of the Council’s staff, of University departments, and of radiotherapy centres, who lent their aid, and particularly on Dr. Court-Brown and Dr. Doll, who planned and directed the investigation. Even so, the findings that were summarized in the White Paper on ‘The Hazards to Man of Nuclear and Allied Radiations’, published in June 1956, could only be a preliminary assessment. The present Report gives a further analysis of the data, and it is gratifying to note that the results are entirely consistent with those reported in the preliminary assessment.

As was said above, the present investigation was undertaken in the hope of obtaining an indication of the effects of small doses of radiation on human beings. From the nature of the case this could not be obtained directly, for few of the patients had received less than a mean dose of 250 r. to the bone marrow; but it was hoped that a sufficiently precise relationship between the high doses of radiation studied and the corresponding increased incidence of leukaemia
PREFACE

could be derived to allow extrapolation to be made with reasonable confidence to lower levels of dosage. Unfortunately this hope was not fully realized, for it is possible to derive more than one type of dose-response relationship from the data. In the opinion of Dr. Court-Brown and Dr. Doll, however, the results can best be explained by the working hypothesis that the incidence of leukaemia, following all but the highest doses of radiation, is directly proportional to the dose received by the bone marrow and that this simple proportional relationship holds even for the lowest doses. If this hypothesis were established, it would clearly be of great importance; although, for practical purposes, the risk to the individual of, for example, exposure to the small doses of radiation used in many radiological diagnostic procedures would be so minute that it could almost always be ignored. The authors are careful to point out, however, that their suggestion is not the only one compatible with the data, and they stress that until much more work has been done it will not be possible to decide between the alternative hypotheses.

Although the results of this investigation fall short of being decisive, they represent the most substantial contribution to date on the increasingly important subject of the relationship between exposure to radiation and the occurrence of ill effects.

MEDICAL RESEARCH COUNCIL,
38 Old Queen Street,
London, S.W.1

18th April, 1957
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LEUKAEMIA AND APLASTIC ANAEMIA
IN PATIENTS IRRADIATED FOR ANKYLOSING SPONDYLITIS

Introduction

The national mortality statistics of England and Wales show an almost unbroken rise in the annual death rate from leukaemia, from 17 per million living persons of both sexes in 1931 to 49 per million in 1954 (Table 1). This increase is substantial, and, according to Hewitt (1955), proportionately greater than that for any other cause of death, apart from cancer of the lung and coronary thrombosis. Similar trends have been noted in other countries; data for Canada, the United States, Denmark, Eire and Scotland are given in Table 2.

To some extent this increase may be due to the change which has taken place in the concept of leukaemia over the past few years, and in particular to the recognition of aleukaemic leukaemia as a form of the disease. Improvements in diagnostic techniques, and the effects of the introduction of the National Health Service in 1948, may also have contributed to the trend, though the rise in the leukaemia mortality figures in countries where there has been no similar reorganization of the medical services argues against this latter possibility.

The changing concept of leukaemia is reflected in the revisions that have been made from time to time in the International List of the Causes of Death. Before 1920, leukaemia, aleukaemic leukaemia and ‘pseudo-leukaemia’ were classified together with Hodgkin’s disease. After that date a separate category was created for leukaemia, though aleukaemic leukaemia was not separated from Hodgkin’s disease and classified with leukaemia until the revision of 1938. Finally, ten years later, leukaemia was recognized as a malignant disease, and a sub-classification was introduced to allow cytological differentiation. In so far as is possible, the Registrar-General has allowed for the effect of the 1938 revision and has published revised figures for the years 1931–39 (Registrar-General, 1940); it is those revised figures that are quoted for this period in Table 1.

It seems likely from these considerations that the increase in the recorded mortality rates for leukaemia may be partly artificial, but the extent of the increase, and its persistence in recent years, suggest that there has also been a real increase in incidence. It may therefore be supposed that some leukaemogenic stimulus in the environment has gradually intensified over the past few decades; and since ionizing radiations are believed, when given in large doses, to be capable of causing leukaemia in man, it has been thought that there may be a connexion between the rising incidence of the disease and the increasing use of nuclear and allied radiations, even in comparatively small amounts. The aim of the present investigation was to test this hypothesis, (a) by determining the incidence of leukaemia and of aplastic anaemia following radiotherapy, and (b) by examining the relationship between the dose of radiation and the subsequent incidence of the diseases for those levels of dose commonly used in radiotherapy, thereby indirectly obtaining an indication of the effect of lower doses.
Radiation and Leukaemia

Table 1
The death rate from leukaemia per million persons: England and Wales, 1931–54

<table>
<thead>
<tr>
<th>Year</th>
<th>Death rate per million persons</th>
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<tbody>
<tr>
<td></td>
<td>Men</td>
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<tr>
<td>1931</td>
<td>19</td>
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<td>1953</td>
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<tr>
<td>1954</td>
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Table 2
The death rate from leukaemia per million persons: various countries, 1940–54*

<table>
<thead>
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<th>Year</th>
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<tr>
<td></td>
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<tr>
<td>1954</td>
<td>51</td>
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</table>

* Data are not available for re-calculating the mortality rates for the years before 1940 on the basis of the 1938 revision.
PART I. THE INCIDENCE OF LEUKAEMIA AND OF APLASTIC ANAEMIA AFTER X-IRRADIATION

Method of Investigation

SELECTION OF PATIENTS FOR STUDY

It was planned to include in the investigation all patients treated for ankylosing spondylitis by means of ionizing radiations during the years 1935–54 at 82 radiotherapy centres in Britain. The diagnosis was taken to include all the conditions listed in the ‘Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death’ (World Health Organization, 1949) under the code number 722-1, i.e. Marie-Strümpell disease, Von Bechterew’s disease, ankylosing spondylitis and spondylitis ankylopoietica and rhizomelicia. Patients diagnosed as having ‘spondylitis’ without qualification were also included, since many patients given this diagnosis in the past would now be diagnosed as having ankylosing spondylitis. The inclusion of this last group of patients is unlikely to have introduced many with conditions other than ankylosing spondylitis, but it is recognized that, from a diagnostic standpoint, the patients do not constitute a completely homogeneous group. This, however, was unavoidable, since the criteria for the diagnosis of ankylosing spondylitis varied, and it was impossible to review the clinical and radiological condition of each patient individually.

Patients were excluded from the series only if they fell into one of three categories as a result of which it would have been difficult or impossible to obtain the relevant details of X-ray dosage and subsequent history. These categories were:

1. patients previously treated by ionizing radiations, (a) abroad, (b) privately,
or a clinic which remained outside the National Health Service, or
at a clinic the specification of which was unknown, or, (c) at any clinic
before 1935;
2. patients known to have been domiciled abroad at the time of first treat-
ment; and,
3. patients whose radiotherapy notes could not be found or were grossly
incomplete.

Patients treated previously at clinics other than those co-operating in the investigation were not excluded, even if the clinics were no longer functioning radiotherapy centres, so long as the hospitals to which they had been attached became part of the National Health Service. No patient having once been accepted into the series was subsequently excluded because of a change of diagnosis or for any other reason.

Of the 82 radiotherapy centres, 81 in fact co-operated in the investigation, namely, 74 out of the 75 centres at which radiotherapy was provided by the National Health Service in England, Scotland and Wales on July 28th, 1955, and 7 centres which had become sub-centres under the National Health Service but which still maintained independent records of the patients treated previously*. Several other sub-centres were known to have kept independent records but they were excluded because these records were no longer available. A list of the co-operating centres is given in Appendix F (p. 131).

* The principal centre not included in the investigation agreed to co-operate but had to be excluded because the record system did not allow the specified patients to be identified in time.
4 RADIATION AND LEUKAEMIA

Data were also collected for as many other patients as could be discovered who had suffered from both ankylosing spondylitis and either leukaemia, aplastic anaemia or myelofibrosis (myelosclerosis).

EPIDEMIOLOGICAL DATA RECORDED

Each centre was visited between August and November 1955, by one or more members of a team of workers (Appendix E, p. 130) and a list was prepared of the patients to be studied. In some cases this was a simple task—for example, when a diagnostic index of patients had been kept by the centre since the beginning of the period under investigation; but often it involved a search through indexes or treatment cards of all the patients treated by radiotherapy for all conditions. Exhaustive efforts were made to identify every patient who should have been included, but some must certainly have been omitted. At some centres the notes of patients treated before a certain date were known to have been destroyed, and sometimes patients whose names had not been recorded initially have been traced as a result of information received from other sources. At other centres it seemed likely that the lists obtained were complete. The effect of the failure to compile complete lists at all the centres is considered in Appendix D (p. 126).

The following data were recorded for each patient:—

Name of patient, and centre reference number
Last known address
Other identification numbers when available (e.g. National Health Service, Ministry of Pensions, or Service numbers)
Married state
Age at first treatment (with date of birth, if known)
Date of first treatment
Date last known to be alive,
or date known to have left Britain permanently,
or date and cause of death
Centres at which any previous radiotherapy had been given, and dates of treatment
Centres at which any subsequent radiotherapy was given, and dates of treatment
Dates of beginning and end of each course of treatment started at the centre before 31st December, 1954
Initial diagnosis
Any subsequent change of diagnosis
Associated clinical conditions, or conditions of special interest developing subsequently.

For the purpose of the investigation a 'course of treatment' was defined as a period during which the patient was irradiated with no interval of more than one calendar month between successive treatments.

IDENTIFICATION OF PATIENTS DEVELOPING ONE OF THE SPECIAL CONDITIONS

Information that a patient had developed leukaemia, aplastic anaemia or myelofibrosis came from the following sources:—

(1) data submitted by physicians,
(2) the follow-up records at the co-operating centres,
(3) the death certificates of patients recorded by the centres as being dead, but for whom the cause of death was not known, and,
The incidence of leukaemia and of aplastic anaemia

(4) Data provided specially by the Registrars-General of the United Kingdom regarding all persons dying of leukaemia or aplastic anaemia.

These last data were obtained for the entire period 1935–54 for persons resident in Northern Ireland, the Isle of Man and the Channel Islands, but for those resident in Scotland only the period 1939–54 was covered, and for those resident in England and Wales only the period 1945–54. The information thus obtained led to the identification of the cause of death for a number of patients in the study series who had been lost sight of before 1955. To compensate for the lack of data for England and Wales for the years before 1945, the national records at Somerset House were searched for deaths occurring prior to 1945 among the patients who were lost sight of before that date at the radiotherapy centres.

Review of Diagnoses

For comparison with national mortality rates it was necessary to classify the dead patients according to the certified cause of death, irrespective of whether this was believed to give the most accurate description of the underlying pathological condition. Copies of the death certificates were therefore obtained for all patients who had died, if it was suspected that they had died of leukaemia or aplastic anaemia; and the deaths were classified, in the first place, according to the cause given on the certificate.

It was also necessary to classify the patients according to what was later thought to be the most accurate diagnosis. Full clinical and pathological data were therefore collected, and the conditions were re-classified on the basis of the best available evidence. Considerable difficulty was encountered with the diagnoses of the patients certified as having died of aplastic anaemia, and accordingly the pathological material for these patients, when available, was submitted to two independent authorities, Professor J. V. Dacie and the late Sir Lionel Whitby, for their opinions.

Data

The Patients in the Study Series

The number of patients listed as having been irradiated for presumed ankylosing spondylitis at the co-operating centres was 13,784. Of these, 432 (3·1 per cent) were excluded from the study series for the reasons given above, i.e., 251 (1·8 per cent) who had been treated at a centre from which dosage data could not readily be obtained, 52 (0·4 per cent) who had been domiciled abroad, and 129 (0·9 per cent) whose radiotherapy notes were unavailable or incomplete. There were, therefore, 13,352 patients left for study. Table 3 shows the patients classified by sex, age and number of courses of treatment; Table 4 shows them classified by sex, number of courses of treatment and year of first treatment. It is clear that the majority of patients given only one course have been treated since 1950, and that most of the patients given multiple courses have been followed for a longer period. It can be seen also that young men have been given, on the average, more courses of treatment than older men and than women. These differences will be taken into account later, when comparisons are made between the incidence of leukaemia in different groups of patients.

Patients reported as having both ankylosing spondylitis and either leukaemia, aplastic anaemia or myelofibrosis, whether included in the study series or not, are discussed in the following section.
### TABLE 3

The patients in the study series classified by sex, age and number of courses of treatment

<table>
<thead>
<tr>
<th></th>
<th>Age at first treatment reported in inquiry (years)</th>
<th>Patients studied</th>
<th>Treatment at 2 or more centres*</th>
<th>Total</th>
<th>%</th>
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* The patients treated at two or more centres include 323 whose first treatment was not reported in the inquiry. Of these patients, at the time of first treatment, 77 men and 8 women were aged 14–24 years, 113 men and 21 women were aged 25–34 years, 54 men and 7 women were aged 35–44 years, 18 men and 4 women were aged 45–54 years, 11 men and 3 women were aged 55 years or over, and 6 men and 1 woman did not have their ages recorded.

Of these same patients, at the time of the first treatment reported in the inquiry, 38 men and 5 women were aged 14–24 years, 115 men and 17 women were aged 25–34 years, 73 men and 14 women were aged 35–44 years, 32 men and 4 women were aged 45–54 years, 15 men and 3 women were aged 55 years or over and 6 men and 1 woman did not have their age recorded.
THE INCIDENCE OF LEUKAEMIA AND OF APLASTIC ANAEMIA

TABLE 4
The patients in the study series classified by sex, number of courses of treatment, and year of first treatment

<table>
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<th>Year of first treatment reported in inquiry</th>
<th>1 course</th>
<th>2 courses</th>
<th>3 courses</th>
<th>4 or more courses</th>
<th>Treatment at 2 or more centres</th>
<th>Total</th>
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<tr>
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<td>87 16</td>
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<td>111 27</td>
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<td>934</td>
</tr>
<tr>
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<td>288 52</td>
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<td>101 15</td>
<td>101 14</td>
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<td>90 9</td>
<td>81 12</td>
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<td>227 68</td>
<td>93 31</td>
<td>52 13</td>
<td>63 11</td>
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<td>54 7</td>
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</tr>
<tr>
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<td>200 45</td>
<td>55 5</td>
<td>14 5</td>
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</tr>
<tr>
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<td>798 162</td>
<td>95 25</td>
<td>11 3</td>
<td>1 0</td>
<td>25 5</td>
<td>930</td>
</tr>
</tbody>
</table>

All years | 6,059 1,156 | 2,306 459 | 1,018 208 | 965 154 | 939 88 | 11,287 2,065 |

PATIENTS DEVELOPING ONE OF THE SPECIAL CONDITIONS

Altogether 72 patients have been reported as having ankylosing spondylitis and one of the special conditions under investigation—49 observed in the study series of 13,352 patients and 23 outside the series.

Irradiated Patients in the Study Series

Data for patients in the study series are summarized in Table 5, which shows: the sex of the patients and their age at the time of first treatment; the date of first treatment and of death; the certified cause of death; and the diagnosis finally preferred. Case histories of the individual patients are given in Appendix A (p. 51). Patients in whom the preferred diagnosis is leukaemia have been divided into two groups, according to the degree of confidence attached to the diagnosis. For those in Group A, the diagnosis is believed to be established; for those in Group B the balance of evidence suggests that leukaemia is the most likely diagnosis, but the diagnosis is not proven. The patients include 23 of the 25 patients previously reported by Court-Brown and Abbott (1955). The 24th patient in their series presented with back pain of short duration and acute myeloid leukaemia; X-ray examination showed no evidence of ankylosing spondylitis, and on review it appears that this patient was never regarded as a
## RADIATION AND LEUKAEMIA

### TABLE 5

Patients reported to have developed leukaemia, aplastic anaemia, or myelofibrosis: study series

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<th>Case no.</th>
<th>Sex</th>
<th>Age at first treatment (years)</th>
<th>Date of first treatment</th>
<th>Date of death</th>
<th>Certified cause of death*</th>
<th>First disease</th>
<th>Clinical type</th>
<th>Cell type</th>
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<td>47</td>
<td>F</td>
<td>44</td>
<td>6.50</td>
<td>21.11.52</td>
<td>Aplastic anaemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>F</td>
<td>52</td>
<td>6.65</td>
<td>27.10.50</td>
<td>Aplastic anaemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>F</td>
<td>56</td>
<td>6.65</td>
<td>21.2.51</td>
<td>Aplastic anaemia</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The condition given is that to which death was attributed according to the Registrar-General’s rules for the classification of causes of death. If death was not attributed to leukaemia or aplastic anaemia but one of these conditions was referred to on the death certificate, that condition is given in parentheses.

† Presenting in an aplastic phase.

‡ Classified with leukaemia (204) by the Registrar-General.
THE INCIDENCE OF LEUKAEMIA AND OF APLASTIC ANAEMIA

genuine spondylitic. The 25th patient (Case 50) has been excluded from the study series for reasons which are given later (p. 10).

Of the 49 special cases, 28 were certified as having died of leukaemia or of an allied condition classified by the Registrar-General with leukaemia*, 12 as having died from aplastic anaemia, and 6 as having died from other conditions but with evidence to indicate that they suffered also from leukaemia or aplastic anaemia†. Three patients known to have leukaemia were still alive at the end of 1955.

The hospital case records of the 28 patients certified as having died of leukaemia (Cases 1, 4–7, 9–13, 15–23, 25–27, 29–31, and 33–35) and of the 3 patients reported as having leukaemia who were still alive at the end of 1955

TABLE 6

Patients certified as dying with aplastic anaemia, showing the minimum length of the latent period and the duration of the illness: study series

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex</th>
<th>Age at first treatment (years)</th>
<th>Date of first treatment</th>
<th>Date of last treatment</th>
<th>Date of onset of illness</th>
<th>Interval between last treatment and onset of illness (months)</th>
<th>Date of death</th>
<th>Duration of illness (months)</th>
<th>Review of pathological material</th>
<th>Preferred diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>M</td>
<td>44</td>
<td>11.40</td>
<td>4.47</td>
<td>&lt; 7</td>
<td>29.8.48</td>
<td>9 to 16</td>
<td>No</td>
<td>Leukaemia (A)</td>
<td></td>
</tr>
<tr>
<td>3*</td>
<td>M</td>
<td>32</td>
<td>4.42</td>
<td>6.46</td>
<td>3.50</td>
<td>45</td>
<td>13.2.51</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>M</td>
<td>69</td>
<td>4.51</td>
<td>6.51</td>
<td>6.53</td>
<td>24</td>
<td>8.9.53</td>
<td>Yes</td>
<td>Leukaemia (B)</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>M</td>
<td>43</td>
<td>1.42</td>
<td>8.52</td>
<td>11.52</td>
<td>3</td>
<td>18.5.53</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>F</td>
<td>53</td>
<td>9.48</td>
<td>5.50</td>
<td>7.52</td>
<td>26</td>
<td>30.8.52</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>F</td>
<td>40</td>
<td>3.49</td>
<td>5.50</td>
<td>2.53</td>
<td>33</td>
<td>6.8.53</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>F</td>
<td>49</td>
<td>9.49</td>
<td>11.00</td>
<td>9.53</td>
<td>34</td>
<td>26.12.23</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>M</td>
<td>70</td>
<td>11.51</td>
<td>1.52</td>
<td>5.55</td>
<td>40</td>
<td>26.7.55</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>M</td>
<td>43</td>
<td>9.44</td>
<td>5.50</td>
<td>9.53</td>
<td>40</td>
<td>13.11.53</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>M</td>
<td>57</td>
<td>3.47</td>
<td>9.52</td>
<td>5.53</td>
<td>8</td>
<td>11.7.53</td>
<td>Yes</td>
<td>Aplastic anaemia</td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>M</td>
<td>40</td>
<td>6.48</td>
<td>6.48</td>
<td>7.48</td>
<td>&lt; 1</td>
<td>14.3.49</td>
<td>Yes</td>
<td>Aplastic anaemia</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>M</td>
<td>55</td>
<td>12.48</td>
<td>3.53</td>
<td>12.53</td>
<td>9</td>
<td>30.4.54</td>
<td>Yes</td>
<td>Aplastic anaemia</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>M</td>
<td>55</td>
<td>7.49</td>
<td>5.50</td>
<td>7.52</td>
<td>26</td>
<td>13.9.52</td>
<td>Yes</td>
<td>Aplastic anaemia</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>M</td>
<td>65</td>
<td>6.50</td>
<td>7.50</td>
<td>8.50</td>
<td>&lt; 1</td>
<td>2.11.52</td>
<td>Yes</td>
<td>Aplastic anaemia</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>F</td>
<td>52</td>
<td>6.45</td>
<td>3.49</td>
<td>?</td>
<td>7</td>
<td>27.10.50</td>
<td>Yes</td>
<td>Aplastic anaemia</td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>F</td>
<td>56</td>
<td>6.45</td>
<td>10.45</td>
<td>4.50</td>
<td>54</td>
<td>21.2.51</td>
<td>Yes</td>
<td>Aplastic anaemia</td>
<td></td>
</tr>
</tbody>
</table>

* Certified diagnosis: 'hypoplastic anaemia'.

(Cases 8, 28 and 36) provided good evidence of the correctness of the diagnosis, with the exception of one case (21) for which the hospital records were missing; in none has the diagnosis been altered. Neither was there any reason to question the diagnosis of leukaemia in the 2 patients certified as having died of other conditions, but in whom leukaemia was mentioned as a contributory cause of death (Cases 14 and 24). In 3 patients (hereafter termed 'co-existent cases') leukaemia is thought to have been already present at the time of first irradiation (Cases 15, 33, 34). This finding is of importance in the interpretation of the results and is discussed later. These 3 patients are excluded from the 'A' series in subsequent analyses of mortality, latent period and dose-response relationship, as, in the authors’ opinion, the occurrence of their disease cannot be related to their exposure to therapeutic radiation.

The result was different when the case records were examined of the 12 patients certified as having died of aplastic anaemia (Cases 2, 32, 37–44, 46

* Erythraemic myelosis (Case 29); malignant myelosclerosis (Case 27)
† Including one diagnosed as hypoplastic anaemia (Case 3)
and 49) and of the 4 others in whom aplastic anaemia was reported (Cases 3, 45, 47 and 48). In only 2 of these patients did the disease follow immediately after irradiation (Cases 44 and 47). In most of the others the onset of the disease was a year or more after the cessation of radiotherapy, and its progress was rapid, and unaffected by blood transfusion. In one patient (Case 2), a period in which a diagnosis of aplastic anaemia was considered probable was followed by clear evidence of leukaemia, and this diagnosis was firmly established before the patient died. In several other instances, blood counts or marrow smears suggested that the true diagnosis might have been aleukaemic leukaemia. Finally it was decided that in 4 patients there was insufficient evidence for a definitive diagnosis to be made; in 4 the certificated diagnosis has been accepted; in 3 a diagnosis of leukaemia is considered to have been established (‘A’ cases); and in 5 it is considered probable (‘B’ cases). Details of all these cases are given in Table 6. The criteria for the diagnosis of aplastic anaemia and for the classification of a case as probably one of leukaemia are discussed on p. 16.

Irradiated Patients not in the Study Series

Fifteen additional patients, not in the study series, are known to have had their spondylitis treated with X-rays before the onset of leukaemia, aplastic anaemia or myelofibrosis became apparent; data concerning them are summarized in Table 7. Seven of the patients were treated in Holland, and case histories were published by van Swaay (1955); the data are reproduced in the table for ease of comparison (Cases 58–64). Histories of the remaining 8 cases (50–57) are given in Appendix A (p. 89). Of these patients, 2 were treated in Canada (Cases 54–55) and 2 in the U.S.A. (Cases 56 and 57); the data for one of these were reported in response to a request in the British medical press by the Medical Research Council. Some of the data relating to one of the American cases (Case 57) and references to the 2 Canadian cases have been published previously (Wyatt and Sommers, 1950; Robinson and Lampe, 1948). The remaining 4 patients were treated in Britain; 2 were treated for their spondylitis privately at clinics not covered by the study (Cases 51 and 52); one was treated at one of the co-operating centres, but was not included in the series because the diagnosis had been altered to osteo-arthritis immediately before radiotherapy was begun (Case 50*); the fourth was also treated at one of the co-operating centres, but was overlooked initially when the list of patients was prepared (Case 53).

The diagnosis of leukaemia was established in 11 cases. One patient was diagnosed as having died of myelofibrosis, and 3 were considered to have died of aplastic anaemia; in none of these 4 patients was pathological material available for review. The patient diagnosed as having myelofibrosis did not present the syndrome characteristically associated with myelofibrosis and he may, perhaps, be regarded as having had an atypical form of leukaemia; the pathological data and the progress of the disease are reminiscent of two patients in the study series in whom an atypical myelofibrosis was reported (Cases 27 and 41, Appendix A). In the patients reported as having had aplastic anaemia the disease does not conform to the type which follows immediately after a limited period of intensive radiation and it is possible that one or more of them may have had aleukaemic leukaemia.

* The orthopaedic surgeon in charge of this case continued to prefer the diagnosis of ankylosing spondylitis.
### Table 7

Patients known to have developed leukaemia, aplastic anaemia or myelofibrosis after irradiation for ankylosing spondylitis: additional cases not in the study series

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex</th>
<th>Age at first treatment (years)</th>
<th>Date of first treatment</th>
<th>Date of death</th>
<th>Diagnosis*</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>M.</td>
<td>35</td>
<td>12.50</td>
<td>18.5.54</td>
<td>Leukaemia</td>
<td>Present investigation</td>
</tr>
<tr>
<td>51</td>
<td>M.</td>
<td>42</td>
<td>11.52</td>
<td>22.1.56</td>
<td>Leukaemia</td>
<td>Dr. J. H. L. Easton, Britain (personal communication)</td>
</tr>
<tr>
<td>52</td>
<td>F.</td>
<td>59</td>
<td>6.45</td>
<td>24.9.53</td>
<td>Leukaemia</td>
<td>Present investigation</td>
</tr>
<tr>
<td>53</td>
<td>M.</td>
<td>61</td>
<td>9.52</td>
<td>12.10.54</td>
<td>Aplastic anaemia ? Leukaemia</td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>M.</td>
<td>41</td>
<td>6.42</td>
<td>21.12.45</td>
<td>Leukaemia</td>
<td>Drs. D. C. and W. Graham, Canada (personal communication)</td>
</tr>
<tr>
<td>56</td>
<td>M.</td>
<td>51</td>
<td>7.48</td>
<td>Alive 6.55</td>
<td>Leukaemia</td>
<td>Dr. S. C. Sommers, U.S.A. (personal communication)</td>
</tr>
<tr>
<td>57</td>
<td>M.</td>
<td>44</td>
<td>c.11.38</td>
<td>21.12.45</td>
<td>Myelofibrosis</td>
<td>Dr. S. C. Sommers, U.S.A. (personal communication)</td>
</tr>
<tr>
<td>58</td>
<td>M.</td>
<td>25</td>
<td>?</td>
<td>At age 35</td>
<td>Leukaemia</td>
<td>van Swaay (1955)</td>
</tr>
<tr>
<td>59</td>
<td>M.</td>
<td>41</td>
<td>7.43</td>
<td>5.46</td>
<td>Leukaemia</td>
<td>van Swaay (1955)</td>
</tr>
<tr>
<td>60</td>
<td>M.</td>
<td>55</td>
<td>11.48</td>
<td>11.49</td>
<td>Leukaemia</td>
<td>van Swaay (1955)</td>
</tr>
<tr>
<td>61</td>
<td>M.</td>
<td>56</td>
<td>10.38</td>
<td>11.42</td>
<td>Leukaemia</td>
<td>van Swaay (1955)</td>
</tr>
<tr>
<td>62</td>
<td>F.</td>
<td>62</td>
<td>6.49</td>
<td>8.52</td>
<td>Leukaemia</td>
<td>van Swaay (1955)</td>
</tr>
<tr>
<td>63</td>
<td>M.</td>
<td>46</td>
<td>1.48</td>
<td>9.51</td>
<td>Aplastic anaemia</td>
<td>van Swaay (1955)</td>
</tr>
<tr>
<td>64</td>
<td>M.</td>
<td>58</td>
<td>7.49</td>
<td>5.51</td>
<td>Aplastic anaemia</td>
<td>van Swaay (1955)</td>
</tr>
</tbody>
</table>

* For Cases 50–53 the diagnosis in ordinary type is that certified as the cause of death; for Cases 54–64 it is that preferred by the physician reporting the case. Words in italics are added by the present authors, or represent the diagnosis preferred after review of the data.
† Presenting in aleukaemic phase.
‡ These two cases are those referred to (p. 10) in the discussion of the report by Robinson and Lampe (1948).
§ The case corresponds to Case 5 reported by Wyatt and Sommers (1950).
¶ Dates given by Dr. van Swaay in a personal communication.
12 RADIATION AND LEUKAEMIA

Unirradiated Patients

The remaining 8 patients (Cases 65–72) are not known to have had previous radiotherapy for their spondylitis; data concerning them are given in Appendix A and are summarized in Table 8. Six were recorded in Britain in the course of the present investigation, 2 having come under observation at the co-operating centres (Cases 65 and 66), 3 having been discovered from the

**TABLE 8**

Patients with ankylosing spondylitis known to have developed leukaemia, aplastic anaemia or myelofibrosis and believed not to have been treated with ionizing radiations: all cases

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex</th>
<th>Age at death or, if alive, at 1.56</th>
<th>Date of death</th>
<th>Diagnosis*</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>M</td>
<td>73</td>
<td>8.12.53</td>
<td>Leukaemia</td>
<td>Chronic Lymphatic</td>
</tr>
<tr>
<td>66</td>
<td>M</td>
<td>62</td>
<td>21.7.54</td>
<td>Leukaemia</td>
<td>Chronic Myeloid</td>
</tr>
<tr>
<td>67</td>
<td>M</td>
<td>61 Alive 1.56</td>
<td></td>
<td>Leukaemia</td>
<td>Chronic Lymphatic</td>
</tr>
<tr>
<td>68</td>
<td>M</td>
<td>41</td>
<td>7.4.54</td>
<td>Leukaemia</td>
<td>Acute Myeloid</td>
</tr>
<tr>
<td>69</td>
<td>M</td>
<td>39</td>
<td>26.9.54</td>
<td>Aplastic anaemia Megaloblastic anaemia</td>
<td>—</td>
</tr>
<tr>
<td>70</td>
<td>F</td>
<td>54</td>
<td>25.5.54</td>
<td>Aplastic anaemia Agranulocytosis</td>
<td>—</td>
</tr>
<tr>
<td>71</td>
<td>M</td>
<td>29</td>
<td>24.2.48</td>
<td>Leukaemia</td>
<td>Acute† Myeloid</td>
</tr>
<tr>
<td>72</td>
<td>M</td>
<td>?</td>
<td>5.55</td>
<td>Leukaemia</td>
<td>? Myeloid</td>
</tr>
</tbody>
</table>

* For Cases 65–66 and 68–70 the diagnosis in ordinary type is that certified as the cause of death; for Cases 67 and 71–72, it is that preferred by the physician reporting the case. The diagnosis in italic is that preferred after review of the data.
† Presenting in aleukaemic phase.

association of spondylitis and leukaemia or aplastic anaemia on the death certificates (Cases 68–70) and one having been reported in response to the Medical Research Council's request for information (Case 67). The 2 remaining patients were also reported in response to this request—one from the U.S.A. (Case 71) and one from Hungary (Case 72).

A diagnosis of leukaemia had been made in 6 of the patients. The other 2 patients were certified as having died of aplastic anaemia. The pathological and
THE INCIDENCE OF LEUKAEMIA AND OF APLASTIC ANAEMIA

clinical data obtained for one of them (Case 69) suggest that the patient may have died from megaloblastic anaemia. No post-mortem examination was made in the other (Case 70) but the hospital records suggest that the patient died from a form of agranulocytosis.

Findings

OBSERVED AND EXPECTED DEATHS: THE DIFFERENCE RECORDED

Leukaemia

The number of deaths from leukaemia which could have been expected to occur among the patients in the study series in the absence of any unusual leukaemogenic stimulus was estimated as follows from the general mortality rates recorded in Britain over the years of the survey:

The size of the population at risk was determined separately for each sex, each five-year age group, and each of the years from 1935 to 1954. Each patient was considered to have been at risk for half a year in the year in which he was first treated at one of the co-operating centres. The maximum population at risk was then determined by assuming that each patient was at risk, and one year older, for each succeeding year up to and including 1954, or until the year in which he was known to have died or emigrated, whichever was the earlier. If he was known to have died or emigrated he was regarded as having been at risk for half a year for that year and as not having been at risk in any subsequent year. In the rare instances in which the patient died or emigrated in the year in which he was first treated, he was regarded as having been at risk for a quarter of that year. The numbers of years for which male and female patients were at risk were then added for each five-year age group for each of the twenty years covered by the survey, and the totals were multiplied by the sex- and age-specific mortality rates recorded in Britain for the relevant years.* Finally, the results were added together, and the sums gave, for each sex, the number of expected deaths. These expected deaths are maximum numbers, since they were calculated on the assumption that all the patients who were lost to follow-up survived to the end of 1954. Minimum expected numbers were calculated in a similar way, but on the assumption that all the patients died or emigrated in the year in which they were lost to follow-up. The true expected numbers must be presumed to lie somewhere between these limits—probably much closer to the maximum than to the minimum.

Since the expected numbers of deaths are derived from the mortality data of the Registrars-General, the observed numbers of deaths with which they are compared must be the numbers of deaths certified as due to leukaemia and so classified by the Registrars-General. The numbers of such deaths observed amongst the patients studied during the period 1935–54 and the corresponding maximum and minimum numbers expected are shown in Table 9.

Six deaths among men in the study series in 1955 are known to have been certified as due to leukaemia or to other conditions classified with leukaemia. New patients were not admitted to the population in 1955, and the population at risk in 1955 cannot have been very different from that at risk in 1954. The maximum expected mortality from leukaemia in 1955, must, therefore, be close

* Mortality rates for Britain as a whole were obtained from the data provided separately by the Registrars-General of England and Wales and of Scotland. Some of the Scottish populations in the early years had to be estimated by interpolation. Total populations were used, and civilian and non-civilian deaths were added together.
to the maximum mortality which was expected in 1954, i.e. 0.49. The figures for 1935-55 are, therefore: observed deaths, 28; maximum expected deaths, 2.9.

Three deaths from leukaemia occurred within the first year of treatment; in one of these patients leukaemia is known to have been present before treatment.

**Table 9**
The observed and expected numbers of deaths certified as due to leukaemia and aplastic anaemia, 1935-54: study series

<table>
<thead>
<tr>
<th>Disease group</th>
<th>Sex</th>
<th>Minimum expected</th>
<th>Maximum expected</th>
<th>Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukaemia (International List Code no. 204)</td>
<td>M.</td>
<td>1.25</td>
<td>2.06</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>F.</td>
<td>0.19</td>
<td>0.34</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>M. and F.</td>
<td>1.44</td>
<td>2.40</td>
<td>22</td>
</tr>
<tr>
<td>Aplastic anaemia (International List Code no. 292.4)</td>
<td>M.</td>
<td>0.12</td>
<td>0.20</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>F.</td>
<td>0.03</td>
<td>0.05</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>M. and F.</td>
<td>0.15</td>
<td>0.25</td>
<td>11</td>
</tr>
</tbody>
</table>

Significance of difference between observed and maximum expected number of deaths:

- Leukaemia: \( P < 0.000001 \)
- Aplastic anaemia: \( P < 0.000001 \)

was started, and in the other two it is believed to have been so. If these deaths and the corresponding expected mortality in the first year after treatment are omitted, the observed number and the maximum expected number of deaths for 1935-55 are 25 and 2.4 respectively.

**Aplastic Anaemia**

Data are not available for calculating by the same method the expected number of deaths from aplastic anaemia, since the Registrar-General for Scotland does not publish separate figures for deaths due to aplastic anaemia, and the Registrar-General for England and Wales has published them in detail only since 1950. An estimate of the maximum expected number of such deaths has been made by multiplying the maximum population in each 'sex' and 'age' group for all years added together by mortality rates obtained from the average annual number of deaths recorded in England and Wales in the corresponding 'sex' and 'age' groups over the years 1940-53, and from the population of England and Wales in 1952. The figure so obtained is more likely to be an underestimate than an overestimate of the true expected number, since, according to the Registrar-General, the total mortality from aplastic anaemia remained practically constant between 1940 and 1951 but increased appreciably in 1952 and 1953. The number of deaths which occurred among the patients studied during the period 1935-54 and the corresponding maximum and minimum numbers expected are shown in Table 9.
THE INCIDENCE OF LEUKAEMIA AND OF APLASTIC ANAEMIA

One further death among the patients in the study series is known to have been certified as due to aplastic anaemia in 1955; the corresponding expected mortality is of the order of 0·05. The figures for 1935–55 are, therefore: observed deaths, 12; maximum expected deaths, 0·3.

Limits of Error

The total number of deaths observed is not large, and random errors could have resulted in the excess mortality being appreciably over- or underestimated. Such errors are unlikely to have resulted in an overestimate in the deaths from leukaemia of more than 10, or an underestimate of more than 12; i.e. the ratio of the observed to the expected deaths in a larger series would be likely to lie between 18:2-9 and 40:2-9 or 6:2:1 and 13:8:1.

Systematic errors tending to exaggerate the differences have been largely compensated for by comparing the observed deaths with the maximum number of expected deaths. This would not be the case if the physicians who diagnosed the causes of death had been influenced to make the diagnosis of leukaemia or aplastic anaemia because the patient was a spondylitic or because he had been treated with X-rays; but the authors believe that so far the effect of such a factor has been insignificant. The differences on the other hand, are almost certainly underestimated, since the follow-up of patients has not been complete; 52 per cent were not followed in 1955 and as many as 19 per cent have been lost sight of since 1950 (Table 10). Comparison of the names of the untraced patients

<table>
<thead>
<tr>
<th>Status when last traced</th>
<th>No. of patients</th>
<th>% of total studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died before 31.12.55</td>
<td>352</td>
<td>48·3</td>
</tr>
<tr>
<td>Alive in 1955</td>
<td></td>
<td></td>
</tr>
<tr>
<td>.. 1954</td>
<td>1,991</td>
<td>14·9</td>
</tr>
<tr>
<td>.. 1953</td>
<td>1,019</td>
<td>7·6</td>
</tr>
<tr>
<td>.. 1952</td>
<td>729</td>
<td>5·5</td>
</tr>
<tr>
<td>.. 1951</td>
<td>658</td>
<td>4·9</td>
</tr>
<tr>
<td>.. 1950</td>
<td>585</td>
<td>4·4</td>
</tr>
<tr>
<td>.. 1945-49</td>
<td>1,538</td>
<td>11·5</td>
</tr>
<tr>
<td>.. 1940-44</td>
<td>334</td>
<td>2·5</td>
</tr>
<tr>
<td>.. 1935-39</td>
<td>51</td>
<td>0·4</td>
</tr>
<tr>
<td>Total</td>
<td>13,352</td>
<td>100·0</td>
</tr>
</tbody>
</table>

with the names of all persons certified as having died of leukaemia or aplastic anaemia in Britain will not necessarily have picked up all the relevant deaths; firstly, transcription errors are known to have occurred in the copying of the lists of deaths, and they must sometimes have occurred at various stages of the investigation and also when the hospital case notes were originally compiled; secondly, some women may have married, or re-married, without their change of name being recorded in the hospital notes; thirdly, it has not been possible to check the identity of a number of persons with common names who appear on both lists but with widely separated addresses; fourthly, no lists of deaths
were available for Scotland before 1939 or for England and Wales before 1945. Seven cases of leukaemia or aplastic anaemia were recognized when the list of untraced patients was checked against the lists of deaths provided by the Registrars-General; in the opinion of the authors it is unlikely that as many again should have been missed.

