EXPERIENCE WITH CORTISONE IN THE MANAGEMENT OF RHEUMATOID ARTHRITIS*

REPORT OF A CO-OPERATIVE STUDY CONDUCTED BY A COMMITTEE OF THE AMERICAN RHEUMATISM ASSOCIATION†

(RECEIVED FOR PUBLICATION OCTOBER 6, 1955)

At a meeting of the American Rheumatism Association held in Chicago in June, 1952, a preliminary report was presented of the co-operative clinical trial of ACTH, cortisone, and aspirin in the treatment of rheumatic fever, sponsored by the Medical Research Council of Great Britain and the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association (Joint Report, 1955). This report aroused such interest that it was decided to consider undertaking a similar study of cortisone in the treatment of rheumatoid arthritis. The feasibility of such a study was discussed by an ad hoc committee consisting of Drs Joseph J. Bunim, Gideon K. deForest, Richard Freyberg, William Kammerer, Donald Mainland, Currier McEwen, Felix Moore, Charles Ragan, William Robinson, Edward Rosenberg, Charles L. Short, Charles Slocumb, Charley J. Smyth, and Morris Ziff. The difficulties encountered in the co-operative study of rheumatic fever were weighed, as were the still greater difficulties inherent in a similar study of such a chronic and variable disease as rheumatoid arthritis. It was agreed that it would not be advisable at that time to embark on a “forward-moving” study of new cases—as had been done in the rheumatic fever study—but that it would be worth while to undertake a retrospective analysis of data already accumulated in a selected group of clinics.

Support for the study was provided by the Arthritis and Rheumatism Foundation. Miss Claire Lingg was appointed staff statistician and Mrs. Esther Bigus co-ordinating secretary. Letters were written