THE DIAGNOSIS OF APLASTIC ANAEMIA

Aplastic anaemia and aleukaemic leukaemia are conditions easily confused from the standpoint of diagnosis. In recognition of this fact the available pathological material of the 16 cases in which aplastic anaemia was recorded as either a main or subsidiary cause of death was reviewed by two authorities (p. 5). On the basis of their independent opinions it was decided that in only 4 cases (43, 44, 45, 47) could the diagnosis of aplastic anaemia be upheld, while in 2 cases (42, 46) neither the clinical histories nor the pathological findings justified a diagnosis of either aplastic anaemia or leukaemia. In 2 other cases (48, 49), both female, no definitive diagnoses were possible; in neither case was pathological material available for review, nor was there sufficient information in the clinical histories to permit provisional diagnoses of either leukaemia or aplastic anaemia to be made. Of the remaining 8 cases, 3 were held to be established examples of leukaemia (2, 3, 32), while 5 were considered likely to be cases of leukaemia (37, 38, 39, 40, 41).

The diagnosis of aplastic anaemia was accepted only on the basis of a grossly hypoplastic marrow and the absence of primitive cells in the peripheral blood. Cases 44 and 47 are similar, in that both developed acute anaemia within one month of the completion of their X-ray treatment. Of these, Case 44 presents features akin to those which are known to develop after a single dose of whole body radiation. The patient was treated by a field 20 cm. in breadth over the sacro-iliac joints and fields 12 cm. in breadth over the rest of the spine, with the exception of the cervical spine where the field was 8 cm. in breadth. A mean total dose of 1,034 r. was given to the spinal marrow at a rate of 406 r. per week, and the whole body integral dose was 22:1 Mg. r., given at a rate of 8:6 Mg. r. per week*.

Thus, a large fraction of the trunk was given a large dose of radiation at a high dose rate, and about two weeks later the patient developed acute anaemia. The second case (47) is more difficult to assess. The treatment given was conservative (mean total dose to spinal marrow, 541 r. at the rate of 196 r. per week; whole body integral dose, 9:3 Mg. r. at the rate of 3:4 Mg. r. per week), and it is known that the patient had been anaemic before irradiation. It is also thought that at some time before irradiation he had been treated with amidopyrine, although it has not been possible to verify this. Details of the case have been published previously (Sharp and Esson, 1954; Goodman, 1956). It seems clear that Cases 43 and 45 died from aplastic anaemia although their terminal illnesses developed respectively 8 and 9 months after their last exposure to X-rays. Both patients had several courses of X-ray treatment in none of which was the total dose unduly large. It is possible that the terminal illnesses may have been the result of damage to the bone marrow sustained during each course of treatment, cumulative in its effect, and to which the patients were unusually sensitive. On the other hand, the possibility cannot be excluded that the development of aplastic anaemia was in both cases the result of other causes altogether.

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* See p. 27 for a definition of the megagramme-roentgen (Mg. r.) unit.
THE INCIDENCE OF LEUKAEMIA AND OF APLASTIC ANAEMIA

Three patients whose deaths were reported as due to aplastic or hypoplastic anaemia have been placed in the 'A' series as having had established leukaemia (Cases 2, 3, 32). These patients are notable in that considerable difficulty was encountered in making the diagnoses, and each presented atypical features. Case 2 was under observation for about five months before the leukaemic condition was recognized, and Case 3 was investigated very fully for about six and a half months without a clear diagnosis of leukaemia being made. The histological findings in the liver and spleen of Case 32 suggest an unusual form of leukaemia —in the authors' opinion, possibly erythraemic myelosis. Two other patients in the 'A' series and certified as having died from leukaemia (Cases 24, 29) had also presented difficult diagnostic problems.

Of 5 cases (37, 38, 39, 40, 41) placed in the 'B' series, 4 are distinguished by the development of an acute haemopoietic disorder 26 or more months after the last exposure to X-rays, with no response to blood transfusion and ending fatally within a period of six months. The fifth case (37) died in 1953; the mean dose to the spinal marrow was 1,726 r. in 1942 and 602 r. in 1950, whereas in 1952, when treatment was given only to the right shoulder region, the mean spinal dose was considered too small to calculate; it is difficult to believe that the exposure in 1952 had much influence on the development of the terminal illness, so that the last effective radiation exposure was in October 1950, and was followed by an interval of 25 months before the onset of the terminal illness. In all 5 cases, immature myeloid cells were present at some time in the peripheral blood, while in 2 of them (37, 38) one member of the reviewing panel has made a diagnosis of leukaemia. In one of the remaining cases (40), one reviewer has suggested the possibility of leukaemia, although it is admitted that the evidence from the marrow is weak, because of the poor quality of the preparations. In one case (39), no material was available for review. In the final case of the 'B' series (Case 41), a diagnosis of myelofibrosis was established after death. This case ran a very acute course and during life there was only slight palpable enlargement of the spleen. There is a growing tendency to regard myelofibrosis as a variant of leukaemia, and the findings in Case 27, and possibly in Case 57, are evidence favouring such a concept. It was for this reason that Case 41 was placed in the 'B' series.

THE INCIDENCE OF LEUKAEMIA BY SEX AND AGE

Table 11 gives details of sex, age, and number of courses of treatment for the patients in the study series who developed leukaemia; separate figures are given for patients in whom the diagnosis is believed to be established ('A' cases) and for those in whom it is putative ('B' cases). Incidence rates, computed by dividing the numbers of cases by the corresponding numbers of patients at risk, are given in Table 12. To avoid the difficulty introduced by the fact that some patients treated at two or more centres were not reported by the centre which gave the first treatment, the calculations have been based solely on the data obtained for patients in whom the initial treatment was reported. Consequently 3 patients with leukaemia and 323 spandulitic patients treated at two or more centres have been excluded. Since there was a tendency for women of all ages and men over 35 to be given fewer courses of treatment than men under 35 (Table 3, p. 6), it was necessary to compute standardized rates taking into account the number of courses of treatment received if valid conclusions were to be drawn about the relative sizes of the rates for men and women and for different
Radiation and Leukaemia

Age groups. Standardized rates are, therefore, shown in Table 12 in preference to crude rates.*

From Table 12 it appears that the incidence of leukaemia is some three times greater in men than in women. The lower rate among women does not, however, necessarily mean that women run less risk of developing the disease than men. The numbers observed are small, and much of the observed difference could be due to the play of chance. It must also be borne in mind that follow-up is less efficient for women, because they may change their names and so be less easily identified in, for example, records of deaths. A further consideration is that women tend to be given somewhat less treatment than men, even when given the same number of 'courses', so that the standardized rates shown in Table 12 do not entirely allow for the difference in the amount of treatment received. It is, therefore, not possible to conclude whether or not there is a true sex-difference in the susceptibility to leukaemia following irradiation.

* Includes one patient whose first treatment was not reported in the inquiry; at the time of his first treatment his age was in the same group.
† Includes one patient whose first treatment was not reported in the inquiry; at the time of his first treatment he was aged 42 years.

For the calculation of these rates a standard population has been postulated of the same size as the population of patients studied, with the same total numbers of men and women and with the same totals of patients in the five 'treatment' groups. Within each 'treatment' and 'age' group, however, the proportions of men and women have been made equal to the proportions which obtain for the whole series. The numbers of cases have then been calculated which would have occurred if the observed rates for each 'sex', 'age' and 'treatment' sub-group had held for the corresponding sub-group of the standard population. Standardized rates were finally obtained by adding the calculated numbers of cases in each sub-group for each 'sex', 'age' or 'treatment' group, as the case might be, and dividing the sum by the total population in that group. For the purpose of these calculations, patients in the study series whose ages were not known were assumed to have been distributed among the different age groups in the same proportions as those whose ages were known.

Table 11
Patients in the study series who developed leukaemia, classified by sex, age and number of courses of treatment: 'A' and 'B' cases, excluding co-existent cases

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age at first treatment reported in inquiry (years)</th>
<th>No. of cases of leukaemia</th>
<th>Treatment at 2 or more centres</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 course</td>
<td>2 courses</td>
<td>3 courses</td>
</tr>
<tr>
<td>M.</td>
<td>14---</td>
<td>0 0 0 0</td>
<td>1 0 1 0</td>
<td>1 0 1 0</td>
</tr>
<tr>
<td></td>
<td>25---</td>
<td>2 0 2 0</td>
<td>1 0 4 0</td>
<td>1 0 2 0</td>
</tr>
<tr>
<td></td>
<td>35---</td>
<td>1 0 1 1</td>
<td>1 0 1 0</td>
<td>4* 0 4*</td>
</tr>
<tr>
<td></td>
<td>45---</td>
<td>2 0 0 1</td>
<td>1 0 1 0</td>
<td>2* 2*</td>
</tr>
<tr>
<td></td>
<td>55+</td>
<td>4 1 0 0</td>
<td>0 0 0 0</td>
<td>0 0 0 0</td>
</tr>
</tbody>
</table>
| All ages |                                          | 9 1 3 2 | 4 0 7 0 | 9 2 32 | 5 
| F.  | 25-34                                       | 0 0 0 0 | 0 0 0 0 | 0 0 0 0 | 1 0                |
| All ages |                                          | 0 0 0 0 | 0 0 0 0 | 0 0 1 0 | 1 0                |
| M. and F. |                                          | 9 1 3 2 | 4 0 7 0 | 10 2 33 | 5 

* Includes one patient whose first treatment was not reported in the inquiry; at the time of his first treatment his age was in the same group.
† Includes one patient whose first treatment was not reported in the inquiry; at the time of his first treatment he was aged 42 years.
The increase in incidence with age, from 1·1 per 1,000 aged less than 25 years to 5·6 per 1,000 aged 55 years and over, is too steady and too large to be wholly attributable to chance; it is sufficiently great to have to be taken into consideration when groups of patients within the series are compared with one another. The trend, apparent with the ‘A’ cases, is accentuated when the ‘B’ cases are included. The increase in incidence with the number of courses of treatment reflects the relationship between the incidence of leukaemia and the dose of radiation, which is considered in detail in Part II of the Report. The greatly increased rate among patients treated at two or more centres is due, at least in part, to an underestimate of the total number of such patients at risk (see p. 125).

It should be noted that the incidences discussed in this section have all been based on the total numbers of patients treated; no account has been taken of the varying numbers of years which the patients have lived following treatment. The effect of this variation can have made little difference to the validity of the comparison between the rates for men and for women or between those for the different age groups, but it is important in relation to the amount of treatment received. This last point will be discussed in detail in a later section (p. 27).

**THE LATENT PERIOD FOR LEUKAEMIA**

In this study the 'latent period' has been defined as the interval between the start of treatment and the first occasion on which positive evidence of the presence of the disease was obtained. It would, perhaps, have been more logical
to have set the limit of the period at the onset of symptoms, but several patients suffered from prolonged ill-health before succumbing to a rapidly fatal illness, and it was impossible to decide in any consistent manner the date of onset of the relevant symptoms.

**TABLE 13**
The relative frequency of different latent periods in leukaemia following one course of treatment: male 'A' and 'B' cases, excluding co-existent cases

<table>
<thead>
<tr>
<th>Period following treatment (months)</th>
<th>No. of man-years observed</th>
<th>No. of cases of leukaemia occurring</th>
<th>Morbidity rate per 10,000 man-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-11</td>
<td>10,491</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>12-23</td>
<td>6,570</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>24-35</td>
<td>5,040</td>
<td>2</td>
<td>4.0</td>
</tr>
<tr>
<td>36-47</td>
<td>3,892</td>
<td>4</td>
<td>10.3</td>
</tr>
<tr>
<td>48-59</td>
<td>2,988</td>
<td>4</td>
<td>13.4</td>
</tr>
<tr>
<td>60-71</td>
<td>2,198</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>72 or more</td>
<td>5,378</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

The number of patients available to provide data on the latent period is small, since the majority of the patients suffering from leukaemia had received two or more courses of treatment, and it was impossible in these cases to decide which course was relevant. If the patients with co-existent disease are omitted, there remain only 10 in the study series in whom the preferred diagnosis is leukaemia and who received only one course of treatment. The relative frequency of the different latent periods in these cases is shown in Table 13, together with the total numbers of men given one course of radiation and observed over the same periods, i.e., the numbers of man-years at risk. In the calculation of the man-years at risk, account has been taken of the period between the first and the second course of treatment in all the patients who received multiple courses, because during this period the patient ran the risk of developing the disease following the first course. From the table it is seen that (i) no cases occurred under 24 months from the start of treatment (ii) the maximum incidence was between 36 and 59 months, and (iii) no cases occurred after 60 months.

That cases can occur less than 24 months after the start of treatment is shown by one patient who developed leukaemia after having received three courses, but still only 15 months after the start of his first course (Case 31). In 2 of the cases observed outside the study series the latent period was also less than 24 months—8 months in one and 11 months in the other (Cases 55 and 60).

That cases can occur more than 60 months after treatment is shown by one patient who received three courses of treatment and developed leukaemia 12 years after the last course (Case 1); and by one of the patients outside the series who developed leukaemia 8 years after her only course of treatment (Case 52). It is possible that some, or even all, of these cases are spontaneous and unrelated to the previous irradiation, but it must also be borne in mind that the incidence of cases with long latent periods is likely to be relatively underestimated, because it is difficult to maintain follow-up of patients over a long period.
THE INCIDENCE OF LEUKAEMIA AND OF APLASTIC ANAEMIA

From these minimal data it would appear that the latent period for leukaemia after irradiation is seldom less than two years, that it is more frequently of the order of three to five years, and that longer periods are appreciably less common.

THE SIGNIFICANCE OF CELL TYPE

Since 1950 the Registrar-General has shown the numbers of deaths from leukaemia in England and Wales, separately for each of the principal cytological types. It has therefore been possible to compare the numbers of deaths certified as due to 'lymphatic', 'myeloid', 'monocytic', and 'other and unspecified' leukaemia with the numbers expected in each category. The expected numbers have been obtained by pooling the national data for the years 1950–54 and calculating the proportions attributed to each of the four types of leukaemia in each sex and 5-year age group. The estimated numbers of deaths expected in the spondylitic population in each sex and 5-year age group have then been multiplied by these proportions, and the expected numbers for each cytological type summed for both sexes and all ages. The method is inaccurate in so far as the proportions of the various types occurring since 1950 are not characteristic of the proportions over the whole period of the study; but the differences are unlikely to be large, and, in fact, the great majority of patients have been observed since 1950.

The certified and expected numbers of deaths for each of the four types of leukaemia are shown below, together with an estimate of the probability that differences as great as or greater than those observed could be due to chance.

<table>
<thead>
<tr>
<th>Type of leukaemia</th>
<th>No. of deaths certified</th>
<th>No. of deaths expected</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphatic</td>
<td>4</td>
<td>0.86</td>
<td>0.01</td>
</tr>
<tr>
<td>Myeloid</td>
<td>9</td>
<td>1.49</td>
<td>0.0003</td>
</tr>
<tr>
<td>Monocytic</td>
<td>4</td>
<td>0.34</td>
<td>0.005</td>
</tr>
<tr>
<td>Other and unspecified</td>
<td>11</td>
<td>0.21</td>
<td>&lt; 0.00001</td>
</tr>
</tbody>
</table>

It seems that there is an excess of all types of leukaemia, but that the excess of lymphatic leukaemia is the least marked. It is not possible to make separate estimates of the numbers of deaths which would have been expected to result from the acute and chronic types of leukaemia, but as only one case of chronic lymphatic leukaemia is included in the treated series there is clearly no evidence of an excess of this particular form of the disease.

The comparison made above is unsatisfactory, in that it is based on the certificated cause of death and fails to take into account the more detailed evidence which has been obtained from examination of the full hospital records and, in certain cases, from review of the pathological material. A comparison has, therefore, also been made between the cytological types of leukaemia in all the spondylitic patients known to have been treated with X-rays, and in the patients who are believed not to have had any such treatment. For this purpose all the available information has been taken into account, and the leukaemias have been re-classified according to the 'preferred' diagnoses. The three co-existent cases have been excluded from the 'treated' series; one of them (Case 33) has been omitted altogether, since this patient is now thought not to have had spondylitis; but the other two cases (15 and 34) have been classified with the patients who have not been treated with X-rays, since it is believed that the
leukaemia was present at the time of treatment and cannot, therefore, be attributed to it.

The cytological types observed in the two series are as follows:—

<table>
<thead>
<tr>
<th></th>
<th>'Treated' series</th>
<th>'Untreated' series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphatic leukaemia</td>
<td>3 (8 per cent)</td>
<td>3 (38 per cent)</td>
</tr>
<tr>
<td>Myeloid leukaemia</td>
<td>31 (78 per cent)</td>
<td>4 (50 per cent)</td>
</tr>
<tr>
<td>Monocytic leukaemia</td>
<td>6 (15 per cent)</td>
<td>1 (13 per cent)</td>
</tr>
<tr>
<td>Type unspecified</td>
<td>9*</td>
<td>0</td>
</tr>
</tbody>
</table>

* Including the 5 cases in the 'B' series.

There is a relative deficiency of the lymphatic type of leukaemia among the 'treated' patients and the difference in the proportions in the two series is just significant ($P < 0.05$) despite the small number of patients in the 'untreated' series. The relative incidence of the various types in the treated series varies to some extent with age and with the amount of treatment, but in view of the small number of patients and the lack of certainty about the exact cytology in some cases, it is, in the authors' opinion, unwise to draw any further conclusions.

**Discussion**

The results of the survey show that the mortality from leukaemia among patients treated with X-rays for ankylosing spondylitis has been about ten times greater than the mortality which has occurred in a normal population of the same age- and sex-distribution. It remains to inquire to what extent this increase is due to the use of X-rays.

**ANKYLOSING SPONDYLITIS AND LEUKAEMIA: A POSSIBLE ASSOCIATION**

One possible explanation of the findings could be that sufferers from ankylosing spondylitis are more likely to develop leukaemia than healthy people, irrespective of the method of treatment. In favour of such an association is the occurrence of some cases in which the two diseases were thought to be co-existent—3 in the study series (Cases 15, 33, 34), 4 other British cases (65, 66, 67, 68) and 2 notified from abroad (Cases 71, 72). Case 33 was included in the survey because a diagnosis of ankylosing spondylitis had been preferred by the radiotherapy department, but a review of all the clinical data leaves no doubt that the patient suffered only from leukaemia. Excluding this case, there remain 6 British cases in which the diagnoses of ankylosing spondylitis and leukaemia were authentic.

To view these cases in their correct perspective it is important to remember that it was not until the Second World War that X-irradiation was generally recognized as a valuable method of treatment for spondylitis, and, furthermore, that the severity of the disease varies considerably, so that a number of people who suffer only from a slow and progressive stiffening of the back without much pain do not seek treatment, or, if they do, get adequate relief from physiotherapy. It follows that there must exist in the country many persons with ankylosing spondylitis, both diagnosed and undiagnosed, who have never had X-ray treatment. The size of this population is impossible to estimate, but it is, of course, among these people that the co-existent cases occur.

Three findings suggest that the increased incidence of leukaemia does not arise from a simple association of leukaemia and ankylosing spondylitis:—
THE INCIDENCE OF LEUKAEMIA AND OF APLASTIC ANAEMIA

(1) The distribution of the different cell types among the treated cases is not
the same as among the untreated cases; among the former there is a significantly
smaller proportion of cases of the lymphatic type.

(2) Data have been obtained on the incidence of leukaemia in an unirradiated
population of spondylitic patients. Abbatt and Lea (1956) studied men discharged
from the Armed Services since the outbreak of the last war who had been
awarded pensions for ankylosing spondylitis. Records of 2,026 such patients
were obtained, and it was found that 1,627 had had X-ray treatment and 399
had not. Up to the end of 1955, 13,597 man-years had been observed following
irradiation, and 6,956 without preceding irradiation. Eight cases of leukaemia
(7 certified deaths) had occurred in the former group and none in the latter,
whereas respectively 0.33 and 0.17 deaths would have been expected. The finding
of 8 cases in the irradiated group is consistent with the results in the present
investigation; the incidence of leukaemia in this group is significantly higher
than that in the unirradiated group. These findings are evidence against the
two diseases being associated, provided it can be shown that the two groups
of patients are diagnostically comparable. To test this, 61 cases were selected at
random, using a table of random sampling numbers. X-ray films could not be
obtained for 3 patients, but the remaining 58 sets of films (29 from each group
of patients) were presented to an independent panel of experts, which was
asked to decide in each case whether a diagnosis of ankylosing spondylitis
could be substantiated; the members of the panel were not told from which
group of patients the films came. It was unanimously agreed that the diagnosis
of ankylosing spondylitis could be upheld in 24 cases in each group. The high
and equal proportions of positive diagnoses indicate that the series were reason-
ably comparable. From this, and the finding of 8 cases of leukaemia in the
treated series and none in the untreated, it may be inferred that there is no
important association between leukaemia and ankylosing spondylitis. However,
the unirradiated series is small, and the possibility of there being some slight
association cannot be ruled out on this evidence.

(3) Thirdly, there is the finding (p. 30) that a relationship exists between the
dose of radiation and the incidence of leukaemia. Such a finding is strong
evidence that X-rays played a part in the causation of the cases of leukaemia,
unless it be postulated that the liability to develop leukaemia varies among
sufferers from ankylosing spondylitis in proportion to the severity of the
disease.

THE POSSIBLE INFLUENCE OF DRUGS

When the survey was planned it had been intended to collect evidence on
the use of drugs; it soon became clear, however, that the case records did not
provide enough detail for a special study of this aspect of the problem.

Butazolidine can hardly have played any part in the development of the
reported cases of aplastic anaemia, as it was not in general use until 1952; and,
as far as the authors are aware, it does not cause leukaemia. Gold has been
used for many years, as have many types of analgesics, including amidopyrine.
Both gold and amidopyrine are known to cause aplastic anaemia, but they are
not known to be leukaemogenic.

If it were assumed that drugs were largely responsible for the development
of leukaemia, it would follow from the findings discussed in Part II
that the frequency of their use was directly related to the radiation dosage;
it would also follow that there had been an excessive use of the drugs in the
RADIATION AND LEUKAEMIA

irradiated group of cases quoted by Abbott and Lea in comparison with the unirradiated group. Neither of these postulates seems reasonable.

THE INFLUENCE OF IRRADIATION

A number of reports have been published of leukaemia developing in radiological workers and in persons who have had radiation treatment. In 1942 Dunlap reviewed 24 such cases, and additional ones have been described since. Gerbis (1943) and Lynch (1951) reported acute myeloid leukaemias following the treatment of non-malignant skin conditions, and van Swaay (1955) and Simpson, Hempelmann and Fuller (1955) reported leukaemia after radiation therapy for ankylosing spondylitis and for suspected enlargement of the thymus in infants. The occurrence of leukaemia has also been reported in 7 patients following the administration of radioactive iodine, although in 2 of these cases external irradiation with X-rays had also been given (Abbott, Farran and Greene, 1956; Blom, Querido and Leeksma, 1955; Delarue, Tubiana and Dutreix, 1953; Pochin, Myant and Corbett, 1956; Seidlin, Yalow and Siegel, 1954; Seidlin, Siegel, Melamed and Yalow, 1955). Eight papers have been published claiming an increased death rate from leukaemia among American radiologists (Dublin and Spiegelman, 1947, 1948; Henshaw and Hawkins, 1944; March, 1944, 1947, 1950; Peller and Pick, 1951; Ulrich, 1946). A review of these latter papers suggests that there has probably been an increased mortality from this cause amongst radiologists, although it is not possible to make a reliable assessment of its extent.

Since 1952, five papers have drawn attention to the increased death rate from leukaemia among the survivors of the atom bomb explosions over Hiroshima and Nagasaki in 1945 (Folley, Borges and Yamawaki, 1952; Lange, Moloney and Yamawaki, 1954; Moloney and Lange, 1954; Moloney and Kastenbaum, 1955; Moloney, 1955). More recent data have been published in a Command paper by the Medical Research Council (1956). It is clear that the incidence of leukaemia increased the closer the survivors were to the hypocentre at the time of the explosion, and that it was higher among those who developed radiation sickness than among those who did not. Both these findings point to a relationship between incidence and dose.

Some of the reports quoted refer to isolated cases of leukaemia, and while these, taken individually, do not constitute grounds for assuming a causal relationship, the sum of the evidence indicates that ionizing radiations can cause leukaemia in man. It is reasonable, therefore, to ascribe the majority, if not all, of the excess deaths from leukaemia observed in the present investigation to the effects of such radiations.
PART II. X-RAYS AND LEUKAEMIA: THE DOSE-RESPONSE RELATIONSHIP

At the outset of the survey the authors were asked to investigate the relationship between the incidence of leukaemia and of aplastic anaemia and the radiation dose. It has been seen, however, that the diagnosis of aplastic anaemia could be substantiated in only 4 cases, so that it has not been possible to study the dose-response relationship for this disease. This section of the Report, therefore, deals only with the incidence of leukaemia in relation to the radiation dose.

Method of Investigation

THE SAMPLING PROCEDURE

Because of the large number of patients being studied, it was impracticable to calculate for each individual the amount of radiation received. A first indication of the amount was provided by the number of courses of treatment given, but this proved to be a fallible guide, since instances were discovered in which patients who had had four or more courses had received a lower total dose than the majority of patients who had had only one course. It was therefore decided to estimate the numbers of patients given different amounts of irradiation by means of data collected from a sample of approximately one patient in six. To ensure proper representation of the different centres, the different dates at which treatment was given and the different amounts of treatment, the samples were chosen separately for each centre, for each year (or group of successive years) in which treatment was started, and for each of the five 'amount of treatment' classes used in the analyses of Part I, which were divided as follows:—

Patients receiving:—

(1) one course,
(2) two courses,
(3) three courses,
(4) four or more courses,
(5) treatment at two or more centres.

Within each 'centre', 'date of treatment' and 'amount of treatment' sub-class, the sample cases were selected at random by reference to a table of random numbers.

Patients who had had several courses of treatment were substantially fewer than those who had received only one course; but among the former were what were believed to be the more important cases from the point of view of the investigation, namely, those most heavily treated. Sampling fractions of 1 in 15, 1 in 6, 1 in 3, 1 in 2 and, for the group treated at two or more centres, 1 in 3 were, therefore, taken for the five classes, so that these five sub-samples should be of approximately equal size. The numbers of patients selected to be in each sample and the numbers for whom full dosage data were actually obtained are shown in Table 14.

THE PHYSICAL DATA RECORDED

Details of the amounts of treatment received were extracted from the hospital or radiotherapy notes, and a card was made out for each course of treatment, showing, when known:—

(1) the physical factors for the apparatus used,
(2) the size and situation of the fields irradiated,
(3) the daily and total skin-dose received by each site,
(4) the focus-skin distance and, for opposed fields, the distance between fields,
(5) the dates on which treatments were given.

**TABLE 14**

The number of patients selected for the recording of full dosage data, and the number for whom data were obtained

<table>
<thead>
<tr>
<th>Treatment class</th>
<th>No. of patients in series</th>
<th>No. of patients selected to be in sample</th>
<th>Sampling factor</th>
<th>No. of men in sample</th>
<th>No. of women in sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 course</td>
<td>7,215</td>
<td>488</td>
<td>14:78</td>
<td>409</td>
<td>77</td>
</tr>
<tr>
<td>2 courses</td>
<td>2,765</td>
<td>460</td>
<td>6:00</td>
<td>372</td>
<td>85</td>
</tr>
<tr>
<td>3 courses</td>
<td>1,226</td>
<td>407</td>
<td>3:01</td>
<td>337</td>
<td>65</td>
</tr>
<tr>
<td>4 or more courses</td>
<td>1,119</td>
<td>555</td>
<td>2:02</td>
<td>480</td>
<td>68</td>
</tr>
<tr>
<td>2 or more centres</td>
<td>1,027</td>
<td>344</td>
<td>2:96</td>
<td>280</td>
<td>22</td>
</tr>
<tr>
<td>All classes</td>
<td>13,352</td>
<td>2,254</td>
<td>(5:92)</td>
<td>1,878</td>
<td>317</td>
</tr>
</tbody>
</table>

**ESTIMATES OF THE DOSE RECEIVED**

The dosage data obtained for 2,195 sample patients enabled an estimate to be made of the numbers who had received the various different total doses of radiation. These total doses were expressed in two different ways, as (a) the mean dose to the marrow contained in the whole length of the spinal column, and, (b) the whole body integral dose.

(a) The Mean Dose to the Spinal Marrow

The estimates of this dose were based on the work of a group of physicists and engineers from the Institute of Cancer Research of the Royal Cancer Hospital, the Departments of Physics of the Middlesex and Mount Vernon Hospitals, the Radiobiological Research Unit of the Medical Research Council, and the National Institute for Medical Research. These workers constructed and used for physical measurements a phantom (Plate I, p. 98), in this case a full-scale model of the male trunk, with a human skeleton incorporated, and with imitation lungs made from wood of the appropriate density. The phantom was so devised that ionization chambers could be inserted at three points within the marrow spaces of the vertebral bodies—in the body of the upper sacral vertebra and in the bodies at the mid-points of the dorsal and cervical spines.

The doses contributed to these points were measured for fields directly irradiating the spine and the sacro-iliae joints, and also for a number of extra-spinal sites such as the hip joints and the ischial tuberosities. In some instances the contributions to these points from adjacent fields were calculated, and it was shown by calculation that no appreciable dose would be contributed from
THE DOSE-RESPONSE RELATIONSHIP

the irradiation of such sites as the shoulder joints. Full details of these observations are given in Appendix B. The mean dose was obtained by adding the doses at each of the three sites in the spinal marrow and dividing by 3. It was calculated for each year in which the patient was irradiated, and also for the total amount of irradiation if the patient had been given treatment in more than one year. In the case of the patients who developed leukaemia the mean spinal marrow dose has been recorded for each course of treatment (Appendix A).

(b) The Whole Body Integral Dose

Estimates of the whole body integral dose were made from data provided by the staff of the Institute of Cancer Research of the Royal Cancer Hospital; the theoretical considerations upon which these data were based are described in Appendix C. From their calculations these workers assigned to each field irradiated in each course of treatment, and for every patient in the sample, a value for the integral dose per 100 r. received on the skin. Subsequently the total integral doses were calculated for each year in which radiation was given, and for the whole amount of radiation if treatment was given in more than one year. Members of staff of the Medical Research Council's Radiobiological Research and Statistical Research Units, and of the Department of Social Medicine, University of Oxford, co-operated in this work.

The whole body integral dose was measured in gramme-roentgens, the gramme-roentgen being defined as the energy absorbed in one gramme of air when it is subjected to a uniform dose of one roentgen, i.e., about 85 ergs. In clinical work, however, it is more convenient to deal in megagramme-roentgens (Mg.r.); 1 megagramme-roentgen is thus equal to \(85 \times 10^6\) ergs, or approximately 2 calories.

THE POPULATION AT RISK

It has been shown previously that the incidence of leukaemia has been lower in women than in men, and this is true in the present series, even when patients who have received the same amount of treatment are compared. If, therefore, the whole group of patients were used to investigate the relationship between dose and incidence it would be necessary to make allowance for the different proportions of men and women at each level of dose. Since only one certain case of leukaemia has been recognized in a woman, little information is lost and the presentation is appreciably simplified if the analysis is confined to men. The population at risk has, therefore, been defined as the 11,287 men in the study series.

The numbers receiving the different amounts of treatment have been estimated from the sample of 1,878 men for whom full details of treatment were recorded. If the patients had received all their treatment on one occasion and if the proportions given different doses had remained constant throughout the period under review it would have been possible to measure the incidence of leukaemia in relation to the size of the dose simply by relating the numbers of patients with leukaemia following a given dose to the estimated total numbers of patients given that dose. In the present study, however, a patient who received a mean spinal marrow dose of, say, 2,300 r., may have received 400 r. in 1938, 400 r. in 1939, 800 r. in 1942 and 700 r. in 1949, and it would clearly be improper to regard him as having had the same risk of developing leukaemia by the end of 1955 as a man who had received 2,300 r. in 1938. The difficulty
has been met by estimating the population at risk for each level of dose from the sum of the number of years the patients have survived after receiving that dose and before they have received additional treatment which would place them in the next (arbitrarily-defined) treatment category. Thus, the first patient mentioned above would be regarded as having had 1 year at risk at a level of under 500 r. (1938–39), 3 years at risk at a level of 500–999 r. (1939–42), 7 years at risk at a level of 1,500–1,999 r. (1942–49) and 6½ years at risk at a level of over 2,250 r. (1949 to the end of 1955); on the other hand the patient who received 2,300 r. in 1938 would have been at risk for the whole of the 17½ years at that level.*

This method is, however, appropriate only if leukaemia is equally likely to develop at any time after irradiation; but if there is a specific latent period before the development of leukaemia, and if the period varies within relatively close limits, it follows that outside these limits the patient has not been at risk at all. For example, if the latent period were never less than 8 years, the first patient referred to would not as yet have had any opportunity of manifesting the disease as a result of that fraction of the total dose which was given in 1949. This consideration may be of great importance in the present study, since many of the patients have been treated only in the last few years. From the data given above (p. 20), it seems probable that the latent period is seldom less than 12 months; but whether there is an upper limit, and what the relative frequencies of different latent periods are, is uncertain. From the extensive data obtained following the atomic explosions over the Japanese cities of Hiroshima and Nagasaki, there seems little doubt that cases of leukaemia have continued to develop for up to 10 years (Medical Research Council, 1956, Appendix A), and there is no reason to suppose that the full complement of cases has yet been observed. For the present purpose, therefore, it has been postulated that the risk of the disease being diagnosed within 12 months of exposure is zero, and that subsequently it is constant each year. This postulate is certainly an oversimplification, but it is difficult to be sure that any other would be more appropriate. The method described above for calculating the population at risk at each level of dose has, therefore, been followed, with the modification that during the first year after any given treatment the contribution of that treatment to the total dose has been ignored. As dosage data were extracted for the sample patients up to the end of 1954, it has been possible by this method to extend the period of observation for recording new cases of leukaemia up to the end of 1955. The effect on the calculated dose-response relationship of making other postulates about the length of the latent period is considered later (p. 128).

A further complexity is introduced by the fact, illustrated in Table 12 (p. 19), that the subsequent incidence of leukaemia increases with the age of the patient at the time of irradiation. This increase with age cannot be accounted for by assuming that there is a tendency to give a higher dose to older persons; on the contrary, the data (Table 15) demonstrate that the tendency is to give older persons less treatment. If age-differences are ignored the effect may be to underestimate the relative incidence at higher levels of dose, and it is therefore necessary to standardize the incidence rates for age before comparing them at different levels of dose.

* Some treatments will have been given at the beginning of the year, and some at the end. When dealing with a large number of patients all treatments may be regarded as having been given, on the average, in the middle of the year.
THE DOSE-RESPONSE RELATIONSHIP

In view of the very small numbers of cases in some of the treatment groups, standardized rates have been calculated by the indirect method, as follows. Calculations have been made of the numbers of cases which would have been expected to occur among men in each age group of each of the dosage groups if the patients had been subject to the death rates observed in the same age groups among the whole series of patients. The numbers of cases observed and expected

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Mean spinal marrow dose (r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14--</td>
<td>858</td>
</tr>
<tr>
<td>25--</td>
<td>894</td>
</tr>
<tr>
<td>35--</td>
<td>840</td>
</tr>
<tr>
<td>45--</td>
<td>776</td>
</tr>
<tr>
<td>55+</td>
<td>576</td>
</tr>
<tr>
<td>Not stated</td>
<td>525</td>
</tr>
</tbody>
</table>

in each age group have then been summed for each dosage group, and standardized rates have been found by multiplying the general rates for the whole series by the ratio between the observed and expected cases in the relevant dosage groups. No allowance has been made for any effect due to fractionation of the dose, since there is no evidence to suggest what allowance should be made, and it seems preferable, in the first place, to compare incidence and dose irrespective of fractionation.

RELEVANT CASES OF LEUKAEMIA

Since the population at risk had been defined as the 11,287 men in the study series, the relevant cases of leukaemia were those which occurred in this group. From these it was necessary to exclude the 3 co-existent cases, so the total number available for the analysis of the dose-response relationship was reduced to 32 established cases ('A' series) and 5 probable cases ('B' series). In view of the small number of cases the two series have been combined, but the principal results are also given separately for the 'A' cases.

Findings

THE INCIDENCE OF LEUKAEMIA IN RELATION TO THE RADIATION DOSE

The Mean Dose to the Spinal Marrow

The numbers of men receiving different doses of radiation by December 31st, 1954, and the numbers of man-years at risk at twelve levels of dose, estimated by the method described, are shown in Table 16. Details of the doses received by the 37 patients available for the analysis of the dose-response relationship are shown in Tables 17 and 18; the figures in these tables comparable to those shown in Table 16 for the populations at risk are the total doses received less the amounts received in the 12 months preceding the diagnosis of leukaemia.
RADIATION AND LEUKAEMIA

The data on the leukaemia patients are summarized and shown in Table 19, along with the crude and standardized incidence rates. The rate given for 'zero' therapeutic dose is the corresponding rate among men of the same age-distribution and observed over the same period, calculated from the mortality from leukaemia experienced by the whole male population of Britain.*

### TABLE 16

The number of men receiving therapeutic radiation to the spinal marrow by 31.12.54, and the man-years at risk following exposure to each level of dose throughout the period of observation: study series

<table>
<thead>
<tr>
<th>Mean dose to spinal marrow (r.)</th>
<th>No. of men receiving dose by 31.12.54</th>
<th>No. of man-years at risk following exposure to dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 250</td>
<td>1,153</td>
<td>8,184</td>
</tr>
<tr>
<td>250–499</td>
<td>1,708</td>
<td>10,339</td>
</tr>
<tr>
<td>500–749</td>
<td>1,912</td>
<td>10,126</td>
</tr>
<tr>
<td>750–999</td>
<td>2,268</td>
<td>11,654</td>
</tr>
<tr>
<td>1,000–1,249</td>
<td>2,124</td>
<td>10,632</td>
</tr>
<tr>
<td>1,250–1,499</td>
<td>938</td>
<td>5,098</td>
</tr>
<tr>
<td>1,500–1,749</td>
<td>500</td>
<td>2,437</td>
</tr>
<tr>
<td>1,750–1,999</td>
<td>305</td>
<td>1,550</td>
</tr>
<tr>
<td>2,000–2,249</td>
<td>172</td>
<td>939</td>
</tr>
<tr>
<td>2,250–2,499</td>
<td>118</td>
<td>509</td>
</tr>
<tr>
<td>2,500–2,749</td>
<td>44</td>
<td>283</td>
</tr>
<tr>
<td>2,750 or more*</td>
<td>45</td>
<td>151</td>
</tr>
</tbody>
</table>

| All doses                       | 11,287                                | 61,902                                            |

* Average dose, 3,043 r.

The relationship between the dose received and the standardized incidence rate is shown in Fig. 1 (p. 37). The incidence increases from 0·5 per 10,000 men per year in the absence of treatment, to 72 per 10,000 men per year following a dose of 2,250 r. or more. The points in the graph lie close to a curve which becomes steeper as the amount of radiation received increases; at the lower doses the curve approximates to a straight line, but after a mean dose of over 2,250 r. the incidence is more than treble that which would be expected if a linear relationship held at all levels. There is no suggestion of a threshold

* The number of deaths attributable to leukaemia that would have been expected to occur among the male patients in the study series during the years 1935–54 if they had suffered the same mortality as the male population of Britain of the same age distribution has been shown to be 5·06. To make the figure comparable with the number of cases used in calculating the dose-response relationship, it is necessary (1) to add the number of deaths that would be expected to occur in 1955, (2) to subtract the number of deaths that would be expected to occur in the first year of observation, and (3) to multiply it by a factor to allow for patients being included in the calculation of the dose-response relationship who had not died or whose death was not attributed to leukaemia. The first two corrections approximately cancel each other out. The third is made by multiplying by 32/25 for 'A' cases—i.e. the ratio between the number of 'A' cases shown in Table 19 and the number of observed deaths attributable to leukaemia in 1935–55, less cases occurring in the first year of observation. For 'A' and 'B' cases, the corresponding factor is 37/25. The numbers of cases expected in the absence of therapeutic irradiation are, therefore, 2·64 and 3·05 respectively. Since the number of man-years lived by the population was 61,902, the corresponding morbidity rates are 0·43 and 0·49 per 10,000 men per year.
THE DOSE-RESPONSE RELATIONSHIP

below which no effect is produced, but the population at risk following doses of less than 250 r. is too small to provide direct evidence of an effect. The lowest dose-range to provide such evidence is 0–500 r. (mean dose 265 r.); 4 cases occurred within this range, following doses of 112 r., 315 r., 470 r., and 471 r., and the expected number of cases, calculated from the experience of the general population, was less than 1 (expected number = 0.9; \( P = 0.02 \)).

The measure of dose adopted, i.e. the mean dose received by the spinal marrow, is believed to be the best one possible under the conditions of the investigation. It is, however, unsatisfactory, in that it fails to take into account the considerable amount of radiation which, in some patients, was received by the extraspinal marrow. Patients who received treatment to the spine and sacro-iliac regions only have therefore been considered separately, and data are given in Table 20 and Fig. 2 (p. 37) to show the relationship between dose and incidence in this special group. Patients whose treatment was initially confined to the spine and sacro-iliac joints but who subsequently received extraspinal, including wide-field, irradiation, have been included in the group for that part of their life which intervened between the initial treatment and the first extraspinal treatment. For example, a patient who received treatment in 1942 which was confined to the spine and gave a mean spinal marrow dose of 600 r., and who received further treatment in 1948 including irradiation of the left hip joint, and who survived until 1955, has been regarded as having been observed for 6 years at a level of 500–749 r.

The data in Table 20 are potentially more informative than those in Table 19, since in this group of patients the recorded measure of dose may be presumed to provide a good measure of the actual leukaoenogenic stimulus. They are, however, of limited value because of the small number of cases; with such small numbers the play of chance may result in a gross distortion of the apparent relationship. The difficulty is illustrated by the three graphs in Fig. 2, which represent the relationships obtained by altering the limits of the two upper dosage groups. The line drawn through the points is, in each case, the regression line calculated from the rates for the ten dosage groups of 250 r. given in Table 20, and made to go through the point corresponding to the incidence in the absence of treatment.*

The results obtained clearly do not conflict with the principal conclusions drawn from the results for the whole series. They are consistent with the hypothesis that at moderate and low doses the incidence increases in proportion to the dose; they do not, on the other hand, provide significant evidence about the effect of large doses.

If, in fact, a linear relationship holds at the lower levels of dose, it is possible to calculate from the slope of the regression line the amount of dose which would double the expected incidence of leukemia. For this purpose it is probably best to use the data in Table 20 in preference to those in Table 19, because the measure of dose employed is biologically more accurate. The results indicate that an increment of 0.49 cases per 10,000 men per year corresponds to a mean spinal marrow dose of 94 r.

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* In view of the very small numbers of cases the rates were weighted according to their reliability before the slope of the regression line was calculated. That is, the slope was taken to be \[ \frac{\sum w x (y - b)}{\sum w x^2} \], where \( w = \) variance of \( y \) and the variance of \( y = \frac{P Q}{n} \), where \( n = \) the number of man-years in the dosage group, \( P = \) the corresponding value of \( y \) measured from the unweighted regression line, and \( Q = 1 - P \).
### TABLE 17

Dosage data for male patients who developed leukaemia: 'A' cases, excluding co-existent cases

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age at first treatment (years)</th>
<th>Total dose in r.</th>
<th>Date of last treatment</th>
<th>Date of diagnosis</th>
<th>Interval between last treatment and diagnosis (months)</th>
<th>Total dose less amount in year preceding diagnosis in r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>21.4 7.1</td>
<td>7.4 12.2</td>
<td>7.4 12.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>620 14.6</td>
<td>620 14.6</td>
<td>11.8 13.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>602 20.4</td>
<td>602 20.4</td>
<td>11.8 13.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>194 7.7</td>
<td>194 7.7</td>
<td>194 7.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>37</td>
<td>102 3.3</td>
<td>102 3.3</td>
<td>102 3.3</td>
<td></td>
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<tr>
<td>6</td>
<td>23</td>
<td>1.085 14.4</td>
<td>1.085 14.4</td>
<td>1.085 14.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>31</td>
<td>520 16.7</td>
<td>520 16.7</td>
<td>520 16.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>22</td>
<td>941 20.4</td>
<td>941 20.4</td>
<td>941 20.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>37</td>
<td>757 10.6</td>
<td>757 10.6</td>
<td>757 10.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>36</td>
<td>43 1.0</td>
<td>43 1.0</td>
<td>43 1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>35</td>
<td>948 15.8</td>
<td>948 15.8</td>
<td>948 15.8</td>
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<td></td>
</tr>
<tr>
<td>13</td>
<td>58</td>
<td>746 15.0</td>
<td>746 15.0</td>
<td>746 15.0</td>
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<tr>
<td>14</td>
<td>27</td>
<td>412 8.6</td>
<td>412 8.6</td>
<td>412 8.6</td>
<td></td>
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<tr>
<td>15</td>
<td>42</td>
<td>793 13.4</td>
<td>793 13.4</td>
<td>793 13.4</td>
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<td>17</td>
<td>45</td>
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<td>18</td>
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<td>19</td>
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<tr>
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<td>21</td>
<td>47</td>
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<td>371</td>
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<td></td>
<td></td>
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<tr>
<td>28</td>
<td>44</td>
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<td></td>
<td></td>
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<td>35</td>
<td>26</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Indicates year of death.
† Age at first treatment reported in inquiry, 52 years.
‡ Age at first treatment reported in inquiry, 38 years.
TABLE 18
Dosage data for male patients who developed leukaemia: 'B' cases

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age at first treatment (years)</th>
<th>Radiation received in each year of treatment</th>
<th>Mean spinal marrow dose in r.</th>
<th>(Whole body integral dose in Mg. r.)</th>
<th>Total dose (r. Mg. r.)</th>
<th>Date of last treatment</th>
<th>Date of diagnosis</th>
<th>Interval between last treatment and diagnosis (months)</th>
<th>Total dose less amount in year preceding diagnosis (r. Mg. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>421</td>
<td>1.726</td>
<td>0</td>
<td>0</td>
<td>602</td>
<td>129</td>
<td>1.17</td>
<td></td>
<td>8-52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40-4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>4-23</td>
<td>2-38</td>
</tr>
<tr>
<td>38</td>
<td>53</td>
<td>577</td>
<td>0</td>
<td>124</td>
<td>0</td>
<td>*</td>
<td>901</td>
<td>18-1</td>
<td>8-52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-9</td>
<td>0</td>
<td>5-4</td>
<td>0</td>
<td>*</td>
<td></td>
<td>8-52</td>
<td>27</td>
</tr>
<tr>
<td>39</td>
<td>40</td>
<td>313</td>
<td>157</td>
<td>0</td>
<td>0</td>
<td>*</td>
<td>470</td>
<td>39-0</td>
<td>5-50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20-1</td>
<td>9-9</td>
<td>0</td>
<td>0</td>
<td>*</td>
<td></td>
<td>3-53</td>
<td>34</td>
</tr>
<tr>
<td>40</td>
<td>49</td>
<td>1,044</td>
<td>346</td>
<td>0</td>
<td>0</td>
<td>*</td>
<td>1,390</td>
<td>29-4</td>
<td>11-50</td>
</tr>
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<td></td>
<td>20-7</td>
<td>8-7</td>
<td>0</td>
<td>0</td>
<td>*</td>
<td></td>
<td>11-53</td>
<td>36</td>
</tr>
<tr>
<td>41</td>
<td>70</td>
<td>1,045</td>
<td>17-8</td>
<td>0</td>
<td>0</td>
<td>1-52</td>
<td>1,045</td>
<td>6-55</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td>17-8</td>
</tr>
</tbody>
</table>

* Indicates year of death
† Age at first treatment reported in inquiry, 50 years.
<table>
<thead>
<tr>
<th>No. of men developing leukaemia</th>
<th>Mean dose to spinal marrow (r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0*</td>
</tr>
<tr>
<td>'A' cases</td>
<td></td>
</tr>
<tr>
<td>'A' and 'B' cases</td>
<td></td>
</tr>
<tr>
<td>Crude incidence per 10,000 men per year</td>
<td>0.49</td>
</tr>
<tr>
<td>'A' and 'B' cases</td>
<td></td>
</tr>
<tr>
<td>Standardized incidence per 10,000 men per year</td>
<td>0.49</td>
</tr>
<tr>
<td>'A' and 'B' cases</td>
<td></td>
</tr>
</tbody>
</table>

*The rate given for 'zero' therapeutic dose is the corresponding rate among men of the same age-distribution and observed over the same period, calculated from the mortality from leukaemia experienced by the whole male population of Britain.
<table>
<thead>
<tr>
<th>Mean dose to spinal marrow (r.)</th>
<th>0</th>
<th>Less than 250</th>
<th>250–499</th>
<th>500–749</th>
<th>750–999</th>
<th>1,000–1,249</th>
<th>1,250–1,499</th>
<th>1,500–1,749</th>
<th>1,750–1,999</th>
<th>2,000 or more*</th>
<th>All doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of man-years at risk following exposure to dose</td>
<td>—</td>
<td>5,404</td>
<td>7,673</td>
<td>6,573</td>
<td>8,262</td>
<td>7,411</td>
<td>2,782</td>
<td>897</td>
<td>566</td>
<td>679</td>
<td>40,247</td>
</tr>
<tr>
<td>No. of men developing leukaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>'A' cases</td>
<td>—</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>'A' and 'B' cases</td>
<td>—</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>Crude incidence per 10,000 men per year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>'A' and 'B' cases</td>
<td>0.49</td>
<td>1.53</td>
<td>4.72</td>
<td>6.75†</td>
<td>8.12‡</td>
<td>4.47</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Standardized incidence per 10,000 men per year</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>'A' and 'B' cases</td>
<td>0.49</td>
<td>1.44</td>
<td>4.83</td>
<td>6.82†</td>
<td>8.70‡</td>
<td>4.47</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Average dose, 2,290 r.
† For the group receiving 1,000–1,499 r. the crude incidence is 4.91; standardized incidence 5.06.
For the group receiving 1,000–1,749 r. the crude incidence is 6.31; standardized incidence 6.82.
‡ For the group receiving 1,500 r. or more the crude incidence is 18.68; standardized incidence 19.86.
For the group receiving 1,750 r. or more the crude incidence is 16.07; standardized incidence 16.82.
THE DOSE-RESPONSE RELATIONSHIP

Fig. 1. The incidence of leukaemia, standardized for age, in relation to the mean dose of radiation to the spinal marrow: all male patients in the study series and 'A' and 'B' cases of leukaemia, excluding co-existent cases.

Fig. 2. The incidence of leukaemia, standardized for age, in relation to the mean dose of radiation to the spinal marrow; patients given extraspinal irradiation have been excluded.

Patients receiving the higher levels of dose have been grouped differently in each of the three graphs. In graph A, incidences are plotted for patients given a mean spinal marrow dose of 1,000–1,249 r. and for those receiving 1,250 r. and over; in graph B for those given 1,000–1,499 r. and for those given 1,500 r. and over; in graph C for those given 1,000–1,749 r. and for those given 1,750 r. and over. The line drawn through the points is in each case the regression line calculated from the basic data in Table 20 and weighted according to the reliability of the points.
RADIATION AND LEUKAEMIA

The Maximum Dose in the Spinal Marrow

Results relating the incidence of leukaemia to the maximum dose at any of the three points in the spine at which it was measured have been reported previously by the present authors (Medical Research Council, 1956, Appendix B). They showed "a simple proportional increase at all levels of dose". For reasons which are discussed later (p. 43) it is believed that these results are likely to be of less value than those now obtained by relating the incidence to the mean spinal marrow dose, and they are therefore not considered further.

The Whole Body Integral Dose

The number of man-years observed following six levels of dose, expressed in terms of the total amount of radiation received by the whole body, and the corresponding crude and standardized incidence rates, are shown in Table 21.

<table>
<thead>
<tr>
<th>Whole body integral dose of radiation (Mg. r.)</th>
<th>0</th>
<th>Less than 7-5</th>
<th>7-5-14-9</th>
<th>15-0-22-4</th>
<th>22-5-37-4*</th>
<th>37-5-52-4†</th>
<th>52-5 or more‡</th>
<th>All doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of man-years at risk following exposure to dose</td>
<td>—</td>
<td>10,774</td>
<td>20,654</td>
<td>18,558</td>
<td>8,957</td>
<td>2,243</td>
<td>716</td>
<td>61,902</td>
</tr>
<tr>
<td>No. of men developing leukaemia</td>
<td>—</td>
<td>1</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>4</td>
<td>32</td>
</tr>
<tr>
<td>'A' cases</td>
<td>—</td>
<td>1</td>
<td>8</td>
<td>9</td>
<td>9</td>
<td>5</td>
<td>5</td>
<td>37</td>
</tr>
<tr>
<td>'A' and 'B' cases</td>
<td>—</td>
<td>1</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>4</td>
<td>32</td>
</tr>
<tr>
<td>Crude incidence per 10,000 men per year</td>
<td>—</td>
<td>0:49</td>
<td>0:93</td>
<td>3:87</td>
<td>4:85</td>
<td>10:05</td>
<td>22:29</td>
<td>69:83</td>
</tr>
<tr>
<td>Standardized incidence per 10,000 men per year</td>
<td>—</td>
<td>0:49</td>
<td>0:81</td>
<td>3:94</td>
<td>4:91</td>
<td>11:44</td>
<td>27:87</td>
<td>87:21</td>
</tr>
</tbody>
</table>

* Average dose 28:5 Mg. r.
† Average dose 43:5 Mg. r.
‡ Average dose 63:0 Mg. r.

The relationship between incidence and dose is illustrated in Fig. 3. The points on the graph lie close to a smooth curve which has the same general shape as the curve in Fig. 1. There is no significant evidence of an increased incidence at amounts of less than 7-5 Mg. r., but there is a significant increase at the level of 7-5-14-9 Mg. r. (number of cases observed, 8; number expected, 1-0; P ≈ 0-0001). The figures in Table 21 differ slightly from those published in the preliminary report (Medical Research Council, 1956, Appendix B) as a result of the application of a more rigorous method of estimating the dose received.
**THE DOSE-RESPONSE RELATIONSHIP**

![Graph](image)

**Fig. 3.** The incidence of leukaemia, standardized for age, in relation to the whole body integral dose of radiation: all male patients in the study series and 'A' and 'B' cases of leukaemia, excluding co-existent cases.

**Limits of Error**

The shape of the curves illustrating the relationship between dose and incidence may have been affected to some extent by the errors inherent in the method of the investigation. The effects of these errors are summarized under three heads, depending on the type of error—random, systematic or theoretical. The methods by which they were estimated are described in Appendix D.

**Random errors.** Random errors derive from:

(a) the use of a sample of the patients to provide data for the estimation of the total numbers of patients given different doses, and
(b) the small number of cases.

The maximum error likely to have arisen from the first source is a 17 per cent over- or underestimate of the rate for patients given 2250 r. or more; for patients given less, the maximum error will have been appreciably smaller. Much larger errors may have arisen from the second source. The limiting values of the standardized rates which can be considered at all likely are:

<table>
<thead>
<tr>
<th>Dose Range</th>
<th>Standardized Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 500 r.</td>
<td>0.54–5.1 per 10,000 men per year</td>
</tr>
<tr>
<td>500–999 r.</td>
<td>2.2–6.6</td>
</tr>
<tr>
<td>1,000–1,499 r.</td>
<td>4.3–15.3</td>
</tr>
<tr>
<td>1,500–2,249 r.</td>
<td>5.2–30.8</td>
</tr>
<tr>
<td>2,250 r. or more</td>
<td>26.5–157.1</td>
</tr>
</tbody>
</table>

Such errors could reasonably account for the irregularity of the dose-response curve; indeed they could in themselves be the cause of its departure from linearity. It is however unlikely that large random errors should have occurred in the estimation of successive rates, and that they should have tended in the same direction and so have distorted the curve to any great extent systematically.
Systematic errors. These errors derive from:—
(a) the assumption that the distribution of dose in the sample patients for whom it proved impossible to obtain dosage data was comparable to that in patients for whom data were obtained,
(b) failure to recognize as the same person, persons of the same name treated at different centres,
(c) the exclusion from the survey of patients treated privately or abroad before treatment at one of the co-operating centres, and
(d) failure of the visiting teams to record every spondylitic patient treated since January 1st, 1935.
Systematic errors in estimating the incidence rates at different levels of dose could have been introduced under any of these heads; those introduced under the first head would result in an exaggeration of the populations given large doses of radiation, and those under the last three would result in underestimates of those populations. The maximal effects which could be attributed to these errors have been assessed quantitatively and are shown in Fig. 4; it is clear that they cannot have materially affected the shape of the dose-response curve.

Theoretical errors. A third ('theoretical') type of error will have arisen if the postulate made about the variability of the latent period is incorrect. It has been assumed in the calculations that the risk of leukaemia being diagnosed is nil for the first year following irradiation and constant for all subsequent years. Experience following the atomic explosions over Hiroshima and Nagasaki and clinical observations during the first year after irradiation suggest that this may be approximately true, at least for the greater part of the follow-up period covered by the investigation. On the other hand, observation of the few patients who developed leukaemia after only one course of treatment suggests that there may be a period, about three to five years after irradiation, when the risk of the appearance of the disease is at a maximum. To test the effect of a contrasting hypothesis about the length of the latent period the data have been re-analysed.
THE DOSE-RESPONSE RELATIONSHIP

on the assumption that the relative risks of the appearance of the disease are nil for the first year, 0·1 for the second year, 0·5 for the third year, 1·0 for the fourth and fifth years, 0·5 for the sixth year, and 0·1 for all subsequent years. The resulting rates increase less regularly with dose, but they show the same general trend of an increase in incidence with an increase in dose, and they provide no evidence of the existence of a threshold below which no effect is elicited (Table 4D, p. 129).

To summarize, it seems unlikely that the principal sources of error in the investigation have substantially affected the nature of the relationship illustrated in Fig. 1.

THE EFFECT OF FRACTIONATION OF DOSE

It would have been desirable to investigate the possibility that the incidence of leukaemia following a given total dose of radiation was affected by the way in which the dose was split up. An attempt was made to do this by studying the incidence of leukaemia in relation to the man-years at risk following various levels of mean dose to the spinal marrow and for a number of different ranges of weekly dose. The study failed to reveal any significant influence exerted by the degree of fractionation, but it is felt that it was too incomplete for any value to be attached to this negative finding.

The study was unreliable for a number of reasons: firstly, only 10 cases of leukaemia following a single course of treatment to the spine were available for investigation; secondly, no account could be taken of the dose-rate for any given single fraction of dose; and thirdly, the concept of a weekly dose-rate was misleading, in that the total dose administered to a patient in any one week at any given centre could well be split into one, two, or even as many as five single fractions, depending on the treatment technique in use at that centre. In fact, the effect of fractionation can only be studied if such other factors as the total dose of radiation and the dose-rate of a single fraction are kept constant.

Discussion

THE ESTIMATES OF THE RELEVANT RADIATION DOSE

The great majority of the patients in the survey—more than 90 per cent—were treated only by localized irradiation. In this form of treatment a beam of X-rays, collimated by a suitable applicator, is directed on to a particular anatomical site, and the greater part of the absorbed energy of the beam is received by those tissues that lie within its geometrical limits. These limits are divergent, as the beam is radiated from what is, in effect, a point source—the anode of the X-ray tube. By localizing the X-ray beam in this way, the amount of radiation absorbed in the tissues not affected by the disease under treatment is reduced to a minimum. However, the scattering of part of the radiation of the incident beam by the constituent atoms and molecules of the tissues lying within the geometrical limits results in some energy being absorbed outside the limits. Thus, about 35 per cent of the total energy absorbed from a circular beam 10 cm. in diameter on the skin surface (focus-skin distance, 50 cm; half-value layer, 1·5 mm. Cu) is absorbed in the tissues lying outside the geometrical limits. With single scattering this proportion varies with the dimensions of the incident beam, and is basically determined by the probability of any given quantum of the incident X-rays being scattered outside the geometrical limits; it increases for beams smaller in dimension than that quoted, and decreases for larger beams. In fact, however, the secondary rays are also scattered, and
the extent of the variations is thereby diminished. Any complete expression of the radiation dose in bone marrow must therefore take into account not only the radiation absorbed in the marrow lying within the geometrical limits, but also the amount absorbed in marrow beyond those limits. To express in the most satisfactory way the radiation dose to the bone marrow, the complete distribution of dose within the marrow should be known, and also the quantitative distribution of the marrow itself. A further requirement when dealing with patients is information as to whether, as a result of their disease, the distribution of the marrow differs from normal.

Our present state of knowledge does not admit of a complete evaluation of the radiation dose to the marrow. In this survey the relationship between the incidence of leukaemia and the radiation dose has been examined in four different ways, in all of which the expression of dose falls short of the ideal requirements set out above. Of the four methods, the most satisfactory is that in which the mean spinal marrow dose has been estimated for patients who have received radiation directed only to the spine and sacro-iliac joints, as for these patients the dose to the marrow is known with some accuracy. It is true, however, that more accurate estimates of the mean spinal marrow dose would have been obtained if the dose had been measured at more than three points. This would have enabled the variations in depth of the vertebral bodies from the posterior skin surface to have been allowed for more fully and would also have reduced the possibility of a direct field falling between the selected sites and so being neglected when the average dose was measured. On the other hand, the three points at which measurements were made were chosen because a preliminary study of the radiotherapy records of the sample patients showed that the maximum bone marrow dose was likely to be received at one or other of them; consequently the estimate of the average dose received by the marrow is likely to be higher than if the three points had been selected at random. Other sources of error arise from the variation in the transverse measurements of the fields, which must have resulted in the irradiation of different amounts of marrow in the medial posterior ends of the ribs, and from the failure to take account of the increase in dose resulting from the close proximity of the marrow to bone. This last point is discussed in Appendix B (p. 110), where it is concluded that the estimate of the mean dose absorbed by the marrow may, for this reason, be too low by an amount which, in the extreme case, would not be more than 30 per cent.

The second method of examination, i.e. measurement of the mean dose to the spinal marrow for the whole population of patients, takes into account the significant contributions from the irradiation of such extraspinal areas as the hip joints, the iliac crests, and the ischial tuberosities. While this measure of dose is partially justified, on the grounds that irradiation of a part or the whole of the spine was by far the commonest method of treatment and consequently contributed the greatest part of the dose to the population, it could only be wholly justified if, at each level of dose, the ratio of the amount contributed from spinal irradiation to that from extraspinal irradiation was a constant. This, however, is not the case, as the amount contributed by extraspinal irradiation was greater among those patients receiving a high mean spinal marrow dose. In certain sites, for example the shoulder joints, the radiation fields did not contribute significantly to the dose received in the spinal marrow, although clearly such fields irradiated the red marrow in the bones of the shoulder girdle and the ribs. In other sites a measurable contribution to the spinal dose was
made only if the field exceeded a certain critical area, for example, in the case of fields over the anterior aspects of the hip joints, 100 sq. cm.; but again all such fields directly irradiated red bone marrow. If, in fact, it had been possible to estimate the mean dose to all the red bone marrow the resulting dose-response relationship might have been different from that presented. This criticism does not apply to the results derived from patients who received radiation to the spine alone, as it is a reasonable assumption that in these patients the dose to the marrow in the whole length of the spine represents a fairly constant fraction of the total dose to the red bone marrow.

The incidence of leukaemia in relation to the maximum dose received at a point in the spinal marrow has already been reported by the present authors (Medical Research Council, 1956, Appendix B). The use of this measure of dose, however, resulted in a systematic overestimate of the populations at risk following the higher levels of dose. A simple example will suffice:—

If a patient is treated with a field 30 × 10 cm. in size placed posteriorly over the mid-dorsal spine and given 2,000 r. on the skin, he will receive a dose of 1,140 r. to the marrow in the vertebral body lying in the central axis of the beam. On the other hand, if a patient is given the same skin dose to a 15 × 10 cm. field over the sacro-iliac joints, fields of the same size over the lumbar and cervical spines, and a field 30 × 10 cm. over the dorsal spine, his mean spinal dose will be 954 r., and his maximum spinal dose will still be assessed as 1,140 r. It is illogical to argue that a patient receiving direct irradiation to less than one half of his spinal marrow runs the same risk of developing leukaemia as one whose whole length of spinal marrow is irradiated. Yet if the data are presented in terms of the maximum spinal dose, the first patient is considered equally at risk with the second patient, since the volume of marrow irradiated is ignored. The population at risk following a maximum dose of, say, 1,140 r. will, therefore, consist of some patients who have received extensive spinal irradiation, and others who have received direct irradiation to a section of the spinal marrow only. The cases of leukaemia occurring after the same dose may also comprise those two types of patient, but the proportion who received only local irradiation must be expected to be smaller. Consequently the relationship between dose and incidence will be distorted. In a situation in which there is a positive correlation between disease incidence and volume of irradiated tissue and in which the number of patients receiving a given level of dose falls off rapidly with the dose, the effect will be to lower, artificially, the incidence at high levels in comparison with the incidence at low levels.

The final method of examining the incidence of leukaemia is in relation to the whole body integral dose. The integral doses have been calculated so that as far as possible the total energy absorbed both inside and outside the geometrical limits of the X-ray beam has been taken into account. There are, however, a number of limitations inherent in this measure of dose. Firstly, the calculation of the total energy absorbed by the body takes no account of the distribution of the energy within the body, and in particular its relation to the distribution of the bone marrow. Secondly, the calculation is based on the assumption that the body is of a homogeneous structure throughout, and does not take into account the problems posed by X-ray absorption in bone, as a result of the high mineral content of this tissue. Thirdly, the adoption of the whole body integral dose implies that, from a biological standpoint, equal amounts of energy absorbed in dissimilar tissues will have an equal effect on the individual. It is unlikely that the irradiation of fat or muscle will have the
same leukaemogenic effect as the irradiation of red bone marrow, if indeed it has any at all. The more valid measure of dose would be the total energy absorption in the bone marrow; but to calculate this it would be necessary to know both the distribution of dose in the marrow and the quantitative distribution of the marrow itself.

It can be argued that the whole body integral dose bears some simple relationship to the bone marrow integral dose, and under conditions in which the whole body is uniformly irradiated—for example, in the case of a person standing in the open and exposed to an exploding nuclear weapon—this may be true; but under the conditions of therapeutic irradiation in which a number of limited sections of the body are irradiated, the relationship between the whole body and marrow integral doses must be complex. For those reasons, in any final assessment of the relative value of the four estimates of dose, the whole body integral dose may well be regarded as of less value than the two based on the mean dose to the whole spinal marrow.

THE INCIDENCE OF LEUKAEMIA IN RELATION TO THE RADIATION DOSE

In view of the probable systematic errors involved, no further consideration will be given to the relationship shown previously between the incidence of leukaemia and the maximum radiation dose in the spinal marrow. With each of the three other methods of assessing dose a curve has been obtained showing a progressive rise in the incidence of leukaemia with increasing radiation dose. There are, however, some differences between these curves. Thus, when the population receiving only spinal irradiation is considered, the points relating the incidence of leukaemia to the mean dose to the spinal marrow can be adequately fitted by a straight line (Fig. 2, p. 37). It must be remembered, however, that only 18 cases of leukaemia are involved in this relationship and large random errors may be associated with the points; in fact, slightly varying results are obtained according to the method of grouping adopted for patients exposed to the higher levels of dose. In contrast, when the incidence of leukaemia in the whole population of patients is considered in relation to either the mean spinal marrow dose or the whole body integral dose, only the lower five points can reasonably be fitted to a straight line. Thus, in the case of the mean spinal marrow dose, the annual incidence rises fairly slowly with increase of dose up to about 1,250 r., but thereafter becomes progressively steeper (Fig. 1, p. 37); for the whole body integral dose the curve has a similar slope and becomes appreciably steeper after a dose of about 30 Mg. r. (Fig. 3, p. 39).

Two features are of importance in the low-dose regions of each of the three curves: the significant rise in the number of cases of leukaemia even with conservative levels of X-ray dose, and the apparent absence of a threshold effect.

It has been noted in connexion with the mean spinal marrow dose for the whole population of patients that there is a significant excess of cases among patients given less than 500 r. (p. 31). There is also a significant excess of cases among those given spinal irradiation alone at marrow doses of less than 1,000 r.; 143 cases were expected, but as many as 9 were found ($P < 0.0001$). Similarly, 9 cases were observed in patients receiving integral doses of less than 15 Mg. r. when 1.5 times were to be expected ($P < 0.0001$). It should be remembered also that the number of cases of leukaemia identified may be incomplete. As the follow-up of patients is much more satisfactory among those receiving high doses of
THE DOSE-RESPONSE RELATIONSHIP

Radiation and leukaemia

radiation it is likely that if there are any unidentified cases they will have occurred in the sections of the population receiving low doses.

It has not been established whether leukaemia can be produced by doses of radiation less than those commonly given in the treatment of ankylosing spondylitis. Relatively few patients were given a mean spinal marrow dose of less than 250 r, and the inquiry provides no direct evidence on the effect of doses of this order. If the true dose-response relationship were curvilinear, it could be held that a threshold dose exists below which no increase in the incidence of the disease would occur. On such a hypothesis it might be that small doses of radiation, such, for example, as are employed in diagnostic radiology, would not induce any cases of leukaemia. The authors believe, however, that it is more reasonable to adopt the working hypothesis that there is no threshold dose. This belief is based on the finding of a simple proportional relationship over the range of dose observed among those receiving only spinal irradiation, and the fact that when the mean spinal dose to the whole population of patients is considered, in this case also the incidence increases approximately in proportion to the dose at all but the highest levels.

The hypothesis that a simple proportional relationship holds for the lower doses is not necessarily invalidated by the occurrence of a disproportionately high incidence with very large doses, for the effect of such doses may well be complex, and be exerted, in part directly on the cell, and in part indirectly, through damage to the local or more distant environment. If, therefore, leukaemogenesis results from a single irreversible event in an individual cell, endowing it with malignant or potentially malignant properties, high doses may have the additional effect of enhancing the subsequent rate of growth and spread of these altered cells. On the other hand, the data do not prove that there is no threshold at very low levels of dose, since it is conceivable that other factors, at present unknown, may modify the postulated effect at these levels.

If there is in fact no threshold dose for the induction of leukaemia the situation is analogous to the induction of gene mutations by radiation, and the rate at which the dose is accumulated may not affect the proportional relationship between the dose and the response. From the data obtained by examining the population given only spinal irradiation it has been calculated that the dose to the spinal marrow needed to double the expected incidence of leukaemia (i.e. increase it by 0.5 cases per 10,000 men annually) is approximately 94 r. It is a reasonable assumption that between one-third and one-half of the red marrow of the body is in the spinal column. It may, therefore, be presumed that if the entire red marrow within the body were treated with radiation of the same average energy, a dose of between one-third and one-half of 94 r, i.e. a dose of some 30 to 50 r, would produce the same increase in incidence. It should be noted that this does not mean that the same effect would be produced by a skin dose of 30 to 50 r to the whole body; the skin dose which would produce this effect is clearly dependent on the particular way in which irradiation is carried out and the type of radiation used. It should be understood also that the estimate of dose is necessarily approximate and can provide only an indication of the order of dose which may be expected to produce a given effect; the extent of the errors involved and their implications have already been discussed.

It is important that this quantitative relationship should be used in as many ways as possible to test the validity of the hypothesis that there is no threshold dose for the induction of leukaemia. In particular it will be necessary to examine
the incidence of leukaemia in groups of patients exposed to the comparatively low levels of dose received during diagnostic radiology.*

The only data at present available for testing the hypothesis are those derived from the follow-up of the survivors of the atomic explosion over Hiroshima (Medical Research Council, 1956, Appendix A); and this material is of limited value for the purpose since the radiation doses received are not known with any exactness. The radiation from an exploding nuclear bomb consists of (a) mixed neutron and gamma-radiation—the prompt radiation emitted at the moment of explosion—and, (b) the radiation that may subsequently be received from fall-out. It has been possible, on the basis of data published by the Los Alamos Scientific Laboratory (1950), to estimate the prompt gamma-radiation likely to be received by an individual exposed in the open to the explosion of a nominal atomic bomb, i.e., a bomb of the type assumed to have been used at Hiroshima; thus, it is suggested, would be about 50 r. at 1,750 m. from the hypocentre, about 350 r. at 1,250 m., and at least 1,400 r. at less than 1,000 m. The actual doses received by the survivors at Hiroshima, however, could only be accurately gauged if information were available about the other factors involved. Thus it would be necessary to know the size of the doses resulting from the neutron components of the prompt emission and from any subsequent radioactive fall-out (though it is believed that the contribution from this latter source was minimal at Hiroshima), and also the extent to which the survivors were shielded by building structures. Little is known on any of these points.

Bearing in mind these limitations in our knowledge, it is of interest to approach the problem from another angle, by calculating, from the information on the incidence of leukaemia in Hiroshima survivors‡, the dose these survivors could be expected to have received if the postulated relationship between dose and response holds good. The annual incidence of cases in excess of those expected to occur was 0.3 per 10,000 for survivors 1,500 to 1,999 m. from the hypocentre, 3.3 per 10,000 for those at between 1,000 and 1,499 m., and 14.9 per 10,000 among survivors at less than 1,000 m. Assuming that a dose of some 30 to 50 r. averaged over the entire red marrow of the body increases the incidence of leukaemia by 0.5 cases per 10,000 men per year, as derived above, it is seen that for survivors 1,500 to 1,999 m. from the hypocentre the mean dose to the marrow would be between 18 and 30 r., for those between 1,000 and 1,449 m. it would be between approximately 200 and 330 r., and for those at less than 1,000 m. it would be between approximately 900 and 1,500 r.§

Strictly speaking, these doses are not comparable with the estimated doses from the prompt gamma-radiation based on the data from the Los Alamos Laboratory, because the latter are expressed as whole body doses. In view of the circumstances of irradiation at Hiroshima, however, it seems likely that the average marrow doses will be of the same order as the estimated whole body doses, so that to this extent a comparison may be justified. As can be seen, the two sets of estimates are in reasonably close agreement.

The estimate obtained for persons exposed at less than 1,000 m. is somewhat higher than the survivors would be expected to have received, as doses much

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*Since this Report was written, evidence has been published suggesting that doses of radiation as small as those received by the foetus from radiological examination of the mother's abdomen are leukemogenic (Stewart, Webb, Giles and Hewitt, 1956).

†A nominal atomic bomb is defined as a bomb the energy release of which is approximately equivalent to that of 20 Kilotons of T.N.T., or about $2 \times 10^{11}$ calories.

‡The data for Nagasaki are insufficiently complete to be used in this way.

§In these calculations differences in sex and age distribution have been ignored.
above 500 r. must be presumed to have caused death within, at the most, a few months. This, however, can be accounted for if, as has been suggested previously, heavy doses bring an additional factor or factors into play, causing the incidence of the disease to rise above that which would be expected with a simple proportional relationship. In conclusion, the authors believe that, within the necessary limitations of the available data, the incidence of leukaemia among the survivors in Hiroshima is compatible with the concept that at the lower levels of dose the incidence of leukaemia induced by irradiation is directly proportional to the dose received in the marrow.

There remains the possibility that persons suffering from ankylosing spondylitis are more sensitive to the leukaemogenic effects of irradiation than those in normal health. This question can be finally settled only by a study of the incidence of leukaemia in patients irradiated for other diseases, but from the published evidence there appears to be little doubt that spondylitics, and also people in normal health, are prone to the induction of leukaemia by irradiation. Certainly the findings relating to the presumably healthy population of Hiroshima do not conflict with the results in the present study.

**Implications of the postulated dose-response relationship**

If it is postulated that a simple proportional relationship exists between the incidence of leukaemia and the radiation dose, at least at the lower doses, two important implications result:—

Firstly, it follows that in a proportion of the individuals who develop leukaemia the disease will have been induced by background radiation. The amount of radiation received in the marrow from the natural background by an Englishman of the average age of the men studied in the present investigation (i.e. 35 years) is approximately 5 r. This figure includes the radiation received from the skeletal radium, and is estimated from data published by the Medical Research Council (1956). In comparison, the dose to the marrow which, it is estimated, would have doubled the expected incidence of leukaemia is 30 to 50 r., i.e. six to ten times the dose received from the relevant background radiation. If the induction of leukaemia by radiation is the result of the production of a mutation in a somatic cell, the present hypothesis accords with the view that background radiation is responsible for a proportion of genetic mutations; and it is of interest to note that the dose to the marrow which, it is suggested, would have doubled the incidence of leukaemia expected among the patients studied is not very different from that suggested for the 'doubling dose' to the gonads for gene mutations. The Medical Research Council's Committee on the Hazards to Man of Nuclear and Allied Radiations (Medical Research Council, 1956) and, in America, the Committee of the National Academy of Sciences on the Genetic Effects of Atomic Radiation (National Academy of Sciences, 1956) concluded independently that the representative 'doubling dose' in this case probably lay within the range of 30 to 80 r.

Secondly, it follows from the postulate that any exposure to radiation over and above that from the natural background, however small, must increase the risk of the disease developing, and this may be relevant to the fact that in many countries the annual death rate from leukaemia is rising (Tables 1 and 2, p. 2). There is at present nothing to prove that the rise cannot be accounted for by improvements in diagnostic techniques and changes in diagnostic criteria. The authors believe, however, that some of this rise is real. If this is so, and if the induction of leukaemia is a non-threshold event, some consideration
has to be given to the increasing use of diagnostic radiology as a possible contributory cause of the rise. Several estimates have been made of the size of the dose to the gonads from this source, averaged over the whole population and relative to the dose from natural background radiation. These have ranged in value from approximately 10 per cent for Australia (Martin, 1955) to approximately 58 or 70 per cent for the United States (Clark, 1956; National Academy of Sciences, 1956). Intermediate between these is the estimate of at least 22 per cent for England and Wales (Medical Research Council, 1956; Osborn and Smith, 1956). The dose to the gonads will, of course, be higher than that to the marrow for a given volume of tissue, as, on average, the gonads are more accessible than the marrow. However, about 72 per cent of all diagnostic X-ray examinations are performed on the trunk, and, as such, must irradiate red marrow; in contrast, about 7 per cent of all examinations contributed the major proportion of the gonad dose (Osborn and Smith, 1956). The intensification of the risk of leukaemogenesis associated with any one X-ray examination in any one patient will be very small indeed, but the total population undergoing such examinations is very large. According to Osborn and Smith, between 17 and 18 million X-ray examinations are carried out annually in England and Wales, and these authors further suggest that the annual rate of increase is about 12 per cent. If the basic hypothesis of the non-threshold nature of leukaemia induction by radiation holds good, it must be supposed that some cases of leukaemia have resulted from the use of X-rays in diagnosis. It seems unlikely, however, that radiation alone can account for the whole of the increase in the mortality from leukaemia observed over the last twenty-five years.
PART III. SUMMARY AND CONCLUSIONS

(1) The case records have been studied of 13,352 patients presumed to have ankylosing spondylitis and given X-ray treatment for this condition at 81 British radiotherapy centres between January 1st, 1935 and December 31st, 1954.

(2) A diagnosis of leukaemia, aplastic or hypoplastic anaemia or myelofibrosis was recorded on the death certificates of 46 of the patients who had died by December 31st, 1955. Three patients still alive on December 31st, 1955, were found to have leukaemia.

(3) In 28 of these patients death was certified as attributable to leukaemia; in 12 it was certified as attributable to aplastic anaemia.

(4) The numbers of certified deaths which would have been expected to occur by December 31st, 1955, were 2·9 for leukaemia and 0·3 for aplastic anaemia. The expected deaths were calculated from the national vital statistics on the assumption that all persons untraced in 1955 were, in fact, alive and domiciled in Britain at the end of that year. The increase in mortality from leukaemia and aplastic anaemia is highly significant.

(5) Consideration has been given to the possibility that all or most of the excess deaths from leukaemia could be due to an association between ankylosing spondylitis and leukaemia in the absence of irradiation. Reasons are given for believing that such an association is unlikely; the number of unirradiated patients studied is, however, small, and it is impossible to be certain that some slight association does not exist. There are no grounds for believing that exposure to drugs has caused the excess mortality from leukaemia.

(6) Review of the cases stated to have died from aplastic anaemia showed that half of them were certain or probable cases of leukaemia. Of the remainder there were only 4 in which the diagnosis of aplastic anaemia is believed to have been established, and only one of these was clearly due to X-ray exposure alone.

(7) Data have also been collected for 23 cases of leukaemia and aplastic anaemia occurring in patients with ankylosing spondylitis other than those in the survey; 15 of these patients are known to have been irradiated. Information from these cases has been taken into account in discussions of the latent period and of the cytological types of leukaemia. The proportion of cases which were lymphatic in type was lower among those patients who had been irradiated than among those who had not; only one case of chronic lymphatic leukaemia was found among the irradiated patients.

(8) Details of X-ray dose were obtained from a sample of approximately one in six of the patients, and the doses were expressed in terms of the dose to the bone marrow in the spinal column (roentgens) and also in units of whole body integral dose (megagramme-roentgens). The spinal marrow dose was estimated in two different forms—the mean dose to the marrow throughout the whole length of the spine, and the maximum dose at a point in the spinal marrow. Finally the mean spinal marrow dose was estimated separately for those patients receiving only spinal irradiation.

(9) In the evaluation of the relationship between radiation dose and incidence of leukaemia, the cases used included 32 with an established diagnosis ('A' series) and 5 which were probably cases of leukaemia ('B' series). Eighteen of the 37 cases were patients receiving only spinal irradiation.

(10) The dose-response relationship appeared to be linear under the following conditions:—

(a) when the relevant cases of leukaemia were related to the man-years at
risk following various levels of mean spinal marrow dose for the group of patients receiving only spinal irradiation;
(b) when all the cases of leukaemia were related to the man-years at risk following various levels of maximum spinal marrow dose for all the patients.
The dose-response relationship appeared to be curvilinear under the following conditions:—
(a) when all the cases of leukaemia were related to the man-years at risk following various levels of mean spinal marrow dose for all the patients;
(b) when all the cases of leukaemia were related to the man-years at risk following various levels of whole body energy-absorption for all the patients.
With both these measures of dose the relationship may be linear for all cases other than those given very high doses.
(11) Of the four relationships, that for patients given spinal irradiation alone is considered to be the most informative, as in these patients the distribution of dose in the treated marrow is known with considerable accuracy. The annual incidence of leukaemia among men not given therapeutic irradiation is calculated to be 0.5 cases per 10,000. For men given spinal irradiation alone, the annual incidence rises to between 16 and 17 cases per 10,000 men, following a mean dose in excess of 1,750 r. to the spinal marrow.
For all the patients, the annual incidence rises to 72 cases per 10,000 men following a mean dose to the spinal marrow in excess of 2,250 r.
The relationship based on the whole body integral dose for all the patients shows a rise in the annual incidence to about 87 cases per 10,000 men following a dose in excess of 52.5 Mgy. r. For reasons which are discussed, less confidence is placed in this particular dose-response relationship.
Data have already been published by the present authors on the relationship between the incidence of leukaemia and the maximum dose at a point in the spinal marrow, and they are not reproduced in the Report. Reasons are given for disregarding these findings.
(12) The authors suggest the adoption of the working hypothesis that, for low doses, the incidence of leukaemia bears a simple proportional relationship to the dose of radiation, and that there is no threshold dose for the induction of the disease. In this case the nature of the relationship between the dose of radiation and the induction of leukaemia may be analogous to that postulated for the induction of gene mutations by radiation. Calculations based on this hypothesis and on the data for the incidence of leukaemia among men given only spinal irradiation lead to the conclusion that the dose to the whole marrow which would have doubled the expected incidence of leukaemia may lie within the range 30 to 50 r. for irradiation with X-rays of the same average energy as those used in the treatment of ankylosing spondylitis.
(13) Further implications of a simple proportional relationship between the incidence of leukaemia and the radiation dose at low dose levels are discussed in the light of the rise in the national death rate from leukaemia and the increasing use of X-rays in medical diagnosis.
(14) It is emphasized that a number of approximations have been necessary to arrive at the quantitative estimate of the relationship between the dose of radiation and the incidence of leukaemia; consequently, that estimate may be subject to appreciable error. Moreover, the hypothesis that there is no threshold dose is not the only one compatible with the data, though in the authors' opinion it is a reasonable deduction.
APPENDIX A

Case Histories

NOTES

The following contractions have been used in the case histories:—

- T.N.C. .. total nucleated cell count (marrow)
- N.P. .. neutrophil polymorphonuclear leucocytes
- Eos. .. eosinophil polymorphonuclear leucocytes
- Basos. .. basophil polymorphonuclear leucocytes
- Monos. .. monocytes
- Lymphos. .. lymphocytes
- Retics. .. reticulocytes
- P.C. .. plasma cells
- Hb. .. haemoglobin
- R.B.C. .. red blood cell count
- W.B.C. .. white blood cell count
- M : E .. myeloid-erythroid ratio (marrow)

In the records of the mean spinal marrow dose a dash (—) indicates that the dose was too small to be assessed.

The following dates are printed in bold type:—
(1) the dates of the first course of treatment,
(2) the date of diagnosis of leukaemia or aplastic anaemia,
(3) the date of death.

In the few cases where difficulty has been experienced in determining the date of diagnosis the authors have used their own judgement in deciding the appropriate date.

The case histories of the three living patients are not recorded. Their dosage data is as follows:—

<table>
<thead>
<tr>
<th>Case</th>
<th>Courses</th>
<th>Centre</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mr.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>5</td>
<td>1</td>
<td>1559</td>
<td>36.7</td>
</tr>
<tr>
<td>28</td>
<td>1</td>
<td>1</td>
<td>721</td>
<td>9.8</td>
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<tr>
<td>36</td>
<td>5</td>
<td>2</td>
<td>377</td>
<td>14.6</td>
</tr>
</tbody>
</table>

Histories of Cases 58–64 are not reproduced here, since they are given in full in a paper by van Swaay (1955).
**Case 1. Male. Born 1918. 3 Courses. 1 Centre.**

*Pre-irradiation History*
None available.

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mg. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray treatment to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. 7.40 - 22. 7.40</td>
<td>214</td>
<td>7:1</td>
</tr>
<tr>
<td>lumbar and dorsal spines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. 3.41 - 17. 3.41</td>
<td>91</td>
<td>0:9</td>
</tr>
<tr>
<td>cervical spine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. 4.41 - 15. 7.41</td>
<td>166</td>
<td>4:2</td>
</tr>
<tr>
<td>lumbar and cervical spines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>471</td>
<td>12:2</td>
</tr>
</tbody>
</table>

*Post-irradiation History*

**July 1953**
Admitted with history of malaise since May 1953. Liver and spleen not palpable.
Hb. 53%, R.B.C. 2,500,000, W.B.C. 268,000.

**August 1953**
W.B.C. 193,000, Platelets 8,000, Blasts 80%, Myelocytes 3%, N.P. 7%, Eos. 3%, Basos. 2%, Lymphos. 5%.
*Marrow:* 'The predominant cell is the blast cell, probably of the myeloid series. No megakaryocytes were seen. The red cell series appeared depressed but was normal.'
Treated with blood transfusions and cortisone.

**9.11.53**
Death.
*Certified Causes of Death*
Chronic lymphatic leukaemia.
Terminal exhaustion.

*Preferred Diagnosis*
It is considered that the death certificate diagnosis of chronic lymphatic leukaemia is erroneous. A diagnosis of acute myeloid leukaemia is to be preferred.

**Case 2. Male. Born 1896. 7 Courses. 2 Centres.**

*Pre-irradiation History*
None available.

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mg. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray treatment to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.11.40 - 11.12.40</td>
<td>334</td>
<td>16:3</td>
</tr>
<tr>
<td>trunk</td>
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<td></td>
</tr>
<tr>
<td>25.11.41 - 16.12.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sacro-iliac joints, lumbar and dorsal spines, hip joints</td>
<td>620</td>
<td>14:6</td>
</tr>
<tr>
<td>18.3.42 - 9.4.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sacro-iliac joints, lumbar and dorsal spines</td>
<td>632</td>
<td>13:8</td>
</tr>
<tr>
<td>4.8.43 - 25.8.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sacro-iliac joints and whole spine</td>
<td>365</td>
<td>15:4</td>
</tr>
<tr>
<td>3.1.44 - 31.1.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lumbar spine and L. hip joint</td>
<td>137</td>
<td>8:1</td>
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<tr>
<td>7.7.44 - 31.7.44</td>
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<td></td>
</tr>
<tr>
<td>sacro-iliac joints and whole spine</td>
<td>1044</td>
<td>17:9</td>
</tr>
<tr>
<td>13.2.47 - 1.4.47</td>
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<td></td>
</tr>
<tr>
<td>sacro-iliac joints and hip joints</td>
<td>403</td>
<td>17:7</td>
</tr>
<tr>
<td>Total</td>
<td>3535</td>
<td>103:8</td>
</tr>
</tbody>
</table>

*Post-irradiation History*

**November 1940**
Referred for X-ray treatment

**November 1947**
Admitted to hospital with history of dyspnoea on exertion for 2–3 years.
Liver and spleen not palpable.
Hb. 44%, R.B.C. 1,540,000, W.B.C. 2,400. No abnormal white cells seen in the blood film. Retics. <2%.
*Marrow:* 'A cellular marrow in which the proportion of myeloid and erythroid cells seemed to be within normal limits. Late normoblasts preponderated in the erythroid series. The myeloid series showed a shift to the left, not of a very marked degree, but the number of early myelocytes seemed to be relatively increased.'
APPENDIX A

Case 2 (contd.)

Between November 1947 and March 1948, 30 further counts were performed. These are summarized as follows:—

Hb. 75-23% ... ... ... (30 observations)
R.B.C. 3,370,000-1,190,000 ... ... ... (20)
W.B.C. 4,000-2,800 ... ... ... (5)
Retics. 5-<2% ... ... ... (19)

No differential counts.

The diagnosis was considered to be severe hypoplastic anaemia and treatment was by blood transfusions.

13.3.48 Discharged home for outpatient treatment with haematinics. Hb. 75%, R.B.C. 3,140,000.

12.4.48 Attending as outpatient and being treated with iron, folic acid and liver preparations.

Hb. 71%, R.B.C. 3,300,000, W.B.C. 33,000. The film showed 'marked shift to the left of the myeloid series. Occasional ? myeloblasts and numbers of pre- and metamyelocytes.'

26.4.48 Hb. 45%, R.B.C. 2,400,000, W.B.C. 40,000.

Marrow: 'This is a cellular hyperplastic marrow, and shows a marked myelocytic reaction with numerous myelocytes of all types and many abnormal forms. The marrow is typical of chronic myeloid leukaemia.'

Between April and August, 1948, the patient was treated with blood transfusions and urethane. Only terminally were the liver and spleen palpable.

29.8.48 Death.

Certified Cause of Death
Aplastic anaemia.

Preferred Diagnosis
Myeloid leukaemia (?) clinical type) presenting in aleukaemic phase.


Pre-irradiation History

July 1941 Referred to hospital with history of pain in R. leg for 15 years, and of back pain for 6 months. Typical findings of ankylosing spondylitis.
Hb. 70%, R.B.C. 4,010,000, W.B.C. 10,800.

April 1942 Referred for X-ray treatment.

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mg. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. 4.42 - 18. 4.42</td>
<td>lumbar and dorsal spines ...</td>
<td>276 7-5</td>
</tr>
<tr>
<td>13. 7.42 - 27. 7.42</td>
<td>lumbar and dorsal spines ...</td>
<td>256 4-7</td>
</tr>
<tr>
<td>6.10.42 - 17.10.42</td>
<td>dorsal spine ... ... ... ... ...</td>
<td>227 3-4</td>
</tr>
<tr>
<td>3.12.42 - 14.12.42</td>
<td>cervical spine ... ... ...</td>
<td>152 1-3</td>
</tr>
<tr>
<td>16. 2.43 - 27. 2.43</td>
<td>lumbar and dorsal spines ...</td>
<td>276 9-4</td>
</tr>
<tr>
<td>29. 4.43 - 11. 5.43</td>
<td>cervical spine ... ... ...</td>
<td>130 1-0</td>
</tr>
<tr>
<td>23. 8.43 - 3. 9.43</td>
<td>sacro-iliac joints ... ... ...</td>
<td>151 3-6</td>
</tr>
<tr>
<td>13. 1.44 - 27. 1.44</td>
<td>hip joints ... ... ... ... ...</td>
<td>371 7-9</td>
</tr>
<tr>
<td>14.12.44 - 28.12.44</td>
<td>R. knee ... ... ... ... ...</td>
<td>371 4-0</td>
</tr>
<tr>
<td>29. 5.45 - 12. 6.45</td>
<td>hip joints and R. knee ... ...</td>
<td>334 9-9</td>
</tr>
<tr>
<td>25. 2.46 - 8. 3.46</td>
<td>elbows and knee joints ...</td>
<td>- 5-2</td>
</tr>
<tr>
<td>4. 4.46 - 16. 4.46</td>
<td>sacro-iliac joints ... ... ...</td>
<td>101 2-4</td>
</tr>
<tr>
<td>4. 6.46 - 15. 6.46</td>
<td>elbows and knee joints ...</td>
<td>- 5-3</td>
</tr>
</tbody>
</table>

Total ... 2622 76-1

(continued overleaf)
Case 3 (contd.)

Post-irradiation History

July 1950

Referred with history of dyspnoea since March 1950. Anaemic. Liver and spleen not palpable.

Hb. 30 %, W.B.C. 4,500, Platelets 125,000, Myelocytes 1 %, Bands 11 %, N.P. 43 %, Eos. 3 %, Monos. 11 %, Turk cells 1 %, Lymphos. 30 %, Retics. 0-4 %.

1.8.50 – 29.1.51

30 blood counts performed. Patient had numerous blood transfusions. Counts varied between the following limits:—

Hb. 52–22 %
W.B.C. 9,300–2,400
Platelets 185,000–57,500
Blasts 6–1 %
Premyelocytes 12–1 %
Myelocytes 24–2 %
Bands 29–6 %
N.P. 59–14 %
Eos. 9–1 %
Basos. 6–1 %
Monos. 9–1 %
Lymphos. 39–12 %
Retics. 2–6<1 %

(Marrow: Sternal marrow was examined on 2 occasions and iliac crest marrow once. All 3 reported as highly cellular with shift to left of myeloid series. The cells found on 2 occasions were: Myeloblasts 11–1, 8–9 %, Premyelocytes 12–4, 11–8 %, Myelocytes 15–7, 13–5 %, Myelocytes 19–5, 14–3 %, N.P. 2–5, 7–3 %, Lymphos. 3–6, 6–3 %, Haemoloblasts 3–5, 2–8 %, Normoblasts 30–3, 34–4 %.)

13.2.51

Death.

Certified Causes of Death

Ankylosing spondylitis.
Hypoplastic anaemia.

Post-mortem Findings


The post-mortem material was submitted to two independent authorities. Their opinions were as follows:—

Opinion A

Marrow: Increased cellularity with numerous early forms with excess of plasma cells and megakaryocytes. Abundant eosinophil leucocytes. Much haemosiderosis.


Spleen: Myelocytes and megakaryocytes numerous.

Liver: Infiltration of portal systems with mononuclear cells. Haemosiderosis.

Comment: Marrow not typical of leukaemia, but general findings favour an atypical manifestation of this disease. (Findings not unlike Case 38.)

Opinion B

The most important finding is in the bone marrow from the tibia and to a lesser extent the marrow from the sternum. The marrow was clearly hyperplastic, but there was a deficiency of differentiated cells of the
APPENDIX A

Case 3 (contd.)

myeloid series, an excessive number of myelocytes and possibly some increase in myeloblasts. The numbers of normoblasts present were almost certainly reduced. These findings are certainly not compatible with the final post-mortem findings of death from anaemia. They are much more compatible with, and in fact, could only be explained on the basis of, a diagnosis of leukaemia. Examination of the extramedullary organs shows no convincing evidence of leukaemic infiltration, and it is felt that the case is one of an early sub-leukaemic myeloid leukaemia with little or no spread of the process outside the bone marrow.

Preferred Diagnosis
The case is regarded as a definite case of leukaemia although possibly atypical. Classified in the 'A' series. Acute myeloid leukaemia presenting in aleukaemic phase.

Case 4. Male. Born 1911. 9 Courses. 2 Centres.

Pre-irradiation History

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean spinal marrow dose (c.)</th>
<th>Integral dose (Mg. c.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray treatment to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30. 4.42 – 18. 5.42</td>
<td>whole trunk</td>
<td>194</td>
</tr>
<tr>
<td>12. 2.43 – 26. 2.43</td>
<td>sacro-iliac joints and whole length of spine</td>
<td>1245</td>
</tr>
<tr>
<td>12. 7.43 – 26. 7.43</td>
<td>both hip joints</td>
<td>240</td>
</tr>
<tr>
<td>20. 7.44 – 2. 8.44</td>
<td>cervical spine</td>
<td>431</td>
</tr>
<tr>
<td>6. 4.45 – 20. 4.45</td>
<td>both shoulders</td>
<td>—</td>
</tr>
<tr>
<td>18.12.45 – 3. 1.46</td>
<td>L. shoulder</td>
<td>—</td>
</tr>
<tr>
<td>26. 4.46 – 15. 5.46</td>
<td>ischial tuberosities and L. hip joint</td>
<td>398</td>
</tr>
<tr>
<td>19. 9.46 – 26. 9.46</td>
<td>cervical spine</td>
<td>198</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>2706</td>
</tr>
</tbody>
</table>

Post-irradiation History
March 1947
Hb. 50%, W.B.C. 380,000, Myeloblasts 1%, Myelocytes 34%, N.P. 60%, Eos. 1% Lymphos. 4%.

October 1947
General health poor. Pulmonary tuberculosis. Lower pole of spleen palpable 15 cm. below xiphisternum.
Hb. 58%, W.B.C. 39,200, Platelets 2,860,000.

19.11.47
Death.

Certified Causes of Death
Leukaemia, 14 months.
Pulmonary tuberculosis, 2 months.

Preferred Diagnosis
Chronic myeloid leukaemia.
RADIATION AND LEUKAEMIA

Case 5. Male. Born 1905. 5 Courses. 2 Centres.

Pre-irradiation History

December 1942
Referred for X-ray treatment with history of back pain for 3 years.

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mg.r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.12.42 – 7.1.43 lumbar and dorsal spines</td>
<td>102</td>
<td>3.3</td>
</tr>
<tr>
<td>28.11.50 – 14.2.51 sacro-iliac joints and whole spine</td>
<td>813</td>
<td>15.0</td>
</tr>
<tr>
<td>7.12.51 – 24.12.51 Partial trunk irradiation</td>
<td>77</td>
<td>6.8</td>
</tr>
<tr>
<td>24.1.52 – 15.4.52 &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot;</td>
<td>249</td>
<td>14.8</td>
</tr>
<tr>
<td>11.6.53 – 29.6.53 &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot;</td>
<td>77</td>
<td>5.4</td>
</tr>
<tr>
<td>9.6.54 – 25.6.54 &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot; &quot;</td>
<td>77</td>
<td>5.4</td>
</tr>
<tr>
<td>Total</td>
<td>1395</td>
<td>50.7</td>
</tr>
</tbody>
</table>

Post-irradiation History

September 1954
Admitted to hospital with weakness, anorexia and loss of weight since December 1952. Severely anaemic. Liver and spleen not palpable. Hb. 29%, W.B.C. 1,900, N.P. 60%, Eos. 2%, Monos. 6%, Lymphos. 32%. Some anisocytosis. Platelets are scanty, and of abnormal size and shape.

Sternal marrow: ‘Marrow cells are quite numerous in the film. Erythropoiesis is normoblastic and cells present are of normal pattern. Basophilic normoblasts and erythroblasts are not readily demonstrable, nor are myeloblasts and premelocytes, but myelocytes are quite prominent. Findings consistent with a degree of general hypoplasia.’

From September 1954 to February 1955 treated with blood transfusions,

February 1955
Hb. 26%. Blood film: ‘This specimen is characterized by a feature not previously apparent, the presence of primitive white cells in appreciable numbers. These are of blast type and often show clearly-defined nucleoli. Some present monocytic features.’

12.4.55
Death.

Certified Causes of Death
(1a) Leukaemia.
(2) Ankylosing spondylitis.

Preferred Diagnosis
Acute leukaemia (?cell type) presenting in aleukaemic phase.

Case 6. Male. Born 1920. 4 Courses. 2 Centres.

Pre-irradiation History

August 1943
Referred for X-ray treatment. History of back pain since 1939. No other details available.

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mg.r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30. 8.43 – 15.9.43 sacro-iliac joints and whole spine</td>
<td>321</td>
<td>12.7</td>
</tr>
<tr>
<td>8.11.43 – 7.12.43 whole trunk</td>
<td>49</td>
<td>13.2</td>
</tr>
<tr>
<td>30.11.43 (Hb. 90%, W.B.C. 4,300)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20.4.44 – 17.5.44 sacro-iliac joints and whole spine</td>
<td>1085</td>
<td>14.4</td>
</tr>
<tr>
<td>12.10.48 – 12.11.48 sacro-iliac joints and whole spine</td>
<td>1011</td>
<td>16.0</td>
</tr>
<tr>
<td>Total</td>
<td>2466</td>
<td>56.3</td>
</tr>
</tbody>
</table>
APPENDIX A

Case 6 (contd.)
Post-irradiation History

January 1950
Diagnosis of leukaemia made. Spleen not palpable.
Hb. 56%, R.B.C. 3,910,000, W.B.C. 70,800, Myeloblasts 0-5%, Myelocytes 18-5%, N.P. 72%, Eos. 2%, Monos. 3%, Lymphos. 6%.
Between January 1950 and death, treated with X-rays and chemotherapy.
Terminally developed acute phase.

October 1951
Hb. 50%, W.B.C. 100,000, Platelets 45,000. Myeloblasts 91%, Myelocytes 1%. Metamyelocytes 2%, N.P. 4%, Basos. 2%, 1 Normoblast/100 W.B.C.

25.12.51
Death.

Certified Cause of Death
(1a) Myeloid leukaemia.

Preferred Diagnosis
Chronic myeloid leukaemia.

Case 7. Male. Born 1913. 7 Courses. 1 Centre.
Pre-irradiation History

September 1939
Passed Grade I on enlistment in Armed Services.

July 1942
Admitted to hospital with back pain. Diagnosis of ankylosing spondylitis.

March 1944
Referred for X-ray treatment.

Irradiation History

<table>
<thead>
<tr>
<th>Irradiation</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mg. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray treatment to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. 3.44 – 24. 3.44</td>
<td>whole spine</td>
<td>520</td>
</tr>
<tr>
<td>26. 4.44 – 28. 4.44</td>
<td>both iliac crests</td>
<td>—</td>
</tr>
<tr>
<td>9.11.45 – 4.12.45</td>
<td>both shoulders and lumbar spine</td>
<td>31</td>
</tr>
<tr>
<td>24. 1.46 – 25. 1.46</td>
<td>both knees</td>
<td>—</td>
</tr>
<tr>
<td>7. 9.48 – 13. 9.48</td>
<td>cervical spine</td>
<td>221</td>
</tr>
<tr>
<td>22. 8.49 – 31. 8.49</td>
<td>R. hip joint</td>
<td>177</td>
</tr>
<tr>
<td>3. 4.50 – 10. 5.50</td>
<td>both hip joints</td>
<td>354</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1303</td>
</tr>
</tbody>
</table>

Post-irradiation History

January 1953
Admitted to hospital with history of weakness and anorexia since December 1952. Purpuric rash for 2 weeks.
Hb. 54%, R.B.C. 3,040,000, W.B.C. 21,000, Platelets 24,000. Blasts 94%, N.P. 10%, Lymphos. 5%. Clotting time 3-25 min., Bleeding time >15 min.

16.1.53
Death.

Certified Causes of Death
Acute leukaemia.
Ankylosing spondylitis.

Post-mortem Findings
Leukaemic infiltration of liver and spleen. Red marrow extended into lower third of femur and was hypercellular, with over 90% 'blast' cells which could not be identified with any precision.

Preferred Diagnosis
Acute leukaemia, ? type.
RADIATION AND LEUKAEMIA


Pre-irradiation History
October 1944
Discharged from Army with ankylosing spondylitis and referred for X-ray treatment.

Irradiation History

<table>
<thead>
<tr>
<th>Date</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mr. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.11.44 – 4.12.44</td>
<td>757</td>
<td>10.6</td>
</tr>
<tr>
<td>21.11.46 – 29.11.46</td>
<td>302</td>
<td>2.6</td>
</tr>
<tr>
<td>Total</td>
<td>1059</td>
<td>13.2</td>
</tr>
</tbody>
</table>

Post-irradiation History
July 1948
Admitted to hospital with history of vomiting for 3 weeks, and purpuric rash for 2 days. Petechiae on trunk, face, limbs and oral mucosa. Generalized gland enlargement. Liver enlarged to umbilicus and spleen palpable. No blood counts available.

8.11.48
Death.

Certified Cause of Death
Cerebral haemorrhage due to leukaemia.

Post-mortem Findings
Brain: Large haemorrhage into left capsule which had ruptured into the lateral ventricle.
Liver, spleen, lymph glands, marrow: Appearances compatible with those of leukaemia.
Histological examination showed the condition to be one of monocytic leukaemia with involvement of the brain.

Preferred Diagnosis
Acute monocytic leukaemia.

Case 10. Male. Born 1909. 2 Courses. 2 Centres.

Pre-irradiation History
None available.

Irradiation History

<table>
<thead>
<tr>
<th>Date</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mr. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24. 1.45 – 7. 2.45</td>
<td>43</td>
<td>1.0</td>
</tr>
<tr>
<td>15. 5.51 – 28. 5.51</td>
<td>69</td>
<td>17.3</td>
</tr>
<tr>
<td>Total</td>
<td>112</td>
<td>18.3</td>
</tr>
</tbody>
</table>

Post-irradiation History
August 1955
Admitted to hospital, length of history not stated. Gross enlargement of liver and spleen. Enlarged glands on both sides of the neck and the R. axilla.
Hb. 23%. R.B.C. 1,580,000, W.B.C. 420,000. The white cells were almost entirely mature lymphocytes. Retics. 0-4%.

28.10.55
Death.

Certified Causes of Death
(1a) Congestive cardiac failure.
(1b) Lymphatic leukaemia.
(2) Ankylosing spondylitis.

Preferred Diagnosis
Chronic lymphatic leukaemia.
## APPENDIX A

### Case 11. Male. Born 1910. 5 Courses. 1 Centre.

**Pre-irradiation History**
- July 1941: Passed fit (Grade II) on enlistment in the Armed Services.
- April 1944: Diagnosis of ankylosing spondylitis.

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mg. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12. 4.45 – 7. 5.45</td>
<td>474</td>
<td>7.9</td>
</tr>
<tr>
<td>1. 5.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30. 7.45 – 27. 8.45</td>
<td>474</td>
<td>7.9</td>
</tr>
<tr>
<td>1. 4.46 – 16. 4.46</td>
<td>420</td>
<td>4.2</td>
</tr>
<tr>
<td>22. 3.48 – 9. 4.48</td>
<td>231</td>
<td>5.7</td>
</tr>
<tr>
<td>20.11.51 – 7.12.51</td>
<td>165</td>
<td>2.1</td>
</tr>
<tr>
<td>Total</td>
<td>1763</td>
<td>27.8</td>
</tr>
</tbody>
</table>

**Post-irradiation History**
- December 1952: Admitted to hospital with history of dyspnoea on exertion and fatigue, from October 1951. Scattered purpuric patches were present on the limbs and trunk. Generalized glandular enlargement was present, but no palpable enlargement of the liver and spleen.
- Hb. 18%, R.B.C. 1,335,000, W.B.C. 88,000, Platelets 38,000, Myeloblasts 54%, Premyelocytes 8%, Myelocytes 4%, Metamyelocytes 20%, N.P. 10%, Lymphos. 4%.
- 10.2.53: Death.

**Certified Cause of Death**
- (1a) Acute leukaemia.

**Post-mortem Findings**
- There was widespread leukaemic infiltration of the liver, spleen and kidneys, the leukaemia being myeloblastic in type.

**Preferred Diagnosis**
- Acute myeloid leukaemia.

### Case 12. Male. Born 1895. 3 Courses. 1 Centre.

**Pre-irradiation History**
- None available.

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mg. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.11.45 – 14.12.45</td>
<td>340</td>
<td>2.1</td>
</tr>
<tr>
<td>24. 1.46 – 28. 2.46</td>
<td>113</td>
<td>0.8</td>
</tr>
<tr>
<td>3. 9.48 – 26.11.48</td>
<td>729</td>
<td>7.6</td>
</tr>
<tr>
<td>Total</td>
<td>1183</td>
<td>10.5</td>
</tr>
</tbody>
</table>

(continued overleaf)
Case 12 (contd.)

Post-irradiation History
The patient suffered repeated attacks of iritis of the left eye.

June 1950
Enucleation of the left eye.

July 1950
Admitted to hospital with purpuric rash on the trunk. Liver and spleen not palpable.
Hb. 54%, R.B.C. 3,180,000, Platelets 50,000, W.B.C. 6,400, Primitive monocytes 41%, Myelocytes 3%, Metamyelocytes 7%, N.P. 10%, Eos. 1%, Lymphos. 38%.
Sternal marrow: Mononuclear blast cells 70-5%, Myeloblasts 3-5%, Premyelocytes 1-5%, Myelocytes 1%, Metamyelocytes 3-5%, N.P. 3%, Lymphos. 5%, Megakaryocytes 1-5%, Unidentified 2%, Normoblasts 8-5%.

17.10.50
Death.

Certified Cause of Death
Chronic leukaemia.

Preferred Diagnosis
Acute monocytic leukaemia presenting in aleukaemic phase.


Pre-irradiation History
March 1946
Referred for X-ray treatment. History of back pain for nearly 2 years.

Irradiation History
X-ray treatment to:
Mean dose (r.)
spinal marrow dose (r.) Integral dose

3. 4.46 - 12. 6.46 sacro-iliaic joints and whole spine .. 746 15:0

Post-irradiation History
February 1951
Admitted with history of tiredness and irregular fever since December 1950. Liver and spleen not palpable.
Hb. 38%, R.B.C. 1,760,000, W.B.C. 6,400, Myeloblasts 19-5%, Premyelocytes 6-5%, Myelocytes 2-0%, Metamyelocytes 1-5%, N.P. 36%, Basos. 1%, Monos. 1%, Lymphos. 24%, Normoblasts 8-5%.

March 1951
Sternal marrow: Myeloblasts 20%, Premyelocytes 1-5%, Myelocytes 5-0%, N.P. 11-5%, Monos. 10%, Lymphos. 6-0%, Pro-erythroblasts 1-5%, Normoblasts 53-5%.

15.3.51
Death.

Certified Cause of Death
(1a) Myeloblastic leukaemia.

Preferred Diagnosis
Acute myeloid leukaemia presenting in aleukaemic phase.
APPENDIX A

Case 14. Male. Born 1919. 4 Courses. 2 Centres.

Pre-irradiation History

February 1941  Passed Grade I on enlistment into Armed Services.
October 1943  Admitted to hospital with pain in legs and spine for 2 years.
May 1946  Diagnosis of ankylosing spondylitis.

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean</th>
<th>Integral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>dose (r.)</td>
<td>spinal marrow dose (Mg. r.)</td>
</tr>
<tr>
<td>X-ray treatment to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. 5.46 – 30. 5.46</td>
<td>137</td>
<td>2.8</td>
</tr>
<tr>
<td>30. 7.46 – 14. 8.46</td>
<td>137</td>
<td>2.9</td>
</tr>
<tr>
<td>21.10.46 – 5.11.46</td>
<td>138</td>
<td>2.9</td>
</tr>
<tr>
<td>9. 9.48 – 18.11.48</td>
<td>718</td>
<td>17.8</td>
</tr>
<tr>
<td>Total</td>
<td>1130</td>
<td>26.4</td>
</tr>
</tbody>
</table>

Post-irradiation History

April 1953  Admitted to hospital with left renal colic. Found to have non-functioning left kidney.
June 1953  Re-admitted with diagnosis of uraemia and chronic nephritis.
           Hb. 77%, W.B.C. 5,200, N.P. 74%, Eos. 1%, Basos. 1%, Monos. 3%.
           Lymphos. 21%, Blood urea 159 mg. %.
October 1953  Persisting uraemia and albuminuria. Transfused.
February 1954  Hb. 41%, R.B.C. 1,900,000, W.B.C. 5,700, Blood urea 156 mg. %.
September 1954  Hb. 47%, R.B.C. 2,700,000, W.B.C. 13,600, Blasts 22%, N.P. 10%.
           Monos. 4%, Lymphos. 64%, Blood urea 195 mg. %.
           Sternal marrow: Myelocytes 1%, Metamyelocytes 3%, N.P. 3%, Monos.
           1%, Lymphoblasts 17%, Lymphos. 70%, Normoblasts 5%.
8.10.54  Death.

Certified Causes of Death
(1a) Uraemia.
(1b) Chronic nephritis.
(2) Lymphatic leukaemia.

Post-mortem Findings
Acute leukaemia. Widespread amyloid disease affecting both kidneys, the spleen and the liver. There was extensive venous calcification of both kidneys. No evidence of arterial degeneration. Macroscopically the findings of note were a normal-sized spleen, widespread lymph-gland enlargement, and a small left kidney with nodular calcification in the peripelvic fat.

Preferred Diagnosis
Acute lymphatic leukaemia.

Case 15. Male. Born 1917. 1 Course. 1 Centre.

Pre-irradiation History


<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean</th>
<th>Integral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>dose (r.)</td>
<td>spinal marrow dose (Mg. r.)</td>
</tr>
<tr>
<td>X-ray treatment to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. 7.46 – 1. 8.46</td>
<td>258</td>
<td>5.8</td>
</tr>
</tbody>
</table>

(continued overleaf)
Case 15 (contd.)

**Post-irradiation History**

26.8.46
Admitted with sore throat, drowsiness and anorexia for 1 week. Pharyngeal ulceration, enlarged glands, enlarged liver and spleen.
R.B.C. 1,360,000, W.B.C. 400,000. Acute monocytic leukaemia.

28.8.46
Death.

**Certified Cause of Death**
(1a) Acute monocytic leukaemia.

**Post-mortem Findings**
Acute myeloid leukaemia with widespread involvement of lymph glands, Peyer's patches, thymus, spleen, diaphragm, liver, kidney, heart and suprarenals.

**Preferred Diagnosis**
This case appears as one of co-existence of leukaemia and ankylosing spondylitis. Review of all the evidence supports this diagnosis. Acute myeloid leukaemia.

---

Case 16. Male. Born 1904. 3 Courses. 1 Centre.

**Pre-irradiation History**

July 1946
Referred for X-ray treatment with history of pain in left side of chest for 2 years. Appearances typical of ankylosing spondylitis.

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean dose</th>
<th>Integral dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray treatment to:</td>
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<td>(Mg. r.)</td>
</tr>
<tr>
<td>17. 7.46 - 13. 9.46</td>
<td>793</td>
<td>15.4</td>
</tr>
<tr>
<td>8. 9.49 - 2.12.49</td>
<td>745</td>
<td>12.0</td>
</tr>
<tr>
<td>4.12.51 - 27.12.51</td>
<td>311</td>
<td>4.4</td>
</tr>
<tr>
<td>Total</td>
<td>1849</td>
<td>31.8</td>
</tr>
</tbody>
</table>

**Post-irradiation History**

January 1952
Patient attended as outpatient with history of febrile upset for 2 weeks.
Hb. 58%, W.B.C. 2,800.

*Sternal marrow:* Myeloblasts 11%, Premyelocytes 2.5%, Myelocytes 8%, Metamyelocytes 8%, N.P. 10.5%, Eos. 0.5%, Basos. 0.5%, Monos. 0.5%, Lymphos. 16%, P.C. 1%, Normoblasts 26.5%, Smear cells 23%.

Treated with blood transfusions. Between January and March, 1952, records are available of 11 further counts, including 8 differential white counts, which are summarized as follows:

- Hb. 68-48%
- R.B.C. 3,300,000-2,090,000
- W.B.C. 2,650-1,300
- N.P. 71-15%
- Eos. 7-1%
- Basos. 1%
- Monos. 4-1%
- Lymphos. 80-26%

On 5 occasions a few myeloblasts and myelocytes were seen. No further data available for the period from mid-March until May 1952.

24.5.52
Death.

**Certified Cause of Death**
(1a) Acute leukaemia.

**Preferred Diagnosis**
Acute myeloid leukaemia presenting in aleukaemic phase.
Case 17. Male. Born 1902. 12 Courses. 2 Centres.

**Pre-irradiation History**

November 1946 Referred for X-ray treatment. History of back pain for 10 years. Examination showed typical changes of advanced ankylosing spondylitis.

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mr. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray treatment to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. 14.7 - 11. 24.7</td>
<td>118</td>
<td>2.4</td>
</tr>
<tr>
<td>17. 3.47 - 3. 4.47</td>
<td>158</td>
<td>3.1</td>
</tr>
<tr>
<td>29. 5.47 - 19. 6.47</td>
<td>158</td>
<td>3.1</td>
</tr>
<tr>
<td>18.11.47 - 12.12.47</td>
<td>119</td>
<td>2.5</td>
</tr>
<tr>
<td>11. 6.48 - 24. 6.48</td>
<td>383</td>
<td>3.8</td>
</tr>
<tr>
<td>26.10.48 - 20.12.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sacro-iliac joints and lumbar spine and L. hip joint</td>
<td>461</td>
<td>15.7</td>
</tr>
<tr>
<td>lumbar spine</td>
<td>35</td>
<td>4.7</td>
</tr>
<tr>
<td>cervical spine and L. hip joint</td>
<td>221</td>
<td>1.9</td>
</tr>
<tr>
<td>L. shoulder</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>L. hip joint</td>
<td>220</td>
<td>6.1</td>
</tr>
<tr>
<td>lumbar and dorsal spines</td>
<td>346</td>
<td>5.4</td>
</tr>
<tr>
<td>sacro-iliac joints and lumbar spine</td>
<td>85</td>
<td>1.6</td>
</tr>
<tr>
<td>Total</td>
<td>2303</td>
<td>51.9</td>
</tr>
</tbody>
</table>

**Post-irradiation History**

March 1955 Seen as an outpatient. Obviously anaemic.

Hb. 69 %, R.B.C. 3,270,000, W.B.C. 5,200, Platelets 134,000, Blasts 1%.

N.P. 74 %, Eos. 4 %, Basos. 0.5 %, Lymphos. 19 %, Monos. 1.5 %.

*Sternal marrow:* Myeloblasts 19.4 %, Premyelocytes 9.8 %, Myelocytes 13.6 %, Metamyelocytes 11.4 %, N.P. 21.8 %, Eos. 0.2 %, Basos. 1.0 %.

Monos. 1.4 %, P.C. 0.6 %, Lymphos. 9.2 %, Normoblasts 10.6 %.

Reticiulum cells 0.2 %, Undifferentiated cells 0.2 %, Mitotic red cells 0.2 %, Mitotic white cells 0.2 %, Megakaryocytes 0.2 %, M:E ratio 7:3:1.

May 1955

Hb. 65 %, R.B.C. 2,910,000, W.B.C. 9,500, Platelets 62,000, Blasts 1.0 %.

Myelocytes 0.5 %, N.P. 73 %, Eos. 2.0 %, Basos. 1.3 %, Lymphos. 17.5 %, Promonos. 1.0 %, Monos. 3.5 %.

August 1955

Hb. 24 %, W.B.C. 151,000, Platelets 24,000, Blasts 86 %, N.P. 14 %.

4.8.55 Death.

**Certified Causes of Death**

(1a) Acute phase of myeloid leukaemia.

(2) Ankylosing spondylitis.

**Preferred Diagnosis**

Acute myeloid leukaemia presenting in aleukaemic phase.
RADIATION AND LEUKAEMIA


Pre-irradiation History


<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mg. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26. 2.47 – 24. 3.47</td>
<td>1045</td>
<td>17.9</td>
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<tr>
<td>29. 4.53 – 26. 5.53</td>
<td>757</td>
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</tr>
<tr>
<td>Total</td>
<td>1802</td>
<td>31.2</td>
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</tbody>
</table>

Post-irradiation History

January 1954 Diagnosis of leukaemia made after admission to hospital with sore throat and glands for 3 weeks.

Hb. 58%. R.B.C. 2,700,000, W.B.C. 2,300, N.P. 50%, Monos. 18%, Lymphos. 32%. Occasional blasts seen in film. Anisocytosis.

Marrow: T.N.C. 147,000, Premyelocytes 4%, Metamyelocytes 11%, N.P. 17%, Monoblasts 38%, Monocytes 22%, Lymphos. 4%, Normoblasts 4%, M : E ratio 8 : 1.

24.5.54 Death.

Certified Causes of Death
(1a) Acute monocytic leukaemia.
(2) Pneumonia.

Post-mortem Findings
Acute monocytic leukaemia with multiple haemorrhages and acute pericarditis.

Preferred Diagnosis
Acute monocytic leukaemia presenting in aleukaemic phase.

Case 19. Male. Born 1884. 1 Course. 1 Centre.

Pre-irradiation History

July 1947 Referred for X-ray treatment. Hb. 82%, W.B.C. 8,900, N.P. 76%, Monos. 3%, Lymphos. 21%.

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mg. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14. 7.47 – 8. 8.47</td>
<td>1016</td>
<td>14.6</td>
</tr>
</tbody>
</table>

Post-irradiation History

June 1952 Seen by general practitioner, complaining of weakness and lethargy since about June 1950.

Hb. 64%, R.B.C. 3,100,000, W.B.C. 156,000, Myelocytes 46.5%, Metamyelocytes 8%, N.P. 37%, Eos. 2%, Basos. 3.5%, Lymphos. 3%, Normoblasts 2/100 W.B.C. No other details available.

27.7.52 Death.

Certified Causes of Death
(1a) Cerebral thrombosis.
(1b) Myelocytic leukaemia.
(2) Spinal spondylitis.

Preferred Diagnosis
Chronic myeloid leukaemia.
APPENDIX A

Case 20. Male. Born 1921. 4 Courses. 1 Centre.

Pre-irradiation History

October 1947
Referred for X-ray treatment with history of pain in the back and the R. hip for 5 years.

Irradiation History

<table>
<thead>
<tr>
<th>Date</th>
<th>Region</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mg. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.10.47 - 15.11.47</td>
<td>lumbar spine</td>
<td>..</td>
<td>31</td>
</tr>
<tr>
<td>15.12.47 - 2.1.48</td>
<td>lumbar spine</td>
<td>..</td>
<td>309</td>
</tr>
<tr>
<td>31.3.53 - 9.4.53</td>
<td>sacro-iliac joints and lumbar spine</td>
<td>..</td>
<td>316</td>
</tr>
<tr>
<td>15.2.54 - 8.3.54</td>
<td>R. ischial region</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>656</td>
</tr>
</tbody>
</table>

Post-irradiation History

August 1954
Last seen in radiotherapy department complaining of some pain in left lower chest.

November 1954
Admitted to hospital with history of severe back pain for 2 weeks, and epistaxes and purpuric rash for several days. Some enlarged glands in both axillae. Abdomen distended and difficult to palpate, but liver and spleen probably not palpable.
Hb. 73%, W.B.C. 13,000. Film showed many blast cells. Bleeding time >12 min. Clotting time 6-7 min.

15.11.54
Death.

Certified Causes of Death
Acute monocytic leukaemia.
Ankylosing spondylitis.

Post-mortem Findings
Leukaemic infiltration of lungs, liver, spleen, kidneys, heart, and spinal dura. Massive peribronchial infiltration in right hilar and sub-carinal regions. Shown on histological examination to be a monocytic leukaemia.

Preferred Diagnosis
Acute monocytic leukaemia.

Case 21. Male. Born 1900. 5 Courses. 1 Centre.

Pre-irradiation History

August 1947
Admitted to hospital with history of melena and haematemesis for about 4 years.
Hb. 41%, R.B.C. 2,400,000, W.B.C. 6,000, N.P. 61%, Eos. 12%, Monos. 4%. Lymphos. 34%. While in hospital was found to be suffering from ankylosing spondylitis.

Irradiation History

<table>
<thead>
<tr>
<th>Date</th>
<th>Region</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mg. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.11.47 - 28.11.47</td>
<td>sacro-iliac joints and whole spine</td>
<td>..</td>
<td>305</td>
</tr>
<tr>
<td>15.12.47 - 6.1.48</td>
<td>sacro-iliac joints and whole spine</td>
<td>..</td>
<td>305</td>
</tr>
<tr>
<td>6.10.48 - 27.10.48</td>
<td>sacro-iliac joints and lumbar spine</td>
<td>..</td>
<td>107</td>
</tr>
<tr>
<td>14.12.49 - 10.1.50</td>
<td>lumbar spine</td>
<td>..</td>
<td>26</td>
</tr>
<tr>
<td>5.4.50 - 26.4.50</td>
<td>sacro-iliac joints and whole spine</td>
<td>..</td>
<td>224</td>
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<tr>
<td>Total</td>
<td></td>
<td></td>
<td>967</td>
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</tbody>
</table>

(continued overleaf)
66 RADIATION AND LEUKAEMIA

Case 21 (contd.)

Post-irradiation History
(The record of this case is incomplete as the hospital notes have been lost.)

September 1951
Admitted to hospital with dyspnoea of 4 days' duration. Signs of pneumonia were present.

October 1951
Hb. 39%, R.B.C. 2,080,000, W.B.C. 1,500, N.P. 42%, Mono. 15%. Lymphos. 57%. 'Several of the lymphocytes look very young. I think this is a blood dyscrasia, possibly leukaemia. . . .'

14.10.51 Death.

Certified Causes of Death
(1a) Myelogenous leukaemia.
(2) Broncho-pneumonia.

Preferred Diagnosis
Acute leukaemia (? cell type) presenting in aleukaemic phase.

Case 22. Male. Born 1922. 4 Courses. 1 Centre.

Pre-irradiation History
None available.

Irradiation History

<table>
<thead>
<tr>
<th>X-ray treatment to:</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mr. r.)</th>
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</thead>
<tbody>
<tr>
<td>26. 1.48 - 1. 3.48</td>
<td>122</td>
<td>2.8</td>
</tr>
<tr>
<td>10. 5.48 - 27. 5.48</td>
<td>284</td>
<td>4.4</td>
</tr>
<tr>
<td>13. 9.48 - 1.10.48</td>
<td>630</td>
<td>11.1</td>
</tr>
<tr>
<td>1. 9.53 - 18. 9.53</td>
<td>1099</td>
<td>17.7</td>
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<tr>
<td>Total</td>
<td>2195</td>
<td>36.0</td>
</tr>
</tbody>
</table>

Post-irradiation History

September 1954
Admitted to hospital with history of increasing fatigue since June 1954. Purpuric rash on shoulders, and bleeding gums. Liver edge palpable 3-4 cm. below costal margin, and tip of spleen palpable. No significant glandular enlargement.

Hb. 70%, R.B.C. 3,850,000, W.B.C. 240,000. 'All leucocytes are of lymphoid series, and approximately 70% are very immature lymphoblasts.'

19.9.54 Death.

Certified Causes of Death
(1a) Cerebral haemorrhage.
(1b) Acute leukaemia—lymphoblastic.

Preferred Diagnosis
Acute lymphatic leukaemia.

Case 23. Male. Born 1915. 2 Courses. 1 Centre.

Pre-irradiation History

March 1948
Referred for X-ray treatment.

Irradiation History

<table>
<thead>
<tr>
<th>X-ray treatment to:</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mr. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. 3.48 - 16. 4.48</td>
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<td>38.4</td>
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<tr>
<td>lumbar spine</td>
<td>47</td>
<td>5.6</td>
</tr>
<tr>
<td>Total</td>
<td>1654</td>
<td>44.0</td>
</tr>
</tbody>
</table>
APPENDIX A

Case 23 (contd.)

Post-irradiation History

August 1951
Admitted to hospital suffering from pneumonia.

June 1952
Re-admitted complaining of anorexia and fatigue of 2 weeks' duration.
No enlarged glands were present but the liver was palpable.
Hb. 39 %, R.B.C. 1,880,000, W.B.C. 3,400, Blasts 61 %, N.P. 8 %,
Lymphs. 31 %. Numerous normoblasts present.

5.7.52
Death.

Certified Cause of Death
Acute leukaemia.

Preferred Diagnosis
Acute leukaemia (? cell type) presenting in aleukaemic phase.

Case 24. Male. Born 1894. 1 Course. 1 Centre.

Pre-irradiation History
June 1948
Referred for X-ray treatment. The radiological findings were not typical
of ankylosing spondylitis, but it was agreed that the case should be
treated as such.
Hb. 92 %, W.B.C. 8,000, N.P. 63 %, Monos. 7 %, Lymphs. 30 %.

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean</th>
<th>Integral</th>
</tr>
</thead>
<tbody>
<tr>
<td>spinal marrow</td>
<td>dose (r)</td>
<td>(Mr. r)</td>
</tr>
<tr>
<td>X-ray treatment to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sacro-iliac joints and whole spine</td>
<td>1016</td>
<td>16-5</td>
</tr>
</tbody>
</table>

Post-irradiation History
February 1953
Referred to hospital with cough, dyspnoea and ankle-swelling, and
repeated attacks of iridocyclitis. Mitral systolic murmur, auricular
fibrillation and ventricular extra-systoles. Liver enlarged. X-ray
examination showed pericardial calcification.
Hb. 51 %, R.B.C. 2,500,000, Retics. 1 %.

April 1953
Admitted to hospital. Findings as before.
8.4.53
Hb. 76 %, R.B.C. 2,900,000, W.B.C. 3,900, N.P. 52 %, Eos. 3 %, Monos.
7 %, Lymphs. 23 %, Retics. 2-8 %.

Sternal marrow: 'The marrow is hyperplastic due to an increase in the
number of the precursors of the red and white cell series. The hyper-
plasia however is affecting erythropoiesis more than granulopoiesis.
Most of the red cells are developing normally but some show early
megaloablastic change, and definite megaloblasts are seen.
Conclusion: 'The marrow is characteristic of a megaloblastic anaemia
after sub-optimal treatment.'

24.4.53
Hb. 59 %, R.B.C. 2,200,000, W.B.C. 3,200, N.P. 52 %, Eos. 11 %, Monos.
7 %, Lymphs. 23 %, Retics. 2-8 %.

25.4.53
Sternal marrow: See report below.

4.5.53
Hb. 66 %, R.B.C. 2,500,000, W.B.C. 4,000, Myelocytes and Metamyelo-
cytes 5 %, N.P. 44 %, Eos. 10 %, Monos. 8 %, Lymphs. 33 %, Retics.
1-1 %.

8.5.53
Iliac crest marrow (combined report on 25.4.53 and 8.5.53): Differential
counts were—Myeloblasts 6-0, 7-5 %, Promyelocytes 2-0, 2-5 %,
Myelocytes 14-5, 11-0 %, Metamyelocytes 11-0, 7-0 %, N.P. 6-5, 3-0 %,
Eos. 1-5, 1-0 %, Pronormoblasts 1-5, 4-0 %, Normoblasts 37-5, 46-0 %,
Lymphs. 5-5, 3-5 %, P.C. 0-5, 0-5 %, Reticulum cells, 4-0, 2-5 %,
Haemocytoblasts 7-0, 7-0 %, Megaloblasts 0-5, 1-5 %. Smudge cells
1-0, 1-5 %. Mitotic figures 0, 1-5 %. 'There is an increase in the propor-
tion of primitive cells (reticulum cells, haemocytoblasts, and myelo-
blasts) and in the proportion of developing red cells. These latter are
68 RADIATION AND LEUKAEMIA

Case 24 (contd.)

still present after treatment with folie acid. The proportion of polymorphs in the marrow is low, suggesting some degree of maturation arrest. Megakaryocytes are numerous.

Conclusion: 'This patient is not suffering from a megaloblastic anaemia. The megaloblast-like changes in the developing cells are too slight compared with the total disturbance of haemopoiesis and these cells were still present after treatment with folie acid. The increased percentage of primitive cells, particularly myeloblasts, in the marrow, associated with a small percentage of these cells in the peripheral blood suggest that this man may be suffering from an atypical form of leukaemia, rather than from a refractory hyperplastic anaemia.'

13.5.53
Hb. 53% R.B.C. 2,000,000, W.B.C. 3,200, Myeloblasts 4%, Myelocytes 7%, Metamyelocytes 2%, N.P. 51%, Eos. 5%, Monos. 13%, Lymphos. 14%, Retics. 5.7%.

22.5.53
Hb. 65%, R.B.C. 2,800,000, W.B.C. 3,300, Myeloblasts 1%, Myelocytes 1%, Metamyelocytes 13%, N.P. 41%, Eos. 2%, Basos. 2%, Monos. 5%, Lymphos. 35%, Retics. 1.8%.

27.5.53
Discharged home. No further details available.

4.1.55
Death.

Certified Causes of Death
(1a) Terminal broncho-pneumonia.
(1b) Pick's disease.
(2) Aleukaemic leukaemia.

Preferred Diagnosis
Acute myeloid leukaemia presenting in leukaemic phase.

Case 25. Male. Born 1921. 1 Course. 1 Centre.

Pre-irradiation History

June 1948

Irradiation History

<table>
<thead>
<tr>
<th>X-ray treatment to:</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mg. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacro-iliac joints and whole spine</td>
<td>609</td>
<td>9.3</td>
</tr>
</tbody>
</table>

Post-irradiation History

May 1952
Referred to hospital, complaining of weakness, lassitude and dyspnoea for 2 years. Both liver and spleen were palpable.

Hb. 40%, R.B.C. 1,720,000, W.B.C. 1,400, N.P. 24%, Lymphos. 36%, Monos. 40%.

June 1952
Hb. 52%, R.B.C. 930,000, W.B.C. 3,400, N.P. 21%, Blasts 11%, Mono-blasts 16%, Monos. 10%, Smear cells 2%.

Marrow: 'The marrow was moderately cellular. Very few nucleated red cells could be seen. The predominant cells were monomucleated cells and eosinophil polymorphs. Reticulum cells were also present in moderate numbers. This picture is compatible with the diagnosis of monoblastic leukaemia.'

11.9.52
Death.

Certified Causes of Death
(1a) Acute lymphatic leukaemia.
(2) Spondylitis.

Preferred Diagnosis
Acute monocytic leukaemia presenting in leukaemic phase.
**APPENDIX A**

Case 26. Male. Born 1898. 4 Courses. 2 Centres.

*Pre-irradiation History*

March 1947

Referred for X-ray treatment. History of back pain for 25 years.

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mg. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26. 7.48 – 10. 8.48</td>
<td>lumbar and dorsal spines . .</td>
<td>397</td>
</tr>
<tr>
<td>21.11.50 – 11.12.50</td>
<td>sacro-iliac joints and whole spine . .</td>
<td>909</td>
</tr>
<tr>
<td>15. 2.51 – 29. 3.51</td>
<td>both hips and shoulders . .</td>
<td>989</td>
</tr>
<tr>
<td>16. 8.51 – 24. 9.51</td>
<td>L. shoulder . . . .</td>
<td>3-7</td>
</tr>
<tr>
<td>Total . . . .</td>
<td>2295</td>
<td>53-1</td>
</tr>
</tbody>
</table>

*Post-irradiation History*

August 1954

Referred to hospital with history of weakness and anorexia for some months. Skin petechiae. Liver and spleen not palpable. No glands palpable.

Hb. 45%, R.B.C. 1,700,000, W.B.C. 2,000, Platelets 110,000.

September 1954

Diagnosis of leukaemia.

Hb. 40%, R.B.C. 1,300,000, W.B.C. 2,000, Platelets 50,000. Bleeding time >10 min. Clotting time 6 min.

*Sternal marrow:* Myeloblasts 37%, Premyelocytes 8%, Myelocytes 6%, N.P. 2%, Lymphos 1%, P.C. 4%, Pronormoblasts 1%, Normoblasts 41%.

2.10.54

Death.

*Certified Cause of Death*

(1a) Acute myeloid leukaemia.

*Preferred Diagnosis*

Acute myeloid leukaemia presenting in aleukaemic phase.

Case 27. Male. Born 1912. 2 Courses. 2 Centres.

*Pre-irradiation History*

September 1949

Referred for X-ray treatment. History of back pain for 9 years.

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mg. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22. 9.49 – 20.10.49</td>
<td>sacro-iliac joints and whole spine . .</td>
<td>388</td>
</tr>
<tr>
<td>20.10.50 – 21.11.50</td>
<td>sacro-iliac joints and whole spine . .</td>
<td>515</td>
</tr>
<tr>
<td>Total . . . .</td>
<td>903</td>
<td>18-8</td>
</tr>
</tbody>
</table>

*Post-irradiation History*

September 1955

Admitted to hospital with a history of malaise for about 1 year, these symptoms becoming severe for 4 months, with dyspnoea on exertion, loss of weight and intermittent claudication. No glandular enlargement. Liver and spleen not palpable.

Hb. 26%, R.B.C. 3,800,000, W.B.C. 1,500, Platelets 24,000, Blasts 2%, Premyelocytes 3%, Myelocytes 1%, Metamyelocytes 7%, N.P. 23%, Monos. 3%, Lymphos. 61%. Sternal puncture failed on two occasions.

November 1955

*Marrow* (obtained by bone biopsy): "There is replacement of the fatty marrow by cellular tissue which is also reducing the haemopoietic tissue. The red and white series present appear normal. The cellular tissue is composed of reticulin cells and megakaryocytes, both of
which are of bizarre shapes with numerous mitoses. They appear malignant. The silver stain shows an increased reticulin. The condition appears to be a malignant myelosclerosis."

From September 1955 to December 1955, 13 further blood counts were performed, including 6 differential counts; the findings were as follows:

- Hb: 82-26% (13 observations)
- W.B.C.: 6,000-500 (11)
- Platelets: 64,000-1,800 (5)
- Blasts: 38-4% (6)
- Premyelocytes: 3-1% (6)
- Myelocytes: 6-1% (5)
- Metamyelocytes: 5-1% (5)
- N.P.: 20-14% (6)
- Eos.: 3-1% (4)
- Basos.: 1% (1)
- Monos.: 4-1% (5)
- Lymphs: 66-26% (6)

The patient was given several blood transfusions. At no time were the liver and spleen palpable.

11.12.55

Certified Causes of Death

(1a) Bleeding duodenal ulcer.
(1b) Myelosclerosis (malignant).
(2) Spondylitis.

Post-mortem Findings (macroscopic)

Liver (2,029 g.): Showed a normal lobular pattern. A small nodule, 1 cm. in diameter, in the R. lobe.

Spleen (544 g.): No thickening of the capsule. Normal architecture replaced by dark or light-coloured firm and soft nodes, which appear to be an exaggeration of splenic tissue rather than discrete infiltration.

Lymph nodes: Slightly enlarged in all areas.

Marrow: In sternum was red and soft although bony trabeculae appeared increased. The vertebral marrow was reddish-grey throughout, with probable increase in trabeculae. Femoral marrow extended the whole length of the shaft.

The post-mortem material was submitted to two independent authorities.

Their opinions were as follows:

Opinion A

Bone marrow: Megakaryocytic myelosis; greatly increased cellularity, large excess of normal and abnormal megakaryocytes, abundant myeloid and erythropoietic cells, some increase in reticulum cells.

Spleen: Numerous blood cells of all types, especially blast cells. Abundant megakaryocytes. Some increase in connective tissue and decrease of cellularity in the vicinity of trabeculae.

Liver: Abundant megakaryocytes and immature blood cells in sinuses. One section includes a nodule of 'leukaemic' infiltration. Haemosiderosis in Kupffer cells.

Stomach: Megakaryocytes and megakaryocytes present in mucosa.

Lymph nodes: Abundant myelocytes in pulp, abundant megakaryocytes in wide sinuses.

The pathological findings are those of myeloid leukaemia with megakaryocytic leukaemia.
APPENDIX A

Case 27 (contd.)

Opinion B

Marrow: Mainly hypercellular, with disappearance of fat cells. Numerous blast cells and many hypochromatic giant cells, with multiple nuclei or lobed nuclei; these may be atypical megakaryocytes. There is a great increase in reticulin throughout.

Interpretation: Acute (malignant) myelosclerosis.

Preferred Diagnosis
Acute myeloid leukaemia (atypical) presenting in aleukaemic phase.

Case 29. Male. \& Born 1885. 1 Course. 1 Centre.

Pre-irradiation History

July 1950
Referred for X-ray treatment. History of back pain for 30 years. Typical findings of ankylosing spondylitis.

Irradiation History

<table>
<thead>
<tr>
<th>Irradiation</th>
<th>Mean</th>
<th>Integral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal marrow</td>
<td>727</td>
<td>24:4</td>
</tr>
<tr>
<td>X-ray treatment to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>whole pelvis and whole spine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

11. 8.50 - 17.10.50
Hb, 74%, W.B.C. 5,500, N.P. 74%, Eos, 2%, Basos, 1%, Monos, 1%
Lymphos. 22%.

Post-irradiation History

September 1954
Admitted to hospital with some months' history of progressive fatigue and pallor. No glandular enlargement. Liver and spleen not palpable.

13.9.54
Hb. 59%, R.B.C. 2,520,000, W.B.C. 2,000, Retics. 0.8%, Platelets 43,000.

15.9.54
Sternal marrow: 'A hyperplastic marrow with active erythropoiesis of megaloblastoid type, and marked depression of leucopoiesis with some maturation arrest'.
T.N.C. 368,000, Myeloblasts 1%, Premyelocytes 3-0%, Myelocytes 6.8%, Metamyelocytes 6.0%, N.P. 3.4%, Monos, 0.6%, P.C. 2.0%, Lymphos. 4.0%, Haemoblasts 1.0%, Pre-erythroblasts 7.0%, Normoblasts 65.4%, M : E ratio 0.3 : 1.

29.9.54
Hb. 61%, R.B.C. 2,810,000, W.B.C. 2,000, Platelets 77,000, Myeloblasts 4%, N.P. 23%, Eos. 8%, Monos. 8%, Lymphos. 42%, Normoblasts 10%, Retics. 2%.

November 1954
A diagnosis of sub-acute erythraemic myelosis was made on the following grounds: (1) peripheral pancytopenia with a hyperplastic, predominantly erythropoietic marrow in which atypical megaloblastoid erythroblasts are to be found, (2) the presence in the marrow of an excess of myeloblasts, (3) the presence in the blood of myeloblasts, about 5%, and only very small numbers of myelocytes.

29.1.55
Death.

Certified Causes of Death
(1a) Failure of the muscles of the heart.
(1b) Severe anaemia.
(1c) Erythraemic myelosis due to deep X-ray therapy.

Preferred Diagnosis
Acute myeloid leukaemia presenting in aleukaemic phase.
RADIATION AND LEUKAEMIA

Case 30. Male. Born 1897. 1 Course. 1 Centre.

Pre-irradiation History

October 1950
Referred for X-ray treatment after physiotherapeutic treatment for 2 years for ankylosing spondylitis.
Hb. 78%.

Irradiation History
X-ray treatment to:

\[
\begin{array}{ccc}
\text{Mean} & \text{spinal marrow} & \text{Integral} \\
\text{dose (r.)} & \text{dose (r.)} & (\text{Mg. r.}) \\
3.10.50 - 29.11.50 & \text{sacro-iliac joints and whole spine} & . & 644 & 12.0 \\
\end{array}
\]

Post-irradiation History

March 1951
Hb. 94%, W.B.C. normal.

June 1954
Admitted to hospital because of continuous bleeding following dental extraction, and development of drowsiness and somnolence.
Hb. 61%, R.B.C. 3,500,000, W.B.C. 155,000, Platelets 500,000. 'Films show a picture of a chronic myeloid leukaemia. I would suspect there is a more acute state arising from the proportion of myeloblasts, but it is difficult to be sure without serial observations.'

Death.

Certified Causes of Death
(1a) Inhalation pneumonia.
(1b) Cerebral haemorrhage.
(1c) Chronic myelogenous leukaemia.

Post-mortem Findings
Liver and spleen were enlarged, the spleen grossly so, and both showed leukaemic infiltration, as also the kidneys. The immediate cause of death was a left-sided cerebral haemorrhage.

Preferred Diagnosis
Myeloid leukaemia (? type)—probably chronic.

Case 31. Male. Born 1924. 3 Courses. 1 Centre.

Pre-irradiation History

June 1950
Referred to hospital with history of back pain for unknown length of time.
Hb. 96%, R.B.C. 5,000,000, W.B.C. 6,400, N.P. 76%, Monos. 1%, Lymphos. 23%.

November 1950
Referred for X-ray treatment.

Irradiation History
X-ray treatment to:

\[
\begin{array}{ccc}
\text{Mean} & \text{spinal marrow} & \text{Integral} \\
\text{dose (r.)} & \text{dose (r.)} & (\text{Mg. r.}) \\
27.12.50 - 17. 1.51 & \text{sacro-iliac joints and whole spine} & . & 315 & 5.7 \\
5. 4.41 - 10. 5.51 & \text{sacro-iliac joints and whole spine} & . & 308 & 6.2 \\
10.10.51 - 30.10.51 & \text{sacro-iliac joints and whole spine} & . & 308 & 6.3 \\
\text{Total} & . & 931 & 18.2 \\
\end{array}
\]

Post-irradiation History

March 1952
Admitted to hospital with history of abdominal pain, vomiting and bruising for 10 days. Petechiae were present on the limbs and trunk. Generalized glandular enlargement. The liver was palpable 2 cm. below the costal margin and the tip of the spleen was also palpable.
Hb. 46%, R.B.C. 1,960,000, W.B.C. 220,000, Myeloblasts 52%, Premyelocytes 33%, Myelocytes 4%, N.P. 5%, Lymphos. 6%.
APPENDIX A

Case 31 (contd.)
17.3.52

Death.

Certified Cause of Death
1a) Sub-acute myeloid leukaemia.

Preferred Diagnosis
Acute myeloid leukaemia.

Case 32. Male. Born 1882. 1 Course. 1 Centre.

Pre-irradiation History

April 1951
Referred for X-ray treatment. No clinical details available.

Irradiation History

<table>
<thead>
<tr>
<th>X-ray treatment to:</th>
<th>Mean</th>
<th>Integral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacro-iliac joints and whole spine</td>
<td>. .</td>
<td>840</td>
</tr>
</tbody>
</table>

Post-irradiation History

At some time after irradiation, possibly about 6 months before his terminal illness, the patient was said to have been treated with butazolidine, dosage not known.

June 1953
Admitted to hospital complaining of breathlessness and anorexia, length of history not stated. The patient was severely anaemic and had retinal haemorrhages. Liver and spleen apparently not palpable.
Hb. 26% R.B.C. 1,400,000, W.B.C. 4,000, Bands 4%, N.P. 74%, Basos. 1%, Monos. 6%, Lymphos. 15%. No abnormal white cells seen.

Sternal marrow: Myeloblasts 0-4%, Premyelocytes 0-2%, Myelocytes 5%.
Bands 14-2%, N.P. 17-4%, Lymphoblasts 0-2%, Lymphos. 11-2%.
Monoblasts 0-2%, Monos. 1-6%, Erythroblasts 18-4%, Erythropoiesis 7%.
Normoblasts 22-4%, Cells in mitosis 1-6%.

July 1953
Hb. 32%, W.B.C. 2,000, Bands 8%, N.P. 64%, Eos. 2%, Monos. 5%.
Lymphos. 21%. 'Red cells show marked anisocytosis. Normal in shape and colour, apart from a moderate number of polychromatic cells. A few normoblasts and more primitive cells of the erythroid series seen.'

August 1953
Hb. 28%, W.B.C. 5,000, Bands 7%, N.P. 57%, Eos. 2%, Monos. 4%.
Lymphos. 30%.

8.9.53
Death.

Certified Cause of Death
1a) Aplastic anaemia.

Post-mortem Findings

The findings of note refer to the liver and spleen. The liver weighed 1,840 g. and was described—'cut surface pale creamy colour—? leukaemic'. The spleen weighed 1,100 g. and was described—'cut surface soft, pale creamy-pink in colour with a few scattered hyperplastic nodules'. Histologically the spleen was 'disorganized by a massive infiltration with what appear to be primitive blood cells, reticulum cells and megakaryocytes'. Irregularly scattered collections of similar cells were seen in the liver. No bone marrow was examined.
The post-mortem material was submitted to two independent authorities. Their opinions were as follows:

Opinion A

Spleen: The red pulp is grossly abnormal in structure, some parts showing an excess of reticulin fibres and erythrocytes, with relatively few
nucleated cells. Other parts are infiltrated by abnormal hyperchromatic reticulum cells. All stages between these cells and typical megakaryocytes can be found. Erythroblasts are abundant, but it is difficult to estimate the number of myeloid cells. A few small Malpighian bodies are still present.

Liver: The sinuses contain numerous nucleated cells similar to those found in the spleen.

Kidney and myocardium: No notable abnormalities.

Conclusions: The diagnosis would appear to lie between Hodgkin's sarcoma (polymorphic reticulosarcoma) and a megakaryocytic myelosis variant of leukaemia. The abundance of erythroblasts and scarcity of mitoses is against the first-named, whilst the apparent scarcity of myeloid cells is against the second.

The histological findings can hardly be regarded as consistent with a diagnosis of aplastic anaemia.

Opinion B

The spleen and liver are infiltrated by a leukaemic process. The cells appear to be of a primitive type and are predominantly myeloblasts with a lesser number of myelocytes. Metamyelocytes and polymorphs are rare. Some of the primitive cells are multi-nucleated. In the liver there is central lobular necrosis and congestion. The reticulin pattern of the liver is intact and there is no reticulin formation by the leukaemic process. Among the leukaemic cells there are monster, mononuclear, bizarre, primitive cells.

The picture is not typical of leukaemia in so far as the spleen cytology is remarkably pleomorphic and includes clumps of erythropoietic-like tissue. In the liver there is unexpectedly little leukaemic infiltration of the portal tracts. The diagnosis, therefore, lies between leukaemia and a myelosclerosis of a rather malignant type. We think that this case could be classed as an atypical myeloblastic leukaemia.

Preferred Diagnosis

Acute myeloid leukaemia (atypical) presenting in aleukaemic phase.

Case 33. Male. Born 1935. 1 Course. 1 Centre.

Pre-irradiation History

January 1952

Referred to hospital with history of pain in the left greater trochanteric region in November 1951, succeeded by further attacks of pain in the lower back, the neck, and in the chest on deep breathing. Extension and flexion of the spine and manipulation of the pelvis were painful. X-ray examination showed deep destruction of both sacro-iliac joints, not like the involvement characteristic of ankylosing spondylitis. There was also a gross periostitis of the left femur.

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Integral</th>
<th>Mean Integral</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray treatment to:</td>
<td>dose r.</td>
<td>(Mg. r.)</td>
</tr>
<tr>
<td>14. 2.52 – 4. 3.52</td>
<td>144</td>
<td>3.3</td>
</tr>
</tbody>
</table>

sacro-iliac joints and lumbar spine

Post-irradiation History

March 1952

Patient admitted to hospital because of deterioration in his health. There was some glandular enlargement in both axillae, and the spleen was possibly just palpable. X-ray examination showed marked osteoporosis and wedging of the lower dorsal vertebrae.

Hb: 60%, R.B.C. 3,000,000, W.B.C. 3,000, Platelets 130,000, Myeloblasts 38%, Metamyelocytes 4%, N.P. 10%, Lymphos. 48%, 1 Normoblast/100 W.B.C. Anisocytosis and poikilocytosis.

Marrow: Hypercellular. Myeloblasts 97%, N.P. 1%, Lymphos. 1%. Reticulum cells 4%.
APPENDIX A

Case 33 (contd.)
27.5.52

Death.

Certified Cause of Death
(1a) Acute paramyeloblastic leukaemia.

Preferred Diagnosis
Review of the evidence in this case leaves little doubt that the patient suffered only from acute leukaemia with bone involvement producing a clinical picture mimicking that of ankylosing spondylitis. Acute myeloid leukaemia presenting in aleukaemic phase.

Case 34. Male. Born 1907. 1 Course. 1 Centre.

Pre-irradiation History
August 1952 Admitted to hospital with history of back pain for 5 years, and recent history of joint pains in ankles and knees for 4 months. Hb. 87%, R.B.C. 4,200,000, W.B.C. 30,000, N.P. 25%, Eos. 1 1/4%, Early monos. 14%, Mature monos. 46%, Lymphos. 14%.
Sternal marrow: showed evidence of a monocytic leukaemia.

October 1952 Referred for X-ray therapy and shown radiographically to have ankylosing spondylitis.

Irradiation History
Mean Integral
spinal marrow dose (r.) (Mg. r.)

X-ray treatment to:
sacro-iliac joints, whole spine and shoulders 390 8.5

28.10.52 – 24.11.52

Post-irradiation History
16.12.52

Death.

Certified Causes of Death
(1a) Broncho-pneumonia.
(1b) Monocytic leukaemia.
(2) Anaemia.

Preferred Diagnosis
This is one of the 2 cases in the study series in which there is unequivocal evidence for the co-existence of ankylosing spondylitis and leukaemia. The patient was included in the survey, as the form of X-ray treatment given was that for the treatment of ankylosing spondylitis. Acute monocytic leukaemia.

Case 35. Male. Born 1927. 1 Course. 1 Centre.

Pre-irradiation History
November 1952 Referred to hospital with history of pain in the L. leg for 6 years. A diagnosis of mild thyrotoxicosis was made.
January 1953 Diagnosis of ankylosing spondylitis.

Irradiation History
Mean Integral
spinal marrow dose (r.) (Mg. r.)

X-ray treatment to:
sacro-iliac joints and whole spine 1053 18.1

19. 1.53 – 16. 2.53

Post-irradiation History
December 1953 Re-admitted complaining of tiredness and loss of weight for 2 months. Hb. 90%, W.B.C. 5,400, N.P. 71%, Eos. 2%, Monos. 6%, Lymphos. 21%. Examination showed evidence of thyrotoxicosis. B.M.R. 45+.

28.12.53 Sub-total thyroidectomy.

(continued overleaf)
Case 35 (contd.)
June 1955

Referred to hospital with severe haematuria.
Hb. 42%, W.B.C. 700, Platelets 13,000, Unclassified 12%, N.P. 28%,
Monos. 2%, Lymphos. 58%, Retics. 1-75%, 4 Normoblasts/100 W.B.C.
Bleeding time 9 min., clotting time 7 min.
Treated with cortisone and blood transfusions.
13.6.55
Hb. 62%, W.B.C. 3,000, Platelets 5,000, Blasts 39%, Premyelocytes
7%, N.P. 3%, Monos. 13%, Lymphos. 38%.
18.6.55
Death.

Certified Causes of Death
(1a) Cerebral thrombosis.
(1b) Acute leukaemia.

Post-mortem Findings
It was only possible to obtain an aspirated sample of marrow. The
sections showed infiltration of all marrow spaces by primitive cells
with appearances suggestive of the monocytic series.

Preferred Diagnosis
Acute monocytic leukaemia presenting in aleukaemic phase.

Case 37. Male. Born 1899. 4 Courses. 2 Centres.

Pre-irradiation History
None available.

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mg. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23. 1.42 - 26. 3.42</td>
<td>928</td>
<td>23.0</td>
</tr>
<tr>
<td>1. 6.42 - 23. 6.42</td>
<td>798</td>
<td>23.3</td>
</tr>
<tr>
<td>8. 8.50 - 18.10.50</td>
<td>602</td>
<td>12.9</td>
</tr>
<tr>
<td>11. 8.52 - 20. 8.52</td>
<td></td>
<td>1.7</td>
</tr>
<tr>
<td>Total</td>
<td>2328</td>
<td>60.9</td>
</tr>
</tbody>
</table>

Post-irradiation History
January 1953
Admitted to hospital with history of recurrent pyrexia since about
November 1952. No cause found.
Hb. 78%, R.B.C. 5,130,000, W.B.C. 5,800, N.P. 70%, Monos. 11%,
Lymphos. 26%.
March 1953
Hb. 72%, R.B.C. 4,020,000, W.B.C. 4,000, N.P. 70%, Monos. 7%,
Lymphos. 23%.
April 1953
Re-admitted after further pyrexia.
Hb. 54%, R.B.C. 3,000,000, W.B.C. 3,800, Platelets 80,000, Bands 23%,
N.P. 3%, Lymphos. 73%, Retics. 0-6%. Bleeding time 5 min. Clotting
time 4 min.

Sternal marrow: 'This marrow contains numerous large cells with many
nucleoli and dark blue granular cytoplasm. Many are multi-nucleate
and they lie singly and in small groups. Peroxidase and Unna
Pappenheim stains are negative. These cells are not apparently
haemopoietic cells, and the picture is very suggestive of secondary
carcinoma.'

May 1953
A supplementary report on the marrow put forward the following
possibilities: 'A hypoplastic marrow following radiotherapy, secondary
 tumour, and an atypical myeloma.' All three were considered
possibilities, with the first suggestion perhaps the most likely.

18.5.53
Death.

Certified Cause of Death
(1a) Aplastic anaemia.
APPENDIX A

Case 37 (contd.)

Post-mortem Findings

No evidence of a primary or secondary tumour was found. The red marrow extended the whole length of the femoral shaft. No histological reports available.

Sections of post-mortem marrow were submitted to two independent authorities. Their opinions were as follows:

Opinion A

Malignant deposit in marrow. No evidence of leukaemia or aplastic anaemia.

Opinion B

Four sections show an extremely cellular bone-marrow, mostly replaced by primitive haemopoietic cells suggestive of an acute leukaemia. Two sections show a fibrotic marrow and very dense bone resembling that seen in Paget’s disease of bone.

Preferred Diagnosis

In view of the post-mortem findings and the second opinion on review of pathological material, regarded as probable case of acute apleukaemic leukaemia (? cell type), and classified in 'B' series.

Case 38. Male. Born 1895. 2 Courses. 1 Centre.

Pre-irradiation History

None available.

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mr. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. 948 – 5.11.48</td>
<td>777</td>
<td>12.9</td>
</tr>
<tr>
<td>28. 2.50 – 2. 5.50</td>
<td>124</td>
<td>5.4</td>
</tr>
<tr>
<td>Total</td>
<td>901</td>
<td>18.3</td>
</tr>
</tbody>
</table>

Post-irradiation History

Admitted to hospital with history of pain and swelling in R. leg for 2 weeks. Liver just palpable. Spleen not palpable. Glands not enlarged. Hb. 40%; R.B.C. 2,120,000, W.B.C. 4,600, N.P. 52%, Lymphos. 43%, Monos. 5%.

2.8.52

Hb. 44%; W.B.C. 5,000, N.P. 59%; Monos. 5%; Lymphos. 36%. Film: ‘White cells show a shift to the left.’

30.8.52

W.B.C. 10,900, Blasts 5%, Myelocytes 5%, Metamyelocytes 38%, N.P. 3%; Immature monos. 5%, Monos. 26%, Lymphos. 9%; Smear cells 2%, Normoblasts 5%.

30.8.52

Death.

Certified Causes of Death

(1a) Broncho-pneumonia.

(1b) Aplastic anaemia.

(2) R. femoral thrombosis.

Post-mortem Findings

Nothing of note in report. Marrow not commented upon and none taken for histological examination.

The post-mortem material was submitted to two independent authorities. Their opinions were as follows:

Opinion A

Lymph nodes: Pulp contains many myelocytes and a few megakaryocytes and plasma cells.

Spleen: Excess of plasma cells and probably myelocytes (difficult to identify, as tissue is not well preserved). Haemosiderosis.

(continued overleaf)
RADIATION AND LEUKAEMIA

Case 38 (contd.)

Liver: Small collections of haemopoietic cells in sinusoids, most of which are normoblasts. Few megakaryocytes.

Kidney: Some cellular infiltration of cortex, having same distribution as leukaemic infiltration.

Comment: Leukaemia. Probably myeloid type.

Opinion B

Lymph nodes: Normal general pattern, rich in plasma cells, very occasional eosinophil myelocyte seen.

Spleen: No leukaemic infiltration. Normal general structure, a moderate number of trapped blasts in the pulp.

Liver: No leukaemic infiltration; however the sinusoids contain occasional free blast cells as found in the blood during life.

Kidney: Contains a few minute foci of apparent extravasation of blood blast cells in the interstitial tissue.

Pancreas: Somewhat adipose, otherwise normal.

Femoral arteries: Organizing thrombus.

No bone-marrow sections available.

Diagnosis: None possible.

Preferred Diagnosis

The findings favour the possibility that the patient died from aleukaemic leukaemia (? type). Diagnosis uncertain, and classified in 'B' series.

---


Pre-irradiation History

January 1949

Referred for X-ray treatment. Indefinite history of intermittent back pain for 10 to 15 years. Clinical findings typical of advanced ankylosing spondylitis.

Irradiation History

<table>
<thead>
<tr>
<th>X-ray treatment to:</th>
<th>Mean spinal marrow dose (r)</th>
<th>Integral dose (Mg r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. 3.49 - 10. 5.49</td>
<td>156</td>
<td>10-0</td>
</tr>
<tr>
<td>17. 6.49 - 22. 8.49</td>
<td>157</td>
<td>10-1</td>
</tr>
<tr>
<td>13. 2.50 - 5. 5.50</td>
<td>157</td>
<td>9-9</td>
</tr>
<tr>
<td>Total</td>
<td>470</td>
<td>30-0</td>
</tr>
</tbody>
</table>

Post-irradiation History

February 1952

Seen in radiotherapy department, and apparently in good health.

March 1953

Admitted to hospital with abdominal pain and diarrhoea since February 1953.

Hb. 68 %, R.B.C. 3,200,000, W.B.C. 2,500-3,000, N.P. 30 %, Eos. 3 %, Monos. 4 %, Lymphos. 63 %. 'Moderate anisocytosis of the red cells with excess diffuse basophilia. Occasional normoblast present. Haemoglobinization is good. There is a neutropenia; in the first film an occasional granulocyte showed a mature cytoplasm but lack of segmentation or indentation of the condensed nucleus (not myelocytes).

Such cells are not seen in the second film. . . . '

April 1953

Marrow: 'There is much peripheral blood admixture. There appears to be an overall reduction of the myeloid elements without increase of blast precursors. Maturation is normal to the metamylocyte stage when in general the nuclei become condensed without segmentation, the cytoplasm continuing to mature. There must be an interference with the release mechanism, as such cells are infrequent in the peripheral blood . . . '

June 1953

Hb. 49 %, R.B.C. 2,120,000, W.B.C. 1,600, 'Pelger-like' polymorphs 5 %, N.P. 21 %, Eos. 2 %, Monos. 5 %, Lymphos. 55 %, degenerate cells 3 %, Normoblasts 5 %.
APPENDIX A

Case 39 (contd.)

Marrow: Myeloblasts 0.5%, Premyelocytes 2%, Myelocytes 14%, Metamyelocytes 4%, Abnormal maturation forms 15%, N.P. 2%, Eos. 0.5%, P.C. 0.5%, Haemocytoblasts 1%, Normoblasts 56%. Cells in mitosis 0.5%. 'Marrow is characterized by the abnormal maturation of the myelocytes into forms with a normal adult cytoplasm and granules but a condensed non-segmented nucleus. There is a considerable variation in the size of these cells, as to a lesser extent in the myelocytes. These forms are not liberated to any degree in the blood. There is also an increase in late normoblasts, suggesting a maturation-upset at this stage. The picture is that of a maturation defect, not leukaemia.'

July 1953

Hb. 31%, R.B.C. 1,200,000, W.B.C. 900, Platelets 20,000, ? Blasts 1%, Myelocytes 4%, 'Pelger-like' polymorphs 20%, N.P. 12%, P.C. 10%, Lymphos. 62%.

It is not recorded whether there was any glandular enlargement, or whether the liver and spleen were palpable.

6.8.53

Death.

Certified Cause of Death

(1a) Primary aplastic anaemia.

No material available for review.

Preferred Diagnosis

The findings in this case are very unusual. In the absence of any evidence to the contrary, as no material is available for review, the case may be an unusual variant of aleukaemic myeloid leukaemia. Classified in 'B' series.

Case 40. Male. Born 1900. 2 Courses. 2 Centres.

Pre-irradiation History

None available.

Irradiation History

<table>
<thead>
<tr>
<th>Date</th>
<th>Site</th>
<th>Spinal Marrow</th>
<th>Dose (G)</th>
<th>Total Dose (G)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20. 9.49 – 3.10.49</td>
<td>sacro-ilie joints and whole spine</td>
<td>. . .</td>
<td>1044</td>
<td>20-7</td>
</tr>
<tr>
<td>26.10.50 – 14.11.50</td>
<td>hips and shoulder joints</td>
<td>. . .</td>
<td>346</td>
<td>8-7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>. . .</strong></td>
<td><strong>1390</strong></td>
<td><strong>. . .</strong></td>
<td><strong>29-4</strong></td>
</tr>
</tbody>
</table>

Post-irradiation History

Admitted to hospital with history of vomiting, dyspnoea and weakness since September 1953. The liver was enlarged and the spleen possibly so. Generalized enlargement of glands. Hb. 30%, R.B.C. 1,500,000, W.B.C. 1,400, Myelocytes 2%, N.P. 10%, Monos. 6%, Lymphos. 82%.

Two sternal-marrow punctures were reported as follows:

(1) 'These are comparatively acellular preparations. They contain a few primitive cells of indefinite morphology. A possible diagnosis is that of a malignant reticulosis.'

(2) 'These marrow films show marked acellularity. There appears to be marked depression of leucopoiesis with reversal of the leuco-erythrogenetic ratio. There are numerous pro-erythroblasts, but the mature normoblasts, although scarce, show no obvious abnormality. Reticulum cells are relatively increased in number. Conclusion: There is no evidence of leukaemia, and this picture is most suggestive of an aplastic anaemia.'

December 1953

Hb. 41%, R.B.C. 2,000,000, W.B.C. 1,600, N.P. 12%, Monos. 2%, Lymphos. 86%, an occasional myelocyte.

26.12.53

Death.

(continued overleaf)
80

RADIATION AND LEUKAEMIA

Case 40 (contd.)

Certified Cause of Death
(1a) Aplastic anaemia.

The marrow films were submitted to two independent authorities.
Their opinions were as follows:

Opinion A

The two marrow-smears from this patient are not very satisfactory, and
do not really allow a proper opinion to be expressed. The specimen
is clearly either very hypocellular or has been grossly diluted. The
nucleated cells, however, show considerable numbers with primitive
features, and not all of these belong to the erythrocyte series. Among
the erythroblasts there is some evidence of megaloblastic change.
This feature is, if anything, suggestive of leukaemia rather than
aplastic anaemia. In effect—without being in any way confident—
that marrow samples might be derived from a case of acute leukaemia
in an aplastic phase, but it is not possible to be more dogmatic than this.

Opinion B

The marrow films appear to contain no visible fragments of bone marrow.
There appears to be a little fat, and amongst the scanty blood cells are
some primitive cells which I am unable to identify. I feel there is
insufficient material in this marrow puncture to justify a diagnosis.

Preferred Diagnosis

Probably a case of acute leukaemia in aleukaemic phase (? cell type).
Classified in 'B' series.

---

Case 41. Male. Born 1881. 1 Course. 1 Centre.

Pre-irradiation History
June 1951
Referred for X-ray treatment. Pain in back for 8 months. Clinical and
radiological findings those of ankylosing spondylitis.

November 1951
Hb. 90%, W.B.C. 11,600, N.P. 79%, Eos. 1%, Monos. 3%, Lymphos.
17%.

Irradiation History
X-ray treatment to:

<table>
<thead>
<tr>
<th>Spinal Marrow</th>
<th>Mean Dose (c.)</th>
<th>Integral Dose (Mg. c.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26.11.51-1.52</td>
<td>1045</td>
<td>17.8</td>
</tr>
</tbody>
</table>

sacro-iliaic joints and whole spine

Post-irradiation History
February 1955
Last seen in radiotherapy department and recorded as being 'very well'.
Admitted to hospital with history of malaise and anorexia since May
1955. Appeared severely anaemic, with signs of a left-sided pneumonia.
No history of exposure to drugs or chemicals. No glandular enlarge-
ment and liver and spleen not palpable.

Hb. 45%, W.B.C. 2,700, Platelets 14,000, N.P. 80%, Monos. 3%,
Lymphos. 17% Retics. <0-1%. Some immature cells seen, possibly
myeloblasts. Sternal puncture failed on two occasions, and biopsy of
R. iliac-crest marrow performed.

Marrow: '... shows very considerable myelopoiesis, moderate erythro-
poiesis and abnormally large numbers of megakaryocytes, mostly not
platelet-producing.'

Death.

Certified Causes of Death
(1a) Lobar pneumonia.
(1b) Aplastic anaemia.
(2) Ankylosing spondylitis.
Case 41 (contd.)

Post-mortem Findings

Macroscopic: The liver and spleen showed no abnormality. Fatty marrow was present in the head of the femur, but in the neck and upper part of the shaft there was gelatinous marrow, red in patches. Microscopic: The liver and spleen showed only siderosis. The bone marrow showed advanced changes of myelosclerosis.

The post-mortem material was submitted to two independent authorities. Their opinions were as follows:—

Opinion A

Bone marrow: The degree of cellularity varies in different parts of the sections, but on the whole it is undoubtedly reduced. In the more cellular parts (e.g. in the marrow from the shaft of the femur) the constitution of the marrow is grossly abnormal, abundance of megalakaryocytes being the most conspicuous feature. Most of the megalakaryocytes are abnormal. Foci of erythropoietic cells are common, granulocytes and precursors are scarce.

Spleen: Severe haemosiderosis. Normal and abnormal megalakaryocytes are frequent. Small Malignant bodies.


The histological findings are those of a hypoplastic anaemia with arrested regeneration. The label 'non-leukaemic megalakaryocytic myelosis' would be justifiable, but it is preferable to emphasize the destructive, rather than the proliferative, features of the disorder.

Opinion B

Marrow: Structure completely disorganized and replaced by oedematous fibroelastic tissue in which are embedded scattered haemopoietic cells. Atypical hyperchromatic megalakaryocytes are conspicuous. A few areas are much more cellular and the appearances approach those of atypical myelosclerosis. There is a great increase of reticulin throughout the marrow.

Interpretation: Myelosclerosis with an unusual degree of atrophy of the marrow.

Preferred Diagnosis

The case may be a variant of acute aleuakemic leukaemia (? myeloid) showing features of myelosclerosis.

Case 42. Male. Born 1901. 8 Courses. 4 Centres.

Pre-irradiation History

November 1939 Passed Grade I on enlistment in Armed Services.
April 1943 Admitted to hospital with enteritis. Found to be case of ankylosing spondylitis.

September 1944 Referred for X-ray treatment.

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mg. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray treatment to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. 9.44 – 23.10.44</td>
<td>sacro-iliac joints and whole spine</td>
<td>346</td>
</tr>
<tr>
<td>14.11.44 – 21.12.44</td>
<td>lumbar and cervical spines</td>
<td>306</td>
</tr>
<tr>
<td>7. 3.45 – 25. 4.45</td>
<td>cervical spine</td>
<td>295</td>
</tr>
<tr>
<td>2. 5.45 – 19. 6.45</td>
<td>lumbar spine</td>
<td>52</td>
</tr>
<tr>
<td>12.10.45 – 23.11.45</td>
<td>lumbar spine</td>
<td>52</td>
</tr>
<tr>
<td>10. 7.46 – 2. 8.46</td>
<td>sacro-iliac joints and lumbar spine</td>
<td>192</td>
</tr>
<tr>
<td>13.11.46 – 4.12.46</td>
<td>dorsal spine</td>
<td>213</td>
</tr>
<tr>
<td>16. 8.46 – 8. 9.46</td>
<td>sacro-iliac joints and whole spine</td>
<td>902</td>
</tr>
<tr>
<td>27. 4.50 – 16. 5.50</td>
<td>cervical spine</td>
<td>360</td>
</tr>
</tbody>
</table>

Total 2718 48-6

(continued overleaf)
Case 42 (contd.)

Post-irradiation History

March 1953
Last seen in radiotherapy department and recorded as being 'well',
Admitted to hospital with history of abdominal pain, pyrexia, and
headache since September 1953. One bout of haematuria. Generalized
abdominal tenderness. Liver not palpable but spleen probably enlarged.
Hb. 46%, R.B.C. 3,150,000, W.B.C. 5,800, N.P. 61%, Eos. 2%, Monos.
5%. Lymphos. 32%. Marked anisocytosis with some hypochromia.

October 1953
Death.

13.11.53
Certified Causes of Death
(1) Aplastic anaemia.
(2) Spondylitis. Thrombophlebitis.

Post-mortem Findings

Mesentery: Appearance consistent with a mesenteric arterial thrombosis.
Sternal marrow: Slightly less cellular than normal, but fair amount of
normoblastic activity as well as granulopoiesis. Not obviously aplastic.
Liver: Cloudy swelling, fatty degeneration. No evidence of leukaemic
infiltration.

Post-mortem material was submitted to two independent authorities.
Their opinions were as follows:—

Opinion A

Marrow: Increased cellularity, early forms numerous, mitoses frequent.
Excess of plasma cells.
Liver: No cellular infiltration in portal systems.
Comment: No evidence of leukaemia, but compare with Case 3. Not
aplastic anaemia.

Opinion B

Marrow: Hyperplastic, active erythropoiesis and leucopoiesis, not sug-
gestive of aplastic anaemia. No certain diagnosis possible.
Liver: Moderate fatty change, somewhat autolysed. No obvious haema-
tological lesion.

Preferred Diagnosis

Though the patient had a severe anaemia, probably related to his
extensive previous irradiation, there was no evidence either of leu-
kaemia or of aplastic anaemia. The immediate cause of death was
thought to be mesenteric arterial thrombosis.

Case 43. Male. Born 1890. 8 Courses. 1 Centre.

Pre-irradiation History
None available.

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mg. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray treatment to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. 3.47 – 30. 4.47</td>
<td>trunk</td>
<td>128</td>
</tr>
<tr>
<td>3. 6.47 – 22. 7.47</td>
<td>trunk</td>
<td>128</td>
</tr>
<tr>
<td>18. 9.47 – 28.10.47</td>
<td>trunk</td>
<td>128</td>
</tr>
<tr>
<td>1. 4.48 – 20. 5.48</td>
<td>trunk</td>
<td>128</td>
</tr>
<tr>
<td>30. 9.48 – 28.10.48</td>
<td>sacro-iliac joints</td>
<td>114</td>
</tr>
<tr>
<td>28. 4.49 – 2. 6.49</td>
<td>sacro-iliac joints</td>
<td>148</td>
</tr>
<tr>
<td>30. 3.50 – 4. 5.50</td>
<td>sacro-iliac joints</td>
<td>148</td>
</tr>
<tr>
<td>14. 8.52 – 18. 9.52</td>
<td>sacro-iliac joints</td>
<td>148</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1070</td>
</tr>
</tbody>
</table>
APPENDIX A

Case 43 (contd.)

Post-irradiation History

July 1953
Admitted to hospital with history of anorexia and loss of weight since May 1953.

8.7.53
Hb. 43%, R.B.C. 2,060,000, W.B.C. 2,600, Myelocytes 2%, N.P. 17%, Monos. 4%, Lymphos. 77%.

11.7.53
Death.

Certified Cause of Death
Aplastic anaemia.

Post-mortem Findings
Cardiac failure secondary to severe anaemia due to marrow aplasia.

The post-mortem material was submitted to two independent authorities.

Their opinions were as follows:—

Opinion A

Marrow: Sclerosis and hypoplasia. Possibly hypoplastic anaemia. No evidence of leukaemia.

Opinion B

Marrow: Marrow hypoplastic. Reticulum cells prominent. If this is sternal marrow the picture is compatible with aplastic anaemia.

Preferred Diagnosis
Aplastic anaemia.

Case 44. Male. Born 1908. 1 Course. 1 Centre.

Pre-irradiation History

June 1948
Referred for X-ray treatment. History of back pain for 4 years and attack of jaundice in March 1948.

Irradiation History

X-ray treatment to:

<table>
<thead>
<tr>
<th>Date</th>
<th>Tissue</th>
<th>Mean</th>
<th>Integral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>spinal marrow</td>
<td>dose (r.)</td>
<td>dose (Mg. r.)</td>
</tr>
<tr>
<td>8. 6.48 – 25. 6.48</td>
<td>sacro-iliac joints and whole spine</td>
<td>1034</td>
<td>22.1</td>
</tr>
</tbody>
</table>

Post-irradiation History

10.7.48
Referred to hospital with severe anaemia. Liver-edge palpable 5 cm. below costal margin. Spleen not palpable.

Hb. 23%, R.B.C. 1,270,000, W.B.C. 2,800, N.P. 71%, Eos. 1%, Basos. 1%, Monos. 2%, Lymphos. 25%, Retics. 4.5%.

From July 1948 until March 1949, there were 26 further blood-counts, including 4 differential white counts, summarized as follows:

Hb. 73–27% ... ... ... ... (26 observations)
R.B.C. 4,300,000–1,280,000 ... ... ... (26 " )
W.B.C. 4,900–1,600 ... ... ... (11 " )
Platelets 450,000 ... ... ... (1 " )
N.P. 75–65% ... ... ... (4 " )
Eos. 4–3% ... ... ... (2 " )
Monos. 2–5% ... ... ... (3 " )
Lymphos. 33–21% ... ... ... (4 " )
Retics. 5.5–1% ... ... ... (11 " )

During this period the patient had repeated blood transfusions.

15.2.49
Terminal admission with melaena, haematuria and abdominal pain.

14.3.49
Death.

(continued overleaf)
RADIATION AND LEUKAEMIA

Case 44 (contd.)

Certified Causes of Death
(1a) Cardiac failure.
(1b) Aplastic anaemia.

Post-mortem Findings
The sternum, vertebrae and femora contained dark red marrow with much sinusoid congestion. Liver (2,000 g.) was pale and fatty with scattered focal necroses. Spleen (400 g.) showed on cut surface black foci representing pigment-laden Malpighian bodies. The abdominal lymph nodes were enlarged, and reddish in colour. The tibia contained only fatty marrow.

The post-mortem material was submitted to two independent authorities. Their opinions were as follows:—

Opinion A
Marrow: The total cellularity of the marrow is considerably less than normal. Myeloid cells are most severely affected; they are greatly reduced in number, and some are atypical in structure. Many foel of erythroproietic cells are present, and there is a relative preponderance of early forms. Plasma cells are more abundant than is normal. Megakaryocytes are very scarce. The histological picture is that seen in hypoplastic anaemia.

Lymph nodes: Haemorrhage in sinuses, and haemosiderosis. Some excess of plasma cells and large lymphocytes. No myelocytes recognized.
Spleen: Severe haemosiderosis. Relative excess of large cells (? large lymphocytes) but no myelocytes, and the picture does not suggest leukaemia.
Conclusion: The findings are those of hypoplastic ('aplastic') anaemia.

Opinion B
Marrow: Gross reduction in myeloid and erythroblastic cells, and in megakaryocytes. Slight increase in reticulin. Excessive plasma cells.
Bone marrow hypoplasia.
Liver: Normal structure slightly siderotic.
Spleen: Normal in structure, rich in siderophages and plasma cells.
Lymph nodes: Normal basic structure, rich in plasma cells.
Small intestine: Autolysed, normal. Scattered thrombi in submucosal venules.
Heart: Normal.

Preferred Diagnosis
Aplastic anaemia.

Case 45. Male. Born 1893. 3 Courses. 1 Centre.

Pre-irradiation History
December 1948 Referred for X-ray treatment. History of psoriasis for 6 years, and of stiffness of joints for 1 year.
Hb. 94%, W.B.C. 9,900.
APPENDIX A

Case 45 (cond.)

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mg. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray treatment to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20.12.48 - 21. 2.49</td>
<td>sacro-ilac joints and whole spine</td>
<td>726</td>
</tr>
<tr>
<td>12. 4.49 - 21. 6.49</td>
<td>shoulders, hips and R. elbow</td>
<td>—</td>
</tr>
<tr>
<td>15. 1.53 - 19. 3.53</td>
<td>L. foot and L. lower ribs</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>735</td>
</tr>
</tbody>
</table>

Post-irradiation History

April 1953
Hypertension, B.P. 220/115, general health poor.

March 1954
Referred to hospital on account of recurrent epistaxes since December 1953, associated with bruising, petechiae and retinal haemorrhages.
Spleen not palpable, liver just palpable.
Hb. 38%, R.B.C. 1,910,000, W.B.C. 4,100, Platelets scanty, N.P. 66.5%.
Monos. 3.5%, Lymphos. 29.4%, atypical cells 1.0%.
Marrow: Slightly hypocellular. Reticulum cells 0-4%, Premyelocytes 0-4%, Myelocytes 2-8%, Metamyelocytes 3-0%, N.P. 24%, P.C. 24%.
Lymphos. 47.4%, Normoblasts 16%.
Treated with blood transfusions with little response.

30.4.54
Death.

Certified Causes of Death
(1a) Coronary thrombosis.
(1b) Aplastic anaemia.
(1c) Myelosclerosis and ankylosing spondylitis.
(2) Acute psoriasis and acute rheumatism.

Death attributed by Registrar-General to myelosclerosis (292.3).

Preferred Diagnosis
Further inquiries indicate that the case is one of aplastic anaemia.

Case 46. Male. Born 1894. 2 Courses. 1 Centre.

Pre-irradiation History
None available, apart from the fact that the patient suffered from diabetes mellitus.

July 1949
Referred for X-ray treatment.

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mg. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray treatment to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. 7.49 - 20. 9.49</td>
<td>whole pelvis and whole spine</td>
<td>721</td>
</tr>
<tr>
<td>20. 4.50 - 2. 5.50</td>
<td>L. sacro-ilac joint</td>
<td>137</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>858</td>
</tr>
</tbody>
</table>

Post-irradiation History

September 1950
Admitted to hospital for a R. inguinal herniorrhaphy. Apparently well otherwise.

July 1952
Re-admitted to hospital with history of severe diarrhoea for 2 weeks.
Patient was anaemic and had lost weight. The liver was grossly enlarged and tender. Alternative diagnoses entertained were carcinoma of the colon with hepatic secondaries, or hepatic cirrhosis. Hb. 60%.
Treated with intravenous iron.

September 1952
Re-admitted with further attack of diarrhoea. Hb. 44%.
Sternal marrow: Myeloblasts 2%, Myelocytes 20%, Bands 17%, N.P. 9%, Eos. 3%, Monos. 1%, P.C. 2%, Lymphos. 31%, Megakaryocytes 1%, Normoblasts 13%, Mitotic figures 1%. 'A very hypoplastic normoblastic marrow.'
No other haematological data available.

13.9.52
Death.

(continued overleaf)
Case 46 (contd.)

Certified Cause of Death

(1a) Aplastic anaemia.

Post-mortem Findings

The only significant finding was that of multilobular hepatic cirrhosis.

Post-mortem material was submitted to two independent authorities.

Their opinions were as follows:

\[\text{Opinion A}\]

- Bone marrow: Gross autolysis prohibiting opinion.
- Spleen: No evidence of leukaemia.
- Liver: Multilobular cirrhosis.
- Comment: No evidence of leukaemia. Not aplastic anaemia.

\[\text{Opinion B}\]

- Bone marrow: Hypercellular marrow, autolyzed. No evidence of aplastic anaemia or leukaemia. No diagnosis possible.
- Spleen: Fibrosis compatible with cirrhosis. No evidence of leukaemia.
- Liver: Active-looking partial cirrhosis.

Preferred Diagnosis

There appear to be no grounds to suspect a diagnosis of aleukaemic leukaemia, or even to support one of aplastic anaemia. The anaemia may well have been associated with the hepatic cirrhosis. Therefore, the case has been discarded from the survey, except for the purpose of comparison between the observed and expected mortalities of cases certified as dying from aplastic anaemia.

Case 47. Male. Born 1906. 1 Course. 1 Centre.

Pre-irradiation History

March 1943 Patient first attended hospital. A diagnosis was made of kyphoscoliosis of dorso-lumbar spine with excessive decalcification.

January 1947 Diagnosis of ankylosing spondylitis.

May 1950 Referred for X-ray treatment. Hb. 64%.

(An entry in the case notes covering the terminal admission in October 1952 states that the patient had had amidopyrine during the pre-irradiation period, but it has not been possible to confirm this.)

<table>
<thead>
<tr>
<th>Mean irradiation History</th>
<th>Integral</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray treatment to:</td>
<td></td>
</tr>
<tr>
<td>spine and whole spine</td>
<td></td>
</tr>
<tr>
<td>23. 6.50 – 7.50</td>
<td>541</td>
</tr>
<tr>
<td>dose (r.)</td>
<td>9.3</td>
</tr>
</tbody>
</table>

Post-irradiation History

August 1950 Admitted to hospital because of severe rectal haemorrhage.

Hb. 34%, R.B.C. 1,840,000, W.B.C. 2,700, N.P. 68%, Lymphos. 32%

(after a transfusion of 3 pints of whole blood).

September 1950 Sternal marrow: 'The marrow is not very cellular and the picture is complicated by treatment. The poor cellularity of the marrow and the ratio between the myeloid and the erythroid series suggest aplastic anaemia, but the presence of myeloblasts and myelocytes and the few early erythroid cells suggests some response to treatment.' Myeloblasts 10%, Myelocytes 13%, Metamyelocytes 14%, N.P. 1%, Lymphos. 8%, Pro-erythroblasts 1%, early normoblasts 9%, intermediate normoblasts 20%, late normoblasts 24%.

From August 1950 until October 1952, the patient was maintained on blood transfusions given at intervals of approximately 4 to 6 weeks. A series of 59 additional counts was performed, among which were 16 white-cell counts varying between 3,400 and 1,000. Differential white counts were done on 11 occasions, the neutrophil polymorphs
APPENDIX A

Case 47 (contd.)

varying between 68% and 40%. At no time were any primitive white
cells noted.

2.11.52

Death.

Certified Causes of Death

(1a) Broncho-pneumonia.
(1b) Aplastic anaemia.
(1c) Ankylosing spondylitis.

Post-mortem Findings

Nothing of note recorded in the post-mortem report apart from the fact
that the marrow from the sternum and iliac crest appeared normally
 cellular.

The post-mortem material was submitted to two independent authorities.
Their opinions were as follows:—

Opinion A

Bone marrow: Great reduction in cellularity, and most of the cells are
reticulum cells, plasma cells, lymphocytes or macrophages; few
haemopoietic cells of any kind. Basophil myelocytes are more
abundant than either neutrophil or eosinophil. Large amounts of
pigment (presumably haemosiderosis), much of it in macrophages.
The histological picture is that of aplastic anaemia.

Liver: Very severe haemosiderosis. Necrosis of liver cells in centre of
lobules. Putrefactive gas formation. There may be slight fibrosis
secondary to the haemosiderosis. No leukaemic infiltration.

Spleen: Severe haemosiderosis. Excess of plasma cells. Some foci of
normoblastis are present. No evidence of leukaemic infiltration. The
pathological findings are typical of hypoplastic "aplastic" anaemia.

Opinion B

Marrow: Reduced cellularity with many fat cells. Reticulum cells con-
spicuous, many laden with iron pigment. Some myeloid cells present;
the majority appear to be lymphocytes. Plasma cells are also
identifiable.

Interpretation: Aplastic anaemia.

Preferred Diagnosis

Aplastic anaemia.

Case 48. Female. Born 1893. 4 Courses. 1 Centre.

Pre-irradiation History

June 1945

Referred for X-ray treatment. History of back pain for 22 years,
previously treated by physiotherapy.

Hb. 90%, R.B.C. 4,000,000, W.B.C. 6,000.

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mg. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. 6.45 – 30. 6.45</td>
<td>572</td>
<td>971</td>
</tr>
<tr>
<td>August 1945</td>
<td>(Hb. 72%, R.B.C. 3,500,000, W.B.C. 3,000)</td>
<td>14.2</td>
</tr>
<tr>
<td>13. 5.47 – 28. 5.47</td>
<td>572</td>
<td>9.8</td>
</tr>
<tr>
<td>31.10.47 – 13.11.47</td>
<td>210</td>
<td>8.8</td>
</tr>
<tr>
<td>November 1948</td>
<td>(Hb. 80%, R.B.C. 4,500,000, W.B.C. 7,900.)</td>
<td></td>
</tr>
<tr>
<td>January 1949</td>
<td>(Hb. 80%, R.B.C. 4,600,000, W.B.C. 7,000.)</td>
<td></td>
</tr>
<tr>
<td>February 1949</td>
<td>(Bands 2%, N.P. 66%, Monos. 1%, Lymphos. 31%)</td>
<td></td>
</tr>
<tr>
<td>7. 3.49 – 29. 3.49</td>
<td>809</td>
<td>10.4</td>
</tr>
<tr>
<td>Total</td>
<td>2562</td>
<td>43.2</td>
</tr>
</tbody>
</table>

(continued overleaf)
RADIATION AND LEUKAEMIA

Case 48 (contd.)

Post-irradiation History
March 1949
Hb. 75%, R.B.C. 3,200,000, W.B.C. 4,300, Bands 3%, N.P. 61%, Eos. 3%, Lymphos. 36%.
The patient became progressively more crippled by her spinal deformity until she was practically bed-ridden.

July 1950
27.10.50
Hb. 48%, R.B.C. 1,930,000.
Death.

Certified Causes of Death
(1a) Aplastic anaemia.
(1c) Spondylitis ankylosa.

Preferred Diagnosis
No information is available about the patient's terminal illness, and no preferred diagnosis is possible.

Case 49. Female. Born 1889. 2 Courses. 1 Centre.

Pre-irradiation History
May 1945
Referred for X-ray treatment. History of back pain for 10 years.

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mg. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray treatment to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21. 6.45 – 28. 6.45</td>
<td>sacro-iliac joints and whole spine</td>
<td>534</td>
</tr>
<tr>
<td>4.10.45 – 17.10.45</td>
<td>sacro-iliac joints and whole spine</td>
<td>484</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1018</td>
</tr>
</tbody>
</table>

Post-irradiation History
June 1950
Admitted to hospital with history of increasing weakness since April 1950. Liver and spleen not palpable.
Hb. 60%; R.B.C. 3,280,000, W.B.C. 3,400, N.P. 39%; Eos. 1%; Basos. 1%; Monos. 5%; Lymphos. 54%; 22 Normoblasts/100 W.B.C.
Marked anisocytosis and poikilocytosis.
Sternal marrow: T.N.C. 143,000, Myeloblasts 1.2%, Pre-myelocytes 0.6%, Myelocytes 1.8%, Metamyelocytes 1.4%, N.P. 2.6%, P.C. 0.4%,
Lymphos. 4.0%, Haemocytoblasts 1.4%, Pro-erythroblasts 7.6%, Normoblasts 75%, Cells in mitosis 3.8%: M:E ratio 0:1:1:0.
'Extreme normoblastic hyperplasia. Many giant normoblasts seen, some with 2 or 3 nuclei. Of the more primitive red cells, many had a vacuolated cytoplasm.'
From June 1950 until February 1951 the patient was maintained on frequent blood transfusions. Ten blood counts were carried out, and the findings were as follows:—

| Hb. 75-28% | ... | ... | (10 observations) |
| R.B.C. 3,770,000-1,670,000 | ... | ... | (10 " " ) |
| W.B.C. 2,800-1,600 | ... | ... | ( 5 " " ) |
| N.P. 72-31% | ... | ... | ( 5 " " ) |
| Eos. 2-1% | ... | ... | ( 4 " " ) |
| Basos. 1% | ... | ... | ( 1 " " ) |
| Monos. 3-1% | ... | ... | ( 5 " " ) |
| Lymphos. 75-25% | ... | ... | ( 5 " " ) |
| Normoblasts/100 W.B.C. 12-8 | ... | ... | ( 2 " " ) |

21.2.51
Death.

Certified Causes of Death
(1a) Heart failure.
(1b) Aplastic anaemia.

Preferred Diagnosis
Neither ante- nor post-mortem material was available for review.
The development of the fatal illness more than 4 years after the
Case 49 (contd.)
patient's last exposure to radiation is more in favour of a malignant condition than aplastic anaemia.

Case 50. Male. Born 1915. 1 Course. 1 Centre.
Pre-irradiation History
June 1950
Referred for X-ray treatment by orthopaedic specialist as a case of ankylosing spondylitis. A diagnosis of osteoarthritis was preferred in the radiotherapy department; for this reason the patient was not included in the survey. However, the diagnosis of ankylosing spondylitis was adhered to by the orthopaedic specialist up to the time of the patient's death. The radiological findings showed sclerosis around both sacro-iliac joints.

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean dose (r.)</th>
<th>Integral dose (Mg. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray treatment to:</td>
<td>spinal marrow</td>
<td></td>
</tr>
<tr>
<td>lorv-iliac joints and whole spine</td>
<td>467</td>
<td>8.9</td>
</tr>
</tbody>
</table>

Post-irradiation History
February 1952
Right antrostomy for severe epistaxis.

Hb. 66%, W.B.C. 82,000, Blasts 1%, Premylocyes 11%, Myelocytes 19%, Metamylocyes 31%, N.P. 30%, Eos. 2%, Pronomonos. 2%, Monos. 3%, Lymphos. 1%.

Ilac-crett marrow: Myeloblasts 3%, Premylocyes 80%, Myelocytes 10%, Bands 45%, N.P. 15%, Lymphos. 20%, Haemocytoblasts 1%, Pronormoblasts 5%, Normoblasts 11%.

18.5.54
Death.

Certified Causes of Death
(1a) Cerebral haemorrhage.
(1b) Myeloid leukaemia.

Preferred Diagnosis
Chronic myeloid leukaemia.

Case 51. Male. Born 1900. 1 Course. 1 Centre.

Pre-irradiation history not known

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean dose (r.)</th>
<th>Integral dose (Mg. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray treatment to:</td>
<td>spinal marrow</td>
<td></td>
</tr>
<tr>
<td>trunk</td>
<td>244</td>
<td>6.6</td>
</tr>
</tbody>
</table>

Post-irradiation History
November 1955
Admitted to hospital with history of tiredness since October 1955. Skin petechiae and bruising. Some enlarged glands, but liver and spleen not palpable.

Hb. 56%, R.B.C. 2,460,000, W.B.C. 3,800, Platelets 180,000. Films suggestive of monocytic leukaemia.

Sternal marrow: Shewed numerous monoblasts and monocytes, many in mitosis.

January 1956
Hb. 44%, R.B.C. 1,980,000, W.B.C. 10,800, Blasts 7%, N.P. 8%, Eos. 1%, Monos. 72%, Lymphos. 12%.

22.1.56
Death.

Preferred Diagnosis
Acute monocytic leukaemia presenting in aleukaemic phase.

(The details of this case were provided by Dr. J. H. L. Easton and Dr. J. C. Valentine, Bedford General Hospital.)
RADIATION AND LEUKAEMIA

Case 52. Female. Born 1886. 1 Course. 1 Centre.

Pre-irradiation History
None available.

Irradiation History
X-ray treatment to:
19. 6.45 - 17. 8.45
lumbar and cervical spines
(Patient treated in private institution.)
Mean spinal marrow dose (r.) Integral dose (Mg. r.)
About 220 About 3-0

Post-irradiation History
June 1953
Admitted to hospital with history of fatigue, dyspnoea and abdominal
pain since January 1953. Skin petechiae were present. No glandular
enlargement was found, and the liver and spleen were not palpable.
Hb. 28 %, W.B.C. 15,800, Blasts 75 %, Bands 4-0 %, N.P. 7-0 %, Eos.
1-0 %, Lymphos. 13-0 %.
24.9.53
Death.

Certified Cause of Death
(1a) Myeloid leukaemia.

Preferred Diagnosis
Acute myeloid leukaemia.

(Details of this case were provided by Dr. R. C. Tudway and Dr.
Brendan T. Hale, Bristol Royal Hospital.)

Case 53. Male. Born 1891. 1 Course. 1 Centre.

Pre-irradiation History
December 1939
Fracture of R. femur.
1951
Development of back pain.
1952
Patient is said to have had 2 blood transfusions. It has not been dis-
covered where or for what reason these were given.

September 1952
Referred for X-ray treatment. Clinically, the patient suffered from
advanced ankylosing spondylitis.

Irradiation History
X-ray treatment to:
Mean spinal marrow dose (r.) Integral dose
30. 9.52 - 30.12.52
whole pelvis and whole spine
About 1033 About 26-9

Post-irradiation History
October 1953
Hb. 92 %, W.B.C. 4,000.
November 1953
Admitted to hospital because of continued back pain.
Hb. 85 %, R.B.C. 4,260,000, W.B.C. 6,100, N.P. 58 %, Eos. 1 %, Monos.
1 %, Lymphos. 40 %.
October 1954
Re-admitted with dyspnoea and swelling of legs since September 1954.
Liver enlarged, but spleen not palpable.
Hb. 25 %, R.B.C. 1,170,000, W.B.C. 2,800, N.P. 40 %, Monos. 8 %,
Lymphos. 52 %, scanty myeloblasts and normoblasts seen.
12.10.54
Death.

Certified Causes of Death
(1a) Pulmonary oedema.
(1b) Acute heart failure.
(1c) Aplastic anaemia.
(2) Ankylosing spondylitis.
APPENDIX A

Case 53 (contd.)

Post-mortem Findings
The bone marrow is reported as being extremely active, with roughly equal numbers of red and white cells. Erythropoiesis is normoblastic. No material available for review.

Preferred Diagnosis
The case has features similar to others in the 'B' series. ? aleukaemic myeloid leukaemia.


Pre-irradiation History

November 1941
Diagnosis of ankylosing spondylitis established. History of back pain for 5 years. Hb. 70%. Film 'normal'.

<table>
<thead>
<tr>
<th>Irradiation History</th>
<th>Mean spinal marrow dose (r)</th>
<th>Integral dose (Me. r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 6.42 – 16. 642</td>
<td>whole spine, hips and shoulders</td>
<td>457</td>
</tr>
<tr>
<td>4. 8.42 – 19. 842</td>
<td>whole spine and shoulders</td>
<td>180</td>
</tr>
<tr>
<td>26.10.42 – 10.11.42</td>
<td>whole spine and shoulders</td>
<td>192</td>
</tr>
<tr>
<td>15. 1.43 – 28. 2.43</td>
<td>whole spine, hips and shoulders</td>
<td>462</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>1291</td>
</tr>
</tbody>
</table>

Post-irradiation History

March 1943
Admitted to hospital with marked weakness and anaemia and a history of epistaxis since January 1943. Liver and spleen not palpable.
Hb. 37%, R.B.C. 1,800,000, W.B.C. 1,100, Platelets 124,000, N.P. 46%, Eos. 2%, Monos. 6%, Lymphos. 46%.
Sternal marrow: T.N.C. 10,600, Myeloblasts 2%, Myelocytes 29%, N.P. 27%, Eos. 2%, Lymphos. 21%, Erythroblasts 8%, Normoblasts 11%.

June 1943
Discharged from hospital much improved after rest and iron therapy.
Hb. 75%, R.B.C. 3,800,000, W.B.C. 7,000, N.P. 53%, Eos. 4%, Basos. 1%, Monos. 10%, Lymphos. 32%.

From the summer of 1943 until October 1945 the patient worked as a lift attendant without further illness until the late summer of 1945, when he developed increasing fatigue and dyspnoea on exertion.

October 1945
Re-admitted to hospital.
Hb. 44%, R.B.C. 2,100,000, W.B.C. 2,500, Platelets 54,000, Myelocytes 2%, N.P. 21%, Eos. 1%, Monos. 1%, Lymphos. 75%.
Sternal marrow: T.N.C. 268,000, Myeloblasts 2%, Myelocytes 64%, N.P. 12%, Lymphos. 4%, Erythroblasts 4%, Normoblasts 11%, Megaloblasts 3%.

November 1945
Hb. 45%, R.B.C. 2,800,000, W.B.C. 2,900, Platelets 46,000, Myeloblasts 35%, Myelocytes 24%, N.P. 36%, Eos. 1%, Lymphos. 4%.
Sternal marrow: T.N.C. 200,000, Myeloblasts 16%, Myelocytes 65%, N.P. 10%, Lymphos. 4%, Erythroblasts 4%, Normoblasts 1%.

21.12.45
Death.

Post-mortem Findings
The marrow from the vertebrae, sternum, mid-femur and mid-tibia was dark-red in colour and markedly hyperplastic. The sinuses of the liver, spleen, lymph nodes and bone marrow contained large numbers of mononuclear cells that appeared to be primitive blood cells, and a few megaloblasts.

Preferred Diagnosis
Acute myeloid leukaemia presenting in aleukaemic phase.

(Thedetails were provided by Drs. D. C. and W. Graham of Toronto, Canada. The case is referred to in a paper by Robinson and Lampe, 1948.)

**Pre-irradiation History**

November 1946
Diagnosis of ankylosing spondylitis. History of back pain for 5 years. Hb. 90%, R.B.C. 4,550,000, W.B.C. 7,000, N.P. 62%, Monos. 8%. Lymphos. 30%. No abnormality of liver, spleen, or lymph nodes.

March 1947

**Irradiation History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Spinal Marrow</th>
<th>Dose (r.)</th>
<th>Integral Dose (Mg. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28. 3.47 - 11. 7.47</td>
<td>...</td>
<td>533</td>
<td>10-7</td>
</tr>
<tr>
<td>14. 8.47 - 22.10.47</td>
<td>...</td>
<td>144</td>
<td>3-5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>...</td>
<td>677</td>
<td>14-2</td>
</tr>
</tbody>
</table>

The patient had frequent blood counts performed between March and October, 1947. From June to September, 1947, the haemoglobin varied between 85% and 100%, and the white-cell count between 5,000 and 8,800. Up to 22.10.47 the blood counts were within normal limits, with the exception of a white-cell count of 4,100 on 16.10.47.

**Post-irradiation History**

23.10.47
W.B.C. 2,800.

24.10.47
N.P. 28%, Eos. 5%, Monos. 9%, Lymphos. 58%.

27.11.47
Patient developed exacerbation of sickness which had been present since early November 1947. W.B.C. 3,700, Myeloblasts 38%, Paramyeloblasts 23%, Myelocytes 1%, N.P. 18%, Eos. 3%, Monos. 3%, Lymphos. 8%, Erythroblasts 3%. Normoblasts 3%. Liver and spleen were not palpable.

2.12.47
**Sternal marrow:** Myeloblasts 74±8%, Paramyeloblasts 10±2%, Myelocytes 5±2%, N.P. 3-4%, Eos. 2-4%, Basos. 0-4%, Lymphos. 1-4%, Erythroblasts 0-2%, Normoblasts 2-2%.

3.12.47
W.B.C. 19,800, Blast cells 8%.

5.12.47
W.B.C. 36,000.

9.12.47
W.B.C. 98,000.

11.12.47
Death.

**Preferred Diagnosis**

Acute myeloid leukaemia. This case is well documented, and regular examinations from November 1946 until October 1947 showed no evidence of leukaemia in the peripheral blood; leukaemia became apparent in November 1947 at the earliest.

(The details were provided by Drs. D. C. and W. Graham of Toronto Canada. The case is referred to in a paper by Robinson and Lampe, 1948.)


**Pre-irradiation History**

1948
Referred for X-ray treatment. History of back pain for 10 years.

**Irradiation History**

1948 - 1950
X-ray treatment on several occasions. No details available.

**Post-irradiation History**

February 1951
W.B.C. 12,400.

August 1953
W.B.C. 90,000 with clear picture of chronic myeloid leukaemia.

(The details of this case were provided by Dr. William J. Tighe, San Diego, California, U.S.A., in response to the Medical Research Council's request for information in the British medical press in January 1955.)
APPENDIX A

Case 57. Male. Born 1898.

Pre-irradiation History
None available.

Irradiation History

<table>
<thead>
<tr>
<th>Date</th>
<th>Treatment to:</th>
<th>Mean spinal marrow dose (r.)</th>
<th>Integral dose (Mr. r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.11.38</td>
<td>cervical and dorsal spines</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

(Treatment stopped because of severe hypoplastic anaemia.)

May 1942 site unknown
August 1942 site unknown
February 1943 site unknown

Post-irradiation History

February 1943 Hb. 35%, R.B.C. 1,800,000, W.B.C. 1,100, N.P. 46%, Lymphos. 46%, Endothelial 6%.
March 1943 Marrow: T.N.C. 10,000, Myeloblasts 19%, Myelocytes 30%, N.P. 22%, Erythroblasts 8%, Normoblasts 20%.
October 1945 Hb. 45%, R.B.C. 2,300,000, W.B.C. 3,900, Myeloblasts 4%, Myelocytes 7%, N.P. 37%, Lymphos. 46%.
November 1945 Marrow: T.N.C. 265,000, Myeloblasts 2%, Myelocytes 64%, N.P. 12%, Lymphos. 4%, Erythroblasts 4%, Normoblasts 11%.

Death.

Post-mortem Findings

Bone marrow: A slight increase in size and number of bony trabeculae. The outstanding finding is the cellularity of the marrow. This proliferation is both within and outside the marrow sinuses. The hematopoietic elements represented are of diverse character with marked variability in type and pattern-distribution; blast cells with open vesicular nuclei surrounded by immature granulocytes, megalakaryocytic forms and young nucleated red cells. The background is of a loose granulomatosing nature. Eosinophilic granular material scattered between the proliferated cells is another feature. In some regions the proliferated marrow cells sit naked in this eosinophilic granular matrix. In the femoral bone-marrow nuclear activity is, if anything, more pronounced, particularly in the 'blast and megakaryocytic forms'. The diversity of cell types persists. Erythropagocytosis is frequent. Tibial bone-marrow is composed principally of fat, with only the occasional focus of extrasinusoidal immature haematopoietic elements.

Spleen: Intrasinusoidal and extrasinusoidal haematopoietic cells are frequent. These cells consist of blast forms, immature granulocytic elements and erythroblastic forms. The occasional atypical megakaryocytic form is scattered irregularly throughout the ectopic haematopoietic tissue. The lymphoid follicles are not invaded. The trabeculae are intact.

Liver: There is no portal-tract invasion with immature haematopoietic cells. Many of the sinuses of the liver show an admixture of atypical megakaryocytic elements, polynuclears and immature erythrocytic forms. In some regions the polynuclears are gathered up into intrasinusoidal foci.

Lymph nodes: The lymphoid architecture in the cortical portions is preserved. In the sclerosed medulla there is a diffuse scattering of lymphoid cells, extracapillary foci of megakaryocytic elements, eosinophilic myelocytes and erythroblasts. Erythropagocytosis is a frequent finding.

(Some details of this case were published by Wyatt and Sommers (1950). Additional information has been provided by Dr. S. Sommers, Boston, Mass., U.S.A.)

* Data incomplete.
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This patient was reported during the survey by one of the co-operating centres. He is regarded as having had ankylosing spondylitis for many years, in addition to the chronic lymphatic leukaemia which was diagnosed in 1930.

June 1950

Hb. 100%, R.B.C. 5,000,000, W.B.C. 85,000, Platelets 135,000, N.P. 10%, Lymphos. 90%.

8.12.53

Death.

Certified Cause of Death
Chronic lymphatic leukaemia.

Preferred Diagnosis
Chronic lymphatic leukaemia.


September 1951

Referred to hospital with fatigue, breathlessness and glandular enlargement. Examination revealed enlargement of the liver and spleen. Hb. 67%, R.B.C. 3,200,000, W.B.C. 790,000, Platelets 160,000, N.P. 0-4%, Monos. 0-4%, Lymphos. 99-2%.

The patient was also found radiographically to have ankylosing spondylitis, for which he had not had X-ray treatment. He was given X-ray treatment to the spleen on 3 occasions.

21.7.54

Death.

Certified Cause of Death
(1a) Chronic myeloid leukaemia.

Preferred Diagnosis
Chronic lymphatic leukaemia.

(The details of this case were provided by Professor B. W. Windyer, Meyerstein Institute of Radiotherapy, the Middlesex Hospital. The cause of death was certified incorrectly, the patient having died while away from hospital.)


January 1955

The patient attended hospital with persistent tachycardia. Clinical examination revealed chronic lymphatic leukaemia, and, with X-ray confirmation, ankylosing spondylitis. The patient had been complaining of pain in the back for only 2 years.

Preferred Diagnosis
Chronic lymphatic leukaemia.

(The details of this case were provided by Dr. C. F. J. Cropper, Worcester Royal Infirmary, in response to the Medical Research Council’s request for information in the British medical press in January 1955.)
APPENDIX A


This case was identified while a search was being made for leukaemia deaths amongst the survey population not known to be alive or dead in 1955. Extensive inquiries have shown that the patient was not at any time given X-ray treatment. The diagnosis of ankylosing spondylitis was established in June 1943.

7.4.54
Death.

Certified Causes of Death
(1a) Broncho-pneumonia.
(2b) Acute myeloid leukaemia.
(2) Ankylosing spondylitis.

Preferred Diagnosis
Acute myeloid leukaemia.


This case was identified while a search was being made for deaths from aplastic anaemia amongst the survey population not known to be alive or dead in 1955. Inquiries have shown that the patient was not at any time given X-ray treatment.

26.9.54
Death.

Certified Causes of Death
(1a) Aplastic anaemia.
(2) Ankylosing spondylitis.

Post-mortem material was submitted to an independent authority. The findings revealed no evidence of leukaemia or of aplastic anaemia. Megaloblast-like cells were present in the marrow, suggesting a diagnosis of megaloblastic anaemia.

Case 70. Female. Born 1900.

This case was identified while a search was being made for deaths from aplastic anaemia amongst the survey population not known to be alive or dead in 1955. Inquiries have shown that the patient was not at any time given X-ray treatment. She discharged herself from hospital 4 months before she died. Review of the hospital records shows that she had a severe hypochromic anaemia with a persistent neutropenia of extreme degree (34 to 226 per cu.mm.).

25.5.54
Death.

Certified Causes of Death
(1a) Aplastic anaemia.
(2) Ankylosing spondylitis.
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RADIATION AND LEUKAEMIA


April 1948 Admitted to hospital with a history of weakness and anaemia since December 1947. A diagnosis of ankylosing spondylitis was made in 1944, for which the patient had received various forms of treatment including gold. There is no record of X-ray treatment. Examination revealed the presence of skin petechiae and retinal haemorrhages. There was no enlargement of the liver or spleen. Hb. 40%. R.B.C. 1,910,000, W.B.C. 3,850. Platelets 38,200, Blasts 23%. Myelocytes 2%. Bands 4%. N.P. 6%. Prolymphos. 13%. Lymphos. 52%.

Illic crest marrow: Bone marrow showed extreme hyperplasia of myeloid elements, characteristic of leukaemic infiltration.

24.2.48 Death.

Preferred Diagnosis
Acute myeloid leukaemia presenting in the aleukaemic phase.

(The details of this case were provided by Dr. Donald A. Futsia of New Kensington, Pa., U.S.A., in response to the Medical Research Council's request for information in the British medical press in January, 1955.)

Case 72. Male. Born ——.

1954 Diagnosis of ankylosing spondylitis and myeloid leukaemia established simultaneously. Patient not given X-ray therapy prior to this.

May 1955 Death.

Preferred Diagnosis
Myeloid leukaemia (? clinical type).

(The details of this patient were provided by Dr. E. Kelemen, Szeged, Hungary, following the publication of a paper by Court-Brown and Abbott in 1955.)
PLATE 1

The phantom used for the measurement of the radiation dose received in the spinal marrow.

Anteroposterior radiograph of the chest of the phantom.
APPENDIX B

The Measurement of the Distribution of Radiation Dose in the Spinal Marrow

An analysis of the case records of the sample patients showed that the maximum bone marrow dose of radiation would be received at one of three likely points in the cervical, dorsal, and sacral regions of the spine. Estimates of the doses received at these points based on depth dose data derived from observations made in a homogeneous scattering medium would not have been sufficiently accurate, since no account would have been taken of the problems posed by X-ray absorption in a non-homogeneous medium, in particular in a medium containing bone and air-spaces. To overcome this difficulty a phantom was constructed with radiation-absorbing and scattering properties similar to those of the living body. Two series of measurements were carried out on this phantom: firstly, measurement was made of the doses at the chosen points resulting from radiation given to fields on the posterior skin surface directly over those points; and secondly, measurement was made of the doses from a number of fields applied to anatomical sites other than the spine. Finally, the dose-contributions to the three points from spinal fields immediately adjacent to those situated over the points were estimated, and the validity of these estimates was checked by means of measurements in a smaller phantom of more simple construction.

THE CONSTRUCTION OF THE PHANTOM

B. M. Wheatley, Ph.D., and W. C. Lister, B.Sc.

The larger phantom (Plate 1) was constructed around a human skeleton, complete but for the extremities. After immersion in molten 'Mix D', a tissue-equivalent wax (Jones and Raine, 1949), the skeleton was mounted in a Bexoid shell, care being taken to avoid the use of materials of high atomic number in articulating and mounting the bones. The shell was moulded around the plaster cast of a living person whose thoracic cage had similar dimensions to those of the available skeleton, and the position of the spine inside the shell was determined by means of anatomical studies from typical radiographs and an autopsy. Lungs were represented by Bexoid shells packed with sawdust to a mean density of 0.30 g./c.c. The shape of the lung shells was determined from anatomical diagrams which were suitably enlarged and distorted optically to give a good fit to the rib-cage of the skeleton; from these diagrams a positive plaster mould was made on which the Bexoid shells were formed. After the lungs had been mounted in the thorax, the interstices of the phantom were filled with Lincolnshire Bolus, a granular material with radiation-absorbing properties similar to those of soft tissue (Lindsay and Stern, 1953). The bolus was uniformly distributed by means of a vibrator applied to the outer shell of the phantom.

To facilitate measurements at the three chosen points, small slides, terminating in thin aluminium holders drilled to carry intracavitary chambers (Farmer, 1945) in the position of the marrow canal, were placed in the anterior surface of the phantom. The slides (Fig. 1B) were made of 'Mix D' wax, and ran in rectangular guides of 1 mm. 'perspex'. Indentations were made in the posterior surface of the phantom opposite each of the three chosen points, so that intracavitary chambers, placed with their sensitive volumes at surface level, could measure the surface dose for comparison during the experimental work.
Radiation and leukaemia

The depths of the three spinal measurement sites below the posterior surface of the phantom were determined by means of radiographs, one of which, the anteroposterior view of the chest, is reproduced in Plate I. The depths were found to be 6-9 cm. (cervical site), 6-0 cm. (dorsal site), and 6-6 cm. (sacral site).

Fig. 1B. Diagram showing one of the aluminium chamber-holders fixed to the end of a slide.

The Measurement of the Dose-Contributions from the Main Treatment Fields

D. E. A. Jones, B.Sc., and R. E. Ellis, B.Sc.

The experimental section of the work was planned to provide, either directly or by interpolation, a measure of the dose delivered to the spinal bone marrow for the majority of the treatment fields used in the sample cases. The three measurement sites chosen were:

1. the sacrum (2nd segment)
2. the dorsal spine (8th dorsal vertebra)
3. the cervical spine (5th cervical vertebra)

The first position was chosen in preference to the 5th lumbar vertebra in order to take into account contributions of dose from sacro-iliac fields while at the same time representing fields directed on to the lumbar spine.

The Treatment Parameters

The main parameters to be considered were the area of skin irradiated, the focus-skin distance (F.S.D.) and the radiation quality. The following sections give the variations found for these parameters in the sample cases, and outline the methods used to provide adequate experimental cover for the wide ranges encountered.

Skin-field Area

Fig. 2B shows the variations in field dimensions which had to be taken into consideration. This information is more briefly summarized in Table 1B, which also gives the maximum elongation (i.e., the ratio of the long to the short edges) of the rectangular fields and the diameter of any circular fields occurring at the various sites.

In the experimental work the fields were restricted to six sizes, obtained by placing lead sheets 2 mm. thick on the surface of the phantom, having cut them away centrally to expose square areas of sides 3, 5, 7, 10, 15 and 22.5 cm. 'Open' fields were used occasionally; their areas were found radiographically. For the shorter F.S.D.'s the size of the open field precluded the use of the larger sizes of
square fields. Circular fields were treated as square fields of the same area. The reduction of percentage depth dose for a given field area resulting from the

Fig. 2B. The range of rectangular skin-field dimensions for spinal and sacro-iliac fields. X denotes the more frequently used field sizes.

A—Fields localized to individual sacro-iliac joints
B—Fields irradiating both sacro-iliac joints
C—Fields irradiating lumbar spine
D—Fields irradiating dorsal spine
E—Posterior fields irradiating cervical spine
F—Lateral fields irradiating cervical spine
TABLE 1B

The dimensions of the treatment fields to the spine and sacro-iliac joints, excluding open fields

<table>
<thead>
<tr>
<th>Site</th>
<th>Range (cm.)</th>
<th>Maximum elongation</th>
<th>Circles (cm, diam.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimum</td>
<td>Maximum</td>
<td></td>
</tr>
<tr>
<td>A. Individual sacro-iliac joints</td>
<td>6 × 5</td>
<td>15 × 15</td>
<td>2</td>
</tr>
<tr>
<td>B. Both sacro-iliac joints</td>
<td>10 × 5</td>
<td>25 × 20</td>
<td>2.5</td>
</tr>
<tr>
<td>C. Lumbar spine</td>
<td>6 × 4</td>
<td>20 × 16</td>
<td>5</td>
</tr>
<tr>
<td>D. Dorsal spine</td>
<td>7 × 7</td>
<td>40 × 15</td>
<td>6.7</td>
</tr>
<tr>
<td>E. Post-cervical spine</td>
<td>6 × 4</td>
<td>20 × 16</td>
<td>5</td>
</tr>
<tr>
<td>F. Lateral cervical spine</td>
<td>6 × 4</td>
<td>18 × 10</td>
<td>3</td>
</tr>
</tbody>
</table>

colonization of rectangular fields was allowed for, using the area reduction factors of Jones (1949).

Focus-skin Distance

The majority of treatments were carried out at distances of between 15 and 60 cm., and the remainder at distances of between 100 and 200 cm. The effects of focus-skin distances of 20, 40 and 60 cm. were studied for the three harder qualities of radiation (see below) and of distances of 15, 30 and 60 cm. for the two softer qualities. Measurements were also made of the dose contributions to the marrow from posteriorly-directed open fields at 150 cm. distance from the skin surface. The data from these latter measurements enabled assessments to be made of the doses at the three points from similar wide-field techniques but in which the focus-skin distances varied between 100 and 200 cm. It should be noted in this connexion that percentage depth dose is not improved significantly by increasing the F.S.D. beyond 100 cm., particularly for very wide fields.

X-ray Quality

In about half the total number of cases the radiation quality was recorded in terms of the half-value layer (H.V.L.) in millimetres of aluminium or copper. In

TABLE 2B

The six experimental X-ray qualities

<table>
<thead>
<tr>
<th>Half-value layer (mm.)</th>
<th>Aluminium</th>
<th>Copper</th>
<th>Kilovoltage</th>
<th>Added filter (mm.)</th>
<th>Equipment used</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) 1.1</td>
<td>---</td>
<td>---</td>
<td>90</td>
<td>---</td>
<td>Watson XT, 150</td>
</tr>
<tr>
<td>(2) 1.55</td>
<td>---</td>
<td>---</td>
<td>105</td>
<td>0.25 Al</td>
<td>&quot; &quot; &quot;</td>
</tr>
<tr>
<td>(3) 3.45</td>
<td>(0.1)</td>
<td>90</td>
<td>120</td>
<td>1.0 Al</td>
<td>220 kV Keleket</td>
</tr>
<tr>
<td>(4) 5.25</td>
<td>(0.2)</td>
<td>120</td>
<td>1.0 Al</td>
<td>&quot; &quot; &quot;</td>
<td>&quot; &quot; &quot;</td>
</tr>
<tr>
<td>(5) 8.2</td>
<td>0.4*</td>
<td>120</td>
<td>1.0 Al</td>
<td>&quot; &quot; &quot;</td>
<td>&quot; &quot; &quot;</td>
</tr>
<tr>
<td>(6) 12.0</td>
<td>0.9</td>
<td>120</td>
<td>0.25 Cu + 1.0 Al</td>
<td>&quot; &quot; &quot;</td>
<td>220 kV Keleket</td>
</tr>
</tbody>
</table>

* Interpolated.
APPENDIX B

the remaining cases only the kilovoltage and the filter were recorded, so that an approximate assessment of the H.V.L. had to be made from published data (Binks, 1936). The quality range extended from 0.8 mm. Al to 2.4 mm. Cu H.V.L.

In order to take into account the variations in quality of the X-ray beam noted in the sample cases, five qualities were chosen for investigation; data concerning a sixth quality (H.V.L. 0.4 mm. Cu) were obtained by interpolation (Table 2B).

The Technique of Dose Measurement

The records of treatment gave information only on the skin dose (in roentgens) delivered to each irradiated field, i.e., the dose with back-scatter at the centre of the irradiated area. Since it was necessary to know for each relevant field the dose at one of the three chosen sites below the surface relative to the appropriate skin-point, it was found convenient to measure the skin- and depth-doses simultaneously. Farmer's small-cavity condenser-type ionization chambers were used for this purpose; it was believed that the ratio of the response of two such chambers, one placed on the surface of the phantom at the centre of the irradiated field and the other at the appropriate point in the marrow, would give a direct measure of the percentage depth dose, irrespective of any changes in the X-ray tube output during the period of exposure. Measurement of the voltage loss resulting from X-ray exposure was made on a dosemeter electrometer (Farmer, 1942).

The two ionization chambers to be used were selected by means of tests for consistency of behaviour and low inherent electrical leakage. Comparison of each chamber with a secondary standard integrating dosemeter for a full range of exposures at two X-ray qualities (3.4 mm. Al and 0.9 mm. Cu H.V.L.) showed that the relationship between voltage drop and dose for each chamber was linear to a very close approximation. There was a small but appreciable change in sensitivity with X-ray quality which was not the same for the two chambers, the relative change in sensitivity being about 3 per cent.

The technique used throughout was to place one chamber at the skin site and the other in the appropriate slide-holder, and to expose to the radiation for a suitable period, the exposure being monitored by an independent integrating dosemeter; the chamber positions were then reversed and the exposure repeated, the mean of the two percentage depth doses being accepted as the appropriate figure. It was assumed that there was no difference in local X-ray quality between the skin and marrow sites. It was found necessary to apply a correction for the X-ray absorption in the aluminium sleeves, 0.5 mm. thick, which had been provided to support the chambers at the bone marrow sites. The extent of this correction at the various qualities was determined by comparing the response of each chamber when embedded 0.5 cm. deep in a 'Mix D' phantom, first with and then without the sleeve; an X-ray field 7 cm. square at 40 cm. F.S.D. was used. The correction ranged from 3 per cent at 0.9 mm. Cu H.V.L. to 18 per cent at 1.1 mm. Al H.V.L.

Experimental Results

Direct Spinal Fields

The results of the systematic measurements at the three posterior spinal sites are given graphically in Figs. 3B, 4B and 5B for 20 cm., 40 cm. and 60 cm., F.S.D. and for the six X-ray qualities. Percentage depth doses for square or
Fig. 3B. Percentage depth doses at the sacral site for 20, 40 and 60 cm. F.S.D., and for the 6 experimental X-ray qualities (Table 2B, p. 102). Depth: 6.6 cm.

circular fields could be read directly from the graphs, while a family of curves (Fig. 6B), derived from Jones's data (1949) on the area reduction factor, provided a simple means of correcting for field elongation.
Fig. 4B. Percentage depth doses at the dorsal site for 20, 40 and 60 cm. F.S.D., and for the 6 experimental X-ray qualities (Table 2B, p. 102). Depth: 60 cm.
Radiation and leukaemia

Anterior and posterior whole-trunk treatments were simulated by open-field irradiations at 150 cm. F.S.D. with the beam axis passing through a point midway between the dorsal and sacral sites; the results are given in Table 3B. Some additional direct abdominal wide-field treatments at 60 cm. F.S.D. were investigated over the whole quality range, with the beam axis centred over the dorsal

![Graph showing percentage depth doses for different F.S.D. and areas of field.](image)

**Fig. 5B.** Percentage depth doses at the cervical site (posterior fields) for 20, 40 and 60 cm. F.S.D. and for the 6 experimental X-ray qualities (Table 2B, p. 102). Depth: 6.9 cm.
APPENDIX B

point. Parallel measurements at 50 cm. F.S.D. at three qualities, with the beam centred over the sacral site were found to give very similar results (Fig. 7B). Treatment by direct lateral cervical fields was difficult to reproduce experimentally owing to the rigidity of the phantom. The use of lead sheets for defining the field areas was also precluded, and experimental data were obtainable only for the larger field areas. The trend of the depth dose curves (Fig. 8B) for the smaller field areas was assumed to be the same as that of the curves for the direct spinal fields.

EXTRASPIINAL FIELDS

Data were also needed for some fields which, while not primarily directed at the spine, might make significant dose-contributions to the sacral site. With these fields, in contrast to the spinal fields, it was not possible to provide more than an approximation to the probable treatment technique employed, and measurements were made only with radiation quality 0.9 mm. Cu H.V.L.

**TABLE 3B**

<table>
<thead>
<tr>
<th>Aspect</th>
<th>Half-value layer (mm)</th>
<th>Percentage depth dose to sites</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Dorsal</td>
</tr>
<tr>
<td>Posterior</td>
<td>0.9 Cu</td>
<td>70.5</td>
</tr>
<tr>
<td>Anterior</td>
<td>0.9 Cu</td>
<td>25.9</td>
</tr>
<tr>
<td></td>
<td>5.25 Al</td>
<td>15.0</td>
</tr>
</tbody>
</table>

**Fig. 6B.** Correction chart for elongated areas; e.g., for the purpose of estimating the percentage depth dose, a 20 x 5 cm. field (area, 100 cm²; elongation ratio, 4) is regarded as a square field of area 58 cm².
FIG. 7B. The variation of percentage depth dose with X-ray quality for wide anterior direct fields.

FIG. 8B. Percentage depth doses for lateral fields to the cervical spine for 40 cm. and 60 cm. F.S.D. and for X-ray qualities Nos. 1, 3 and 4 (Table 2B, p. 102).
APPENDIX B

Hip fields. For direct anterior fields the beam was centred over the joint space. It was demonstrated radiographically that the sacral point could receive a direct contribution of dose only from square fields of 10 cm. edge or larger, at 25 cm. F.S.D. or less. Measurements were made at 25 cm., 40 cm. and 60 cm. F.S.D. for the appropriate field areas. The results showed that at 25 cm. F.S.D. the sacral point would receive 10 to 12 per cent of the skin dose, and that the contribution from smaller fields could be ignored. At 40 cm. and 60 cm. F.S.D. the contributions were 13 to 17 per cent and 15 to 20 per cent respectively, increasing with field area, while the contributions from fields smaller than 12 cm. square were negligible.

Direct posterior hip fields were assumed to be centred over the superior end of the femoral head. The dose contribution to the sacral point would be dependent mainly on the length of the transverse axis of the field; for fields such that this axis exceeded 8 cm. the sacral point would be within the geometrical limits of the beam. It was decided therefore to ignore dose contributions to the sacral point from posterior hip fields having a transverse axis less than 8 cm. For fields with a longer transverse axis the dose contribution was assumed to be the same as if the field had been centred over the sacral point.

Direct lateral fields were centred on the femoral head, and measurements at the sacral site were made at 22 cm., 40 cm. and 53 cm. F.S.D. Square fields of 10 cm. edge and 'open' fields were measured. The results are given in Table 4B.

Table 4B

Depth doses from lateral hip fields measured at the sacral point: H.V.L. 0.9 mm.Cu

<table>
<thead>
<tr>
<th>Focus-skint distance (cm.)</th>
<th>Field area (cm.²)</th>
<th>Sacral dose (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>100</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>144</td>
<td>7.5</td>
</tr>
<tr>
<td>40</td>
<td>100</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>480</td>
<td>13</td>
</tr>
<tr>
<td>53</td>
<td>100</td>
<td>9.5</td>
</tr>
<tr>
<td></td>
<td>840</td>
<td>16</td>
</tr>
</tbody>
</table>

Fields to ischial tuberosities. With the phantom in the prone position the beam axis was aligned in the sagittal plane and directed at an angle of 40° to the horizontal on to the superficial point representing the anus. Square fields of side 7 cm., 10 cm. and 15 cm., together with the 'open' field, were used at

Table 5B

Depth doses from ischial tuberosity fields measured at the sacral point: F.S.D. 50 cm., H.V.L. 0.9 mm. Cu

<table>
<thead>
<tr>
<th>Field area (cm.²)</th>
<th>Sacral dose (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>19</td>
</tr>
<tr>
<td>200</td>
<td>25</td>
</tr>
<tr>
<td>400</td>
<td>28</td>
</tr>
</tbody>
</table>
Radiation and leukaemia

50 cm. F.S.D. The results indicated that, under the prescribed conditions, fields of length less than 10 cm. (parallel to the long axis of the patient) would be unlikely to contribute significantly to the sacral site. An estimate of the likely contribution for square fields of edge 10 cm. or longer is given in Table 5B.

Discussion

The conditions of dose measurement in this experiment were such that the values obtained are relevant only to soft tissue; no account was taken of any increase in the dose absorbed by the bone marrow as a result of its close proximity to bone. Since the marrow space within the vertebrae contains a trabecular bone structure, regions of the marrow lying within the range of the secondary electrons produced within the bony material will absorb a higher dose of radiation than the marrow situated outside this range. From the information given by Spiers (1951), the maximum local increase in absorbed dose above the soft-tissue level could be six-fold at an effective wavelength of 0.5 Å (H.V.L., 1.0 mm. Al) as compared with a four-fold increase at 0.2 Å (H.V.L., 0.9 mm. Cu). On the other hand the effective secondary electron range is only about 10μ in the former case, increasing to about 50μ in the latter.

In a recent personal communication on this subject, Professor Spiers referred to a paper by Robertson and Goodwin (1954), in which it was stated that the trabeculae are from 40 to 250μ thick (i.e. sufficient for electron equilibrium at the X-ray qualities concerned) and that the widths of the marrow inclusions lie within the approximate limits 200 to 700μ. Using the dimensions suggested by Robertson and Goodwin, Spiers has applied the results of his earlier calculations (1951) to derive values for the extra dose to trabecular marrow; the dose has been averaged over the relevant cavity dimensions for electron ranges appropriate to the X-ray qualities used in our experiment. From these values he has calculated the mean excess dose absorbed by the marrow over a range of X-ray qualities and for three widths of bone marrow space, namely 200μ, 400μ and 700μ, covering the range suggested by Robertson and Goodwin. The results are summarized in Table 6B.

TABLE 6B
The calculated excess dose to the marrow in trabecular bone due to the secondary electron emission from bone

<table>
<thead>
<tr>
<th>Effective wavelength (Å)</th>
<th>Approximate H.V.L. (mm.)</th>
<th>Effective electron range (μ)</th>
<th>Excess dose % for marrow thickness of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>200μ</td>
</tr>
<tr>
<td>0.5</td>
<td>1.0 Al</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>0.35</td>
<td>3.0 Al</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>0.25</td>
<td>0.3 Cu</td>
<td>40</td>
<td>32</td>
</tr>
<tr>
<td>0.13</td>
<td>1.5 Cu</td>
<td>80</td>
<td>22</td>
</tr>
</tbody>
</table>

While it is clearly impossible to estimate what correction should be applied to the cases dealt with in the present investigation, the possibility exists of our having underestimated the mean dose absorbed by the marrow by an amount which, under certain conditions, could be as much as 30 per cent. As against this underestimate, a possible over-assessment of dose must also be borne in
APPENDIX B

mind in those cases where the disease may have increased the thickness of calcified material surrounding the bone marrow space to an extent which would appreciably reduce by absorption the dose reaching the central regions of the vertebrae.

An unexpected feature of our depth dose values for the direct posterior fields is that they are appreciably higher than the values calculated from the data of Spiers (1946) for similar fields. Spiers based his calculations on the assumption that the vertebra consists throughout of bone of density 1.85 g./c.c. It is clear however that adult vertebral bone consists largely of relatively coarse cancellous tissue of much lower density. Our recent density measurements on the dorsal vertebrae obtained from two adults at post mortem suggest that the tissue forming the bulk of the vertebral body has a density of 1.1 g./c.c., while the anterior bony material has an average density of about 1.4 g./c.c. If these values are used for the direct spinal field considered by Spiers (1951), his approximate method, using exponential factors, yields a bone marrow dose at 6 cm. depth which is 86 per cent of the soft-tissue value (H.V.L. = 1.5 mm. Cu, F.S.D. = 50 cm., area 100 cm.²); the corresponding value for a bone density of 1.8 g./c.c. is only 55 per cent. At the hardest quality used in our experiments (0.9 mm. Cu H.V.L.) the dose to the dorsal bone marrow (depth 6 cm.) was about 90 per cent of the soft-tissue value given in standard depth dose tables (Scientific Sub-committee of the Hospital Physicians' Association, 1953).

We are grateful to Professor B. W. Windeyer and Professor J. E. Roberts for the use of laboratory space and equipment, and to Professor P. W. Spiers for valuable help and advice. We should also like to thank Sister Leyland of the Radiotherapy Department, the Middlesex Hospital, and Mr. D. W. Lywood of the National Institute for Medical Research, for expert technical assistance.

THE CALCULATION OF THE DOSE-CONTRIBUTIONS FROM ADJACENT FIELDS

J. H. Mulvey, Ph.D., B. M. Wheatley, Ph.D. and A. Alberts, B.Sc.

In many of the treatments there was a small but significant contribution to the dose at one or more of the three chosen points in the spine from radiation scattered from fields adjacent to the direct fields over the points. The contribution of this scattered radiation could not be measured for individual cases in the time available; it was therefore computed by the numerical methods of Worthley and Wheatley (1952), in which the dose of radiation at any point outside a field is related to the scattered radiation at the same depth on the central axis. Two possible sources of error exist with this method of calculation: the first arises from neglecting the effects of inhomogeneity in the irradiated tissue, and the second from the use of simplifying assumptions in the numerical methods. Since the contribution of radiation from adjacent fields is small, it was felt that small errors in estimating its value could be neglected. This was confirmed when experimental measurements on the smaller phantom, using both hard and soft radiation, showed that neither source of error was significant.

The dose contributions from adjacent fields were computed using the tables of Worthley, Tooze, Brown and Fry (1955), and the results are shown in Table 7B, which gives the dose at the chosen point to the nearest 2.5 r. per 100 r. skin-dose applied to an adjacent field. The two parameters used are the area of the adjacent field and the distance of the point of interest from the edge of this field. The three chosen points of interest were assumed to lie at a depth of 7 cm. below the skin, and elongation effects were neglected, so that all adjacent fields...
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TABLE 7B

Contributions to the total dose of radiation from fields adjacent to the direct field

<table>
<thead>
<tr>
<th>Area of adjacent field (cm.²)</th>
<th>Dose contribution per 100 r, skin-dose to adjacent field (r.)</th>
<th>Distance from edge of adjacent field (cm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.5</td>
<td>3.5</td>
</tr>
<tr>
<td>25</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>50</td>
<td>5</td>
<td>5</td>
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<tr>
<td>100</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>150</td>
<td>10</td>
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<td>225</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>400</td>
<td>15</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Hard radiation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>50</td>
<td>5</td>
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<td>100</td>
<td>10</td>
</tr>
<tr>
<td>150</td>
<td>15</td>
</tr>
<tr>
<td>225</td>
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<table>
<thead>
<tr>
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<th>Soft radiation†</th>
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<tr>
<td>225</td>
<td>10</td>
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<tr>
<td>400</td>
<td>10</td>
</tr>
</tbody>
</table>

* H.V.L. ≥0.5 mm. Cu (exact at H.V.L. 1 mm. Cu).
† H.V.L. 6 mm. Al–10 mm. Al (exact at H.V.L. 8 mm. Al). All contributions at H.V.L. <6 mm. Al were negligible.

were considered as squares. A value of 40 cm. was assumed to be representative of the F.S.D. in treatments carried out with an H.V.L. 0.5 mm. Cu, and for the softer range of radiations (H.V.L. 6–10 mm. Al) a value of 30 cm. was chosen. Although in practice the values used ranged from 15 cm. to 200 cm., the values above were typical, and since the contributions from adjacent fields are, in any case, unaffected by variations in F.S.D., no significant error should arise through this simplification. Furthermore, most of the extreme values of F.S.D. occurred with very soft radiations (H.V.L. < 6 mm. Al) for which the adjacent field contribution was negligible.
APPENDIX C

The Methods Used to Estimate the Whole Body Integral Dose of Radiation

B. M. Wheatley, Ph.D., and J. Geilinger, B.Sc.

The whole body integral dose of radiation per 100 r. at the surface was estimated for each field in each case history. The computations were based on the assumption that the body tissues are homogeneous and possess absorption properties similar to those of water. This assumption, although necessary in the present state of mathematical dosimetry, is far from satisfactory when applied to the energy absorbed in bone marrow, since it is in those tissues that the effect of the inhomogeneity introduced by the surrounding bone will be at its greatest. It should therefore be borne in mind that the integral dose data in the Report have this basic limitation.

Some of the case histories contained no record of the half-value layer of the radiation used, although often this could be estimated from the kilovoltage and filtration; and very few of them gave any measurements of the patients' body-thickness; in some cases, also, the field sizes were not stated. With these limitations in the data it was clear that exact methods of calculation were inapplicable and that approximations in the mathematical methods were justified.

OUTLINE

The methods used for calculating the integral doses were grouped into three, according to the clinical techniques employed. These were:

(a) deep therapy (H.V.L. > 0.5 mm. Cu; area 0–500 cm.²),
(b) superficial therapy (H.V.L. < 0.5 mm. Cu; area 0–500 cm.²),
(c) wide-field therapy (fields more than covering the body).

Deep Therapy

For this range of conditions Mayneord's approximate formula (Mayneord, 1940) was used:

\[ \Sigma = \frac{100A}{\mu} \]  

(1)

where \( \Sigma \) is the integral dose in gr. per 100 r. surface dose with backscatter, \( A \) is the area of the field at the surface, and \( \mu \) is the apparent absorption coefficient of water.

In the range of deep therapy conditions the value of \( \mu \) does not change greatly with either H.V.L. or F.S.D.; thus the use of a mean value was justifiable, and the one chosen was that for H.V.L. 1-5 mm. Cu, F.S.D. 45 cm. This value was estimated from the 10 cm. depth dose taken from the central axis tables in Supplement 5 of the British Journal of Radiology* (Scientific Sub-committee of the Hospital Physicists' Association, 1953), and it enabled equation (1) to be enumerated for all the field sizes used. Where the body thickness was not stated, it was assumed that it could be taken from Mayneord's standard man (Mayneord, 1944), and the appropriate exit-dose corrections were made to the value of the integral dose. Although the curvature of the body surfaces was neglected, the divergence of the beam of radiation was taken into account.

Superficial Therapy

In this range of radiation qualities, the apparent absorption coefficient of water, \( \mu \) (equation 1), is so dependent on H.V.L. and F.S.D. that the use of

* Hereafter referred to as 'the Supplement'.
a mean value would have led to gross errors. The diversity of conditions encountered in the case histories precluded the rather lengthy computations necessary to calculate each integral dose ab initio. However, a mathematical analysis showed that the integral dose could be derived by compounding simple factors read from specially prepared graphs. In most cases it was necessary to determine the H.V.L. of the radiation from the kilovoltage and filtration quoted, and this necessitated extending the nomograms used for this type of estimation. In many of the treatments the F.S.D. was of the order of 20–30 cm., so that it was not permissible to ignore the divergence of the beam in thick body-sections.

*Wide-field Therapy*

In very few of these cases were the patients' dimensions given, so the dimensions of Mayneord's standard man were assumed, and his method of calculating integral dose in elliptical cylinders was adopted.

The following sections give mathematical extensions of the methods of calculation used in the case of deep therapy and of superficial therapy.

**Mathematical Extensions**

*Deep Therapy*

The approximate formula for integral dose in equation (1) (Mayneord, 1940) is based on the assumption that the isodose surfaces are planes parallel with the surface and extending to the geometrical edges of the beam, which is considered to be non-divergent and incident normally on the patient. It also assumes that the dosage rate decreases exponentially with depth, with an apparent absorption coefficient which we have chosen to calculate from the dose 10 cm. deep on the central axis using the published data for divergent beams given in the Supplement. The inaccuracies resulting from the use of this approximate formula have already been discussed by Mayneord (1940). However, equation (1) becomes a considerably better approximation to the integral dose for a divergent beam when it is multiplied by a correction factor given by equation (2), in which $f$ refers to the F.S.D.:

$$\text{divergence correction factor} = \left(1 + \frac{2}{f\mu} + \frac{2}{(f\mu)^2}\right)^3$$

(2)

The remaining inaccuracies are not as serious as might at first appear, since some of the errors are compensatory. For example, the assumption that the isodose curves are planar overestimates the integral dose within the geometrical limits of the beam; but this is compensated, since it ignores the integral dose due to scattered radiation outside the geometrical limits. Again, although the assumption that the dosage rate decreases exponentially is not strictly accurate, the experimental depth dose curves lie partly above and partly below the exponential curve (Fig. 1C).

Integral doses were evaluated from equation (1) for each field area, H.V.L. and F.S.D. given in depth dose data for open-ended applicators* (Supplement, Table 3); the computation was simplified by rearranging equation (1) in terms of the 10 cm. depth dose, $D_{10}$, read from the data.

* Data for applicators with closed ends were available only for 50 cm. F.S.D. The type of applicator end used (not mentioned in the case histories) will not significantly affect the integral dose.
APPENDIX C

With the assumption that the depth-dose varied exponentially we have:

$$D_{10} = 100 e^{-\mu x}$$

i.e.

$$\mu = 10^{-1} \log_{e} \left( \frac{100}{D_{10}} \right)$$

so that the integral dose per 100 r. surface dose is given by:

$$\Sigma = A \cdot 10^{-2} \log_{e} \left( \frac{100}{D_{10}} \right) \text{Mg. r.}$$ (3)

The variations of this quantity with H.V.L. and F.S.D. are shown in Fig. 2C. For radiations having an H.V.L. greater than 1 mm. Cu the dependence of integral dose on quality of radiation is slight, and for all radiations considered

![Diagram of depth dose curve and exponential curve](image)

**Fig. 1C.** The depth dose curve for a 10 x 10 cm. field (H.V.L. 1.5 mm. Cu; F.S.D. 50 cm.), showing that an exponential curve through the point at 10 cm. deep leads to both positive and negative errors.

the integral dose is almost independent of the F.S.D. From a sample of the case histories it appeared that treatments given with hard radiation usually employed F.S.D.'s of 40 or 50 cm. and H.V.L.'s between 1 and 2 mm. Cu. It was therefore decided to represent all 'deep therapy' treatments, for the purpose of estimating the integral dose, by a mean condition of 1.5 mm. Cu H.V.L. and 45 cm. F.S.D. The divergence correction (equation 2) had the value 1.50 for this condition, with very small departures from this value at other H.V.L.'s and F.S.D.'s occurring within the deep therapy region. The integral dose for this condition was determined by linear interpolation between the integral doses from equation (1) at 1.5 mm. Cu H.V.L. with F.S.D.'s of 40 and 50 cm. respectively. The result of the linear interpolation is shown in Fig. 3C as the curve for an infinite body-thickness. The other curves in Fig. 3C show the integral doses in bodies of finite
thick, in which the radiation was not totally absorbed. These curves were
derived from the curve for infinite body-thickness by introducing a correction
for the exit dose. Thus the integral dose within a body \( t \) cm. thick is given by:

\[
\Sigma_t = \Sigma_{\infty} \left(1 - \frac{D_t}{100}\right)
\]  

(4)

where \( \Sigma_{\infty} \) is the integral dose for a body of infinite thickness given by equation

(3), and \( D_t \) is the percentage depth dose at depth \( t \) read from the tables in the

Supplement. The correction given in equation (4) is only an approximation, as
back-scatter deficiencies cause the exit dose from a thin phantom to be less than
the dose read from tables for the same depth below the surface in a phantom of
infinite thickness. However, the error introduced by this difference is small, and
was considered negligible.

The integral doses calculated from equations (2) and (3) were tabulated for
the field sizes and body thicknesses which occurred most frequently in the case
histories. Table 1C presents data used by the authors and their colleagues in
annotating many of the case histories; to correct for divergence of the beam, each value of integral dose read from this table was multiplied by 1.50. Where body thicknesses were not given on the patients’ notes, the values used by Mayneord (1944) were assumed. Thus, fields applied to the dorsal and lumbar spine were assumed to pass through 20 cm. of tissue, and those to the cervical spine through 12 cm. Where knees, elbows or extremities were irradiated, dimensions were taken from a normal body of average size. The assumption that the body dimensions of a spondylitic patient are normal may not be justified, but the variations to be expected in clinical practice will not significantly affect the integral dose (Table 1C and Fig. 3C).

Superficial Therapy
Although less than half of the case histories concerned patients treated with radiation of H.V.L. 0.5 mm. Cu or less, the calculations for this group were the most time-consuming, since the computations could not be systematized and tabulated in the same way as for harder radiations. When the H.V.L. of the radiation was not given explicitly it was deduced from the kilovoltage and filtration by means of a nomogram (Binks, 1936). This method is clearly subject to some error, as it assumes the same wave-form and inherent filtration in every case. Basically, the method of calculating integral dose was similar to that adopted for deep therapy conditions, and equations (1) and (4) were used. The short F.S.D.’s often employed with soft radiation made it desirable to take into
### Radiation and Leukaemia

#### TABLE 1C

The integral doses for deep therapy conditions, taken from equations (2) and (3) and uncorrected for beam divergence. (To allow for divergence each value of integral dose should be multiplied by 1.5.)

<table>
<thead>
<tr>
<th>Size of field</th>
<th>Integral dose (Mg. r./100 r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Long axis (cm.)</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
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<tr>
<td>6</td>
<td>5</td>
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<tr>
<td>10</td>
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<td>15</td>
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<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

Account the divergence of the beam in the body, so the divergence correction (equation 2) devised by Mayneord was employed. More than twenty different qualities of radiation were encountered in the survey, and each of these was used at several different F.S.D.'s. Because the value of the apparent absorption
APPENDIX C

coefficient, $\mu$, is dependent upon F.S.D. and quality as well as upon area, it was essential to have a rapid method of finding this value. Before explaining the method adopted in the calculation of $\mu$, we shall anticipate, by rearrangement of equations (1) and (4), the final stage in the calculation of integral dose.

From equations (1) and (4),

$$\Sigma_i = 100 \left( \frac{A}{\mu} \right) \left( 1 - e^{-\mu t} \right)$$

which can be written as

$$\Sigma_i = 100 A t \left( \frac{1 - e^{-\mu t}}{\mu t} \right) = 100 V \left( 1 - e^{-x} \right) / x$$

where $V$ is the volume of tissue which would be irradiated if the incident radiation were parallel, and $x$ is the product of patient’s body-thickness and apparent absorption coefficient $\mu$.

The divergence correction (equation 2) by which the uncorrected value of $\Sigma_i$ must be multiplied is also a function of $f/\mu$. Hence, writing $x$ for $\mu t$, the integral dose becomes

$$\Sigma_i = 100 V \left( \frac{1 - e^{-x}}{x} \right) \left[ 1 + \frac{2}{(f/\mu)} + \frac{2}{((f/\mu)^2)} \right]$$

(5)

Once the value of the variable $x = \mu t$ has been determined, reference can be made to graphs which show the values of $(1 - e^{-x})/x$ as a function of $x$, and the divergence factor

$$\left( 1 + \frac{2}{(f/\mu)} + \frac{2}{((f/\mu)^2)} \right)$$

as a function of $f/\mu$. Since such graphs are easily plotted from simple mathematical tables they will not be reproduced here.

Thus the integral doses in superficial therapy may be found by evaluating equation (5). However, before this can be done, it is necessary to evaluate $\mu$ (and hence $x$) for the given radiation conditions, i.e. quality, field area, and F.S.D. In accordance with the preceding calculations for harder radiation, $\mu$ was defined from the equation

$$\mu = \frac{10}{1} \log_6 \left( \frac{100}{D_{10}} \right)$$

when $D_{10}$ is the percentage depth dose at 10 cm. deep. It was found convenient to evaluate $\mu$ for the given conditions of a particular case in a series of stages. Firstly, it was evaluated for the given quality but for an F.S.D. of 30 cm. and a field area of 100 cm.², and then corrected by the addition of differentials to take account of the actual F.S.D. and field area.

By inspecting the central axis depth dose tables in the Supplement it was found that the 10 cm. depth dose may be represented by the approximation $D_{10} = m \log_{10}(KA)$, in which $A$ is the area of the field in cm.² and $m$ and $K$ are numerical parameters. A relationship of this sort holds at each quality and F.S.D. given in the tables in the Supplement. From these empirical equations we can study the variation of the parameters $K$ and $m$ with quality and F.S.D. It is found that $m$ is a linear function of $h$, the H.V.L. in mm. Al. For an F.S.D. of 30 cm., $m$ is given by the empirical relationship

$$m = 2.14 + 1.21h.$$
Radiation and Leukaemia

Substituting these values of \( m \) and tabulated values of the 10 cm. depth dose in 100 cm.\(^2\) fields, \((D_{10})_{100}\), (taken from the Supplement) in the relation

\[
\log_{10}(100K) = \frac{(D_{10})_{100}}{m}
\]

it is found that \( \log_{10}(100K) \) is almost constant, showing a variation of less than \( \pm 5 \) per cent from 1.90 for H.V.L.’s between 1 mm. Al and 8 mm. Al at 30 cm. F.S.D. Ignoring this small variation and putting \( \log_{10}(100K) = 1.90 \) for all conditions, we may express the depth dose at 10 cm. for a 100 cm.\(^2\) field as \((D_{10})_{100} = 1.9 \, m\). If we substitute this value, the apparent absorption coefficient in a 100 cm.\(^2\) field becomes

\[
(\mu)_{100}^{10} = \frac{1}{10} \log_e\left(\frac{100}{1.9m}\right)
\]

Substituting for \( m \) from the linear equation relating this parameter to quality we obtain a useful relationship in terms of H.V.L.

\[
(\mu)_{100}^{10} = \frac{1}{10} \log_e\left(\frac{100}{1.9}\right) - \log_e(2.14 + 1.21h)
\]

For any quality of radiation occurring in the survey this equation gives the value of \( \mu \) for a field area of 100 cm.\(^2\) and an F.S.D. of 30 cm. After multiplication by the thickness, \( t \), the solution of this equation is plotted (Fig. 4C). Taking the value of \((\mu)_{100}^{10}t\) from this figure is the first step in the estimation of that variable for the chosen conditions. Subsequent steps involve adding a correction for the required area at 30 cm. F.S.D. and finally a correction for the required F.S.D. These corrections are small and may be represented with sufficient accuracy by differentials

\[
\delta_A(x)_{100}^{10}, \quad \delta_f(x)_{100}^{10}
\]

so that we may write

\[
t \cdot (\mu)_{100}^{10} = t \cdot (\mu)_{100}^{10} + t \cdot \delta_A(\mu)_{100}^{10} + t \cdot \delta_f(\mu)_{100}^{10}
\]

In the following paragraphs these two differentials will be calculated from the equations already introduced, and from a study of the variation of the numerical parameter, \( m \), with F.S.D.

The differential with respect to area.

Since

\[
\Delta_A(D_{10})_{100}^{10} = (D_{10})_{100}^{10} - (D_{10})_{100}^{10},
\]

and

\[
\Delta_A(\mu)_{100}^{10} = (\mu)_{100}^{10} - (\mu)_{100}^{10},
\]

then it follows from the previous definition,

\[
\mu = \frac{1}{10} \log_e\left(\frac{100}{D_{10}}\right)
\]

that

\[
\Delta_A(\mu)_{100}^{10} = \frac{1}{10} \log_e\left(\frac{100}{(D_{10})_{100}^{10}}\right) - \log_e\left(\frac{100}{(D_{10})_{100}^{10}}\right)
\]

\[
= - \frac{1}{10} \log_e\left(\frac{(D_{10})_{100}^{10} + \Delta_A(D_{10})_{100}^{10}}{(D_{10})_{100}^{10}}\right)
\]

\[
= - \frac{1}{10} \log_e\left(1 + \frac{\Delta_A(D_{10})_{100}^{10}}{(D_{10})_{100}^{10}}\right)
\]
APPENDIX C

This can be expanded as the logarithmic series
\[ \Delta_d(\mu)_{100} = -\frac{1}{10} \frac{\Delta_d(D_{10})_{100}}{(D_{10})_{100}} + \text{higher powers}. \]

Ignoring higher powers of the small fraction \( \frac{\Delta_d(D_{10})_{100}}{(D_{10})_{100}} \), we may equate the differential \( \delta_d(\mu)_{100} \) with the first term of this series expansion, and it remains to substitute for \( \Delta \) and \( (D) \).

![Graph](image)

**Fig. 4C.** The variation of \( (\mu)_{10} \) with H.V.L. (mm. Al) for F.S.D. 30 cm. and field area 100 cm.²

From the approximate equation \( (D_{10})_{10}' = m \log_{10}(KA) \) it follows by subtraction that \( \Delta_d(D_{10})_{100} = m \log_{10} \left( \frac{A}{100} \right) \). Substituting for this and for \( (D_{10})_{100} \) in the expression for \( \delta_d(\mu)_{100} \) it follows that
\[ \delta_d(\mu)_{100} = -\frac{1}{10} \frac{m \log_{10} \left( \frac{A}{100} \right)}{1.9m} = -0.05263 \log_{10} \left( \frac{A}{100} \right). \]
It will be seen that the product \( t \cdot \delta_j(x)_{100}^{120} \) plotted in Fig. 5C, does not depend upon quality or F.S.D. Hence we may correct the value of \( x \) obtained from Fig. 4C by a small quantity dependent only on surface field area.

**The differential with respect to focal skin distance.** By a similar argument to that used in the preceding section it can be shown that

\[
\delta_j(\mu)_{100}^{120} = -\frac{1}{10} \frac{\Delta_j(D_{10})_{100}^{120}}{D_{10}^{120}}.
\]

We will now show that \( \Delta_j(D_{10})_{100}^{120} \) is independent of area. From the relationship

\[
(D_{10})_{120}^{100} = m \log_{10}(KA)
\]

it follows by differentiation that

\[
\frac{\delta(D_{10})_{120}^{100}}{\delta j} = \frac{\delta m}{\delta j} \log_{10}(KA)
\]
APPENDIX C

and since

\[ \Delta_f(D_{10})^{100}_{100} = \frac{\delta(D_{10})^{100}_{100}}{\delta f} \cdot \Delta f \]

substitution in the first equation gives

\[ \delta_f(\mu)^{30}_{100} = -\frac{1}{10m} \left( \frac{\delta m}{\delta f} \right) \cdot \Delta f. \]

If in order to find \( \frac{\delta m}{\delta f} \) we substitute the constant \( \log_{10}(100.K) = 1.90 \) for a 100 cm.² field area we see that

\[ \frac{\delta m}{\delta f} = \frac{1}{1.9} \frac{\delta(D_{10})^{100}_{100}}{\delta f}. \]

To evaluate this function, the values of \( (D_{10})^{100}_{100} \) were plotted against F.S.D. for the four qualities given in the tables in the Supplement. It was found that the available data could be well fitted with four linear functions of F.S.D. The slopes of the four lines show that \( \frac{\delta D_{10}}{\delta f} \) is almost linearly dependent upon quality. An approximate fit to the four values is given by the relationship*

\[ \left( \frac{\delta m}{\delta f} \right)^{30} = 0.026h + 0.066. \]

We may now evaluate the expression for \( \delta(\mu)^{30}_{100} \) in the quality range of interest from this equation and from the equation \( m = 2.14 + 1.21h \). This procedure leads to the value \( \delta_f(\mu)^{30}_{100} = -0.0025\Delta f \) which holds within a few per cent, independently of H.V.L. The calculation of \( x \) for the given radiation conditions is completed by the addition of the differential \( \delta_f(x)^{30}_{100} = -0.0025\Delta f \).

The foregoing mathematical analysis produced a fairly rapid method of calculating integral dose. Most of the mathematical investigation was required to develop a simple method of evaluating the parameters dependent on the apparent absorption coefficient. For various radiation qualities and field areas these parameters may be obtained by reference to Figs. 4C and 5C, with a further simple correction for focal skin distances other than 30 cm. Once these parameters have been evaluated, the integral doses for superficial therapy conditions may be obtained by reference to graphs of the terms in equation (5).

We are most grateful to Professor W. V. Mayneord, in whose department this work was carried out, for his encouragement and advice in the early stages. We should also like to thank those of our colleagues who assisted in the tedious computation and recording of results.

* Confirmation of this approximation is found by using the different linear relationships for \( m \) with quality as at the three F.S.D.'s (15, 20, 30 cm.) given in the tables. Between 30 and 20 cm., \( \Delta \left( \frac{\delta m}{\delta f} \right) \) has the value 0.027. Since \( \frac{\delta}{\delta h} \left( \frac{\delta m}{\delta f} \right) = \frac{\delta}{\delta h} \left( \frac{\delta m}{\delta f} \right) \) this is in good agreement with 0.026 above.
APPENDIX D

Estimate of Error in the Calculation of the Dose-Response Relationship

1. RANDOM ERRORS

(a) Error arising from the use of a sample of the patients to provide data for estimating the total numbers of patients given different doses

Since the numbers of patients in each sample ranged from one fifteenth to one half of the numbers in the corresponding treatment classes, the distribution of dose among the patients remaining after part of the sample had been drawn must have been appreciably affected by the distribution of dose in the first part of the sample. Because of this, the probable limits of the number of sample patients who had received a dose given to a proportion, \( p \), of the parent population are less than the limits calculated from the binomial distribution. The theoretical distribution of the number of sample patients would be hypergeometric, and the 5 per cent limits are, therefore, given approximately by:

\[
np \pm 1.96 \sqrt{pqn (N-n) (N-1) / N-1}
\]

where \( N \) is the number in the parent population, \( n \) is the number in the sample, and \( q = 1 - p \).

Practically the whole sample of the population receiving 2,250 r. or more was drawn from the classes of patients receiving (a) three courses of treatment, (b) four or more courses of treatment, and (c) treatment at two or more centres. If these groups are considered as a whole,

\[
N = 2,922, \quad n = 1,097, \quad p = 0.0708 \quad \text{and} \quad q = 0.9292.
\]

Hence, the limits of the number of patients given 2,250 r. or more which might be expected to be found in the sample are,

\[
77 \pm 13.15
\]

and the over- or underestimate of the size of the corresponding population is unlikely to be more than,

\[
\frac{13.15}{77} \times 100 = 17 \text{ per cent.}
\]

For the populations receiving smaller doses, the probable limits of the over- or underestimates will be appreciably less.

(b) Error arising from the small number of cases of leukaemia

The numbers of patients treated at the different levels of dose are very large in comparison with the numbers of cases of leukaemia observed. In replicate experiments the observed numbers would, therefore, be distributed according to the Poisson distribution, and in this case the limiting values of the means—such that the numbers actually observed, or more extreme numbers, would occur with a probability of less than 0.05—are given by Fisher and Yates (1948) in their Table VIII. To obtain the limiting values after standardization for age, the values obtained from the table were multiplied by the weights required to standardize the observed numbers. The limiting values of the standardized rates were then obtained by dividing the products by the corresponding populations at risk (Table 1D).
APPENDIX D

TABLE 1D
The limiting values of the standardized incidence rates per 10,000 man-years

<table>
<thead>
<tr>
<th>Dose (r.)</th>
<th>Limiting values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 500</td>
<td>1.09 x 0.9167 to 10.24 x 0.9167</td>
</tr>
<tr>
<td></td>
<td>1.8523</td>
</tr>
<tr>
<td></td>
<td>1.8523</td>
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<td>500–999</td>
<td>4.80 x 1.0153 to 18.39 x 1.0153</td>
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<td>2.1780</td>
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<td>1,000–1,499</td>
<td>5.49 x 1.2246 to 19.69 x 1.2246</td>
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<td>1,500–2,249</td>
<td>2.20 x 1.1609 to 13.06 x 1.1609</td>
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<td>0.4926</td>
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<td>2,250 or more</td>
<td>2.20 x 1.1341 to 13.06 x 1.1341</td>
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2. SYSTEMATIC ERRORS

(a) Error arising from the assumption that the distribution of dose in the sample patients for whom it proved impossible to obtain dosage data was comparable to that in patients for whom data were obtained

The numbers of patients selected to be in the samples for the five treatment classes, and the numbers for whom dosage data were obtained, are given in Table 14 (p. 26). The failure to obtain dosage data for a very small proportion of male patients cannot have appreciably affected the results in four of these samples. However, in the fifth sample, that of male patients treated at two or more centres, data were missing for 12 per cent of the cases. In the body of the Report it was assumed that the total doses received by these patients were similar to those received by the other 88 per cent of the sample; but it is possible that some of the data were not obtained because all the patients were not, in fact, treated at all the centres. If, therefore, it is assumed that no treatment was given at the centres for which data are missing, the maximum effect of this type of error will be allowed for; the modified figures are given in Table 2D (p. 127).

(b) Error arising from failure to recognize as the same person, persons of the same name treated at different centres

Patients treated at two or more centres presented a problem of identification which could not always be solved. There was little difficulty so long as one of the centres referred to treatment at the other, but in the case of 6 per cent of the patients for whom treatment at two or more centres was finally confirmed, there was no indication that treatment had been given elsewhere. Identification was then made by comparing the data collected from the different centres for persons of the same name, and finding, for example, that the addresses and ages were the same, or that the same Ministry of Pensions number had been recorded for all of them. Identity was finally established for 1,027 persons, some of whom had been treated at as many as four centres. Many other instances were recorded in which there was suggestive evidence of identity, but, in the absence of proof,
these patients were regarded as separate individuals. Consequently the study series must include a number of patients who have been recorded as having received small or moderate doses of radiation, when, in fact, the same total amount of radiation has been concentrated on half, or less than half, that number of cases; and the estimates of the numbers of persons receiving different doses must be correspondingly inaccurate.

The extent of the error can be evaluated by postulating that those persons whose names and ages corresponded were, in fact, identical. Such a postulate will undoubtedly result in an overestimate of the number of patients given large doses, and the true values will lie somewhere between the two calculated limits. Examination of the record cards indicated that 329 entries were reasonably likely to represent only 162 persons treated at two or more centres. The numbers of man-years at risk following different levels of dose have accordingly been re-calculated on the assumption that these entries related to only 162 patients; the relevant figures are given in Table 2D.

(c) *Error arising from the exclusion from the survey of patients treated privately, abroad, or at a centre whose designation was unknown, before treatment was given at one of the co-operating centres*

This group of 198 patients was excluded because it would have been difficult, if not impossible, to obtain all the relevant dosage data for its members. As far as is known, no case of leukaemia subsequently occurred in the group, and the effect of its exclusion has been to reduce the number of relatively heavily treated patients (since, by definition, all the patients had been treated at least twice) without bringing about any compensatory reduction in the number of patients with leukaemia. An estimate of the effect this has had on the calculation of the dose-response relationship can be made by including the group in the study series and assuming that the patients in it were subject to the same distribution of dose as the patients known to have had treatment at two or more centres for whom dosage data had been obtained. An estimate was made of the number of man-years at risk following different levels of dose after inclusion of this group of patients and on the assumption made in section 2(b) above; the relevant figures are given in Table 2D.

(d) *Error arising from the failure to include in the survey every patient treated for ankylosing spondylitis at the co-operating centres since January 1st, 1935*

It is known that at some centres every patient who should have been included was not discovered, but it is believed that this arose from defects in the system of record-keeping and that it has not biased the results materially where it affected patients treated at only one centre. On the other hand, where it affected patients treated also at a second centre it must have resulted in an understatement of the total dose received. For example, one patient who developed leukaemia (Case 40) was initially reported as having received a mean spinal marrow dose of 1,044 r. at one centre in 1949; but the notes of the hospital where he was treated for his terminal illness revealed that he had also been treated at another centre in 1950. Inquiry at the second centre showed that he had been given a further mean spinal marrow dose of 346 r. there; it was not known that the patient had died, and no reason could be discovered for his records having been overlooked initially.

It has not been possible to make an accurate estimate of the extent to which this source of error has resulted in understatement of the doses received by
patients in the study series as a whole, but an approximate estimate has been made with the assistance of the Ministry of Pensions. Dr. A. J. Lea, one of the Ministry's medical officers, chose at random (by means of a table of random numbers) a sample of 145 Service pensioners with ankylosing spondylitis who had been treated by radiotherapy. He extracted from the records all reference to the centres at which the men had been treated and the dates of treatment, and checked the statements against those recorded for the same patients in the present study. Of the 145 pensioners, 110 had been included in the study and the pensions records provided evidence of additional treatment in four cases: one man was said to have been treated abroad, one privately, one at an undesignated centre in the Forces, and only one had had an additional treatment at one of the co-operating centres. Service pensioners had, as a rule, been treated before 1948, when records were least complete, so that the results of this inquiry are likely to have overestimated the deficiency in the records of treatment for the whole series. It is, therefore, reasonable to believe that the maximum effect of error resulting from incomplete reporting of patients would be overestimated if it were assumed that the records of treatment in the study series were defective in 5 per cent of patients.

To test the effect of such an assumption, 5 per cent of the patients treated at one centre were subtracted from their respective treatment classes and were added to the group of patients treated at two or more centres; the dose they received was estimated from the experience of the sub-sample of patients treated at two or more centres for whom detailed dosage data were available. Figures for the man-years at risk at the various levels of dose, modified in accordance with this section and with sections 2(b) and (c) above, are given in Table 2D.

Standardized incidence rates, calculated for the limiting populations estimated in accordance with sections 2(a) and sections 2(b), (c) and (d), are given in Table 3D.

### TABLE 2D

*Estimates of the number of man-years at risk following exposure to different levels of dose: (a) as used in the Report and, (b) as modified to allow for the maximum effect of the possible types of systematic error*

<table>
<thead>
<tr>
<th>Estimates of number of man-years at risk</th>
<th>Mean dose to spinal marrow (r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Less than 500</td>
</tr>
<tr>
<td>(a) As used in Report (Table 16, p. 30)</td>
<td>18,523</td>
</tr>
<tr>
<td>(b) As modified in accordance with:</td>
<td></td>
</tr>
<tr>
<td>Section 2 (a)</td>
<td>18,650</td>
</tr>
<tr>
<td>Section 2 (b)</td>
<td>18,183</td>
</tr>
<tr>
<td>Section 2 (b) and (c)</td>
<td>18,439</td>
</tr>
<tr>
<td>Section 2 (b), (c) and (d)</td>
<td>18,250</td>
</tr>
</tbody>
</table>
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RADIATION AND LEUKAEMIA

TABLE 3D

Standardized incidence rates for leukaemia calculated for the limiting populations estimated in accordance with section 2 (a) and sections 2 (b), (c) and (d) above

<table>
<thead>
<tr>
<th>Mean dose to the spinal marrow (r.)</th>
<th>Less than 500</th>
<th>500-999</th>
<th>1,000-1,499</th>
<th>1,500-2,249</th>
<th>2,250 or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>Man-years at risk estimated on basis of section 2 (a)</td>
<td>18,650</td>
<td>21,712</td>
<td>15,648</td>
<td>4,842</td>
<td>901</td>
</tr>
<tr>
<td>Incidence per 10,000 men per year</td>
<td>1-97</td>
<td>4-68</td>
<td>7-25</td>
<td>14-61</td>
<td>75-16</td>
</tr>
<tr>
<td>Man-years at risk estimated on basis of section 2 (b), (c), and (d)</td>
<td>18,250</td>
<td>21,976</td>
<td>16,323</td>
<td>5,630</td>
<td>1,180</td>
</tr>
<tr>
<td>Incidence per 10,000 men per year</td>
<td>2-02</td>
<td>4-56</td>
<td>6-92</td>
<td>12-71</td>
<td>58-51</td>
</tr>
</tbody>
</table>

3. THEORETICAL ERRORS

(a) Error arising from the hypothesis adopted about the length of the latent period in leukaemia

In order to calculate the number of years for which the population had been exposed to risk it was necessary to make some postulate about the length of the latent period. In the body of the Report it has been assumed that leukaemia is equally likely to appear at any time after irradiation with the exception of the first year. An extreme contrasting hypothesis, which is still within the limits of reasonable probability, would be that the relative risk of the disease developing is nil in the first year, 0-1 in the second, 0-5 in the third, 1-0 in the fourth and fifth, 0-5 in the sixth, and 0-1 in all subsequent years after irradiation. On this hypothesis, a man who received a mean spinal marrow dose of 400 r. in 1938, 400 r. in 1939, 800 r. in 1942 and 700 r. in 1949 would be regarded as having been exposed to risk equivalent to treatment with the following doses:

For the 1st year following treatment in 1938 0 r.
   " 2nd" " " " " " " " " " 40+ 0 r.
   " 3rd" " " " " " " " " " 200+ 40 r.
   " 4th" " " " " " " " " " 400+200 r.
   " 5th" " " " " " " " " " 400+400+ 0 r.
   " 6th" " " " " " " " " " 200+400+ 80 r.
   " 7th" " " " " " " " " " 40+200+400 r.
   " 8th" " " " " " " " " " 40+ 40+ 800 r.
   " 9th" " " " " " " " " " 40+ 40+ 800 r.
   "10th" " " " " " " " " " 40+ 40+400 r.
  " 11th" " " " " " " " " " 40+ 40+ 80 r.
   "12th" " " " " " " " " " 40+ 40+ 80+ 0 r.
   " 13th" " " " " " " " " " 40+ 40+ 80+ 70 r.
  " 14th" " " " " " " " " " 40+ 40+ 80+350 r.
   " 15th" " " " " " " " " " 40+ 40+ 80+700 r.
   " 16th" " " " " " " " " " 40+ 40+ 80+700 r.
   " 17th" " " " " " " " " " 40+ 40+ 80+350 r.
and for the last half of 1955 40+ 40+ 80+ 70 r.
APPENDIX D

Similar calculations have been carried out for each of the 1,878 men in the sample for whom full radiation data were extracted, and an estimate has been made of the total number of man-years for which the patients have been exposed to risk following various levels of dose. The results are shown in Table 4D, together with the number of cases observed after each level of 'equivalent' dose and the corresponding annual incidence rates. On the present hypothesis the increase in incidence with dose is less regular than on the hypothesis used in the body of the Report; but there is clearly no evidence of a threshold dose below which no increase occurs, nor is there any indication that the incidence at higher dose levels increases more rapidly than would be expected from a linear relationship.

TABLE 4D

Data on the incidence of leukaemia among the sample patients, calculated on the basis of the hypothesis discussed in section 3 (a)

<table>
<thead>
<tr>
<th>Mean equivalent dose to spinal marrow (r.)</th>
<th>0†</th>
<th>Less than 100</th>
<th>100–249</th>
<th>250–499</th>
<th>500–749</th>
<th>750–999</th>
<th>1,000–1,249</th>
<th>1,250 or more†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of man-years exposed to risk . . .</td>
<td>20,452</td>
<td>12,568</td>
<td>11,033</td>
<td>7,563</td>
<td>4,623</td>
<td>3,649</td>
<td>2,177</td>
<td></td>
</tr>
<tr>
<td>No. of cases of leukaemia . . .</td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>11</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Incidence per 10,000 men per year . . .</td>
<td>0–49</td>
<td>2.44</td>
<td>2.37</td>
<td>5.44</td>
<td>14.54</td>
<td>8.65</td>
<td>10.96</td>
<td>18.37</td>
</tr>
</tbody>
</table>

* The rate given for 'zero' dose represents the corresponding incidence among men of the same age-distribution as those in the study series and observed over the same period, calculated from the mortality from leukaemia experienced by the whole male population of Britain.
† Mean dose, 1,445 r.
APPENDIX E

Workers Participating in the Investigation

*Statistical Research Unit, Medical Research Council*

Miss P. M. Aylward  
Mrs. N. E. Berger  
Mrs. C. Brett-Smith  
Dr. R. Doll*  
Mrs. J. Gilliland  
Mrs. M. Glyn  
Miss B. Hafner

*Institute of Cancer Research, Royal Cancer Hospital*

Miss A. Alberts  
Miss P. E. Davis  
Mr. C. W. Dickens  
Mr. J. Geilingen  
Radiobiological Research Unit, Medical Research Council

Mr. D. G. Jones  
Dr. J. H. Mulvey*  

*Social Medicine Research Unit, Medical Research Council*

Mr. C. Daly  
Dr. A. J. Lea*  

*Ministry of Pensions and National Insurance*

Mr. A. T. Davey  
Mr. C. F. Doré  
Mr. W. C. Lister  

*National Institute for Medical Research*

Mr. R. E. Ellis  
Department of Radiotherapy, Middlesex Hospital

Sister K. M. Leyland  
Department of Physics, Mount Vernon Hospital

Mr. D. E. A. Jones  
Department of Social Medicine, University of Oxford

Mr. D. Hewitt*  
Dr. Alice Stewart*  

Department of Radiotherapy, Churchill Hospital, Oxford

Dr. F. Ellis*  
Department of Radiotherapy, Royal Infirmary, Edinburgh

Dr. W. D. Rider*  

Department of Radiotherapy, University College Hospital

Dr. N. Howard  
Postgraduate Medical School of London

Dr. J. D. Abbatt (M.R.C. Staff)*  
Miss F. M. Callaby (M.R.C. Staff)  
Dr. W. M. Court-Brown (M.R.C. Staff)*

Headquarters Staff, Medical Research Council

Dr. Joan Faulkner*

* Members of the visiting teams.
APPENDIX F

Radiotherapy Centres Co-operating in the Investigation*

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<th>RADIOThERAPIST</th>
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</thead>
<tbody>
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<tr>
<td>Ashton-under-Lyme</td>
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<tr>
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<td>Dr. A. A. G. Fleming</td>
</tr>
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<td>Dudley Road Hospital</td>
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</tr>
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</tr>
<tr>
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<td>Dr. F. E. Chester-Williams</td>
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<td>Westminster Hospital</td>
<td>Dr. F. M. Allehin</td>
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* Includes the centre at which the records were not examined.
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REFERENCES


DUNLAP, C. E. (1942). Effects of radiation on the blood and the haemopoietic tissues, including the spleen, the thymus, and the lymph nodes. Arch. Path., 34, 562.


REFERENCES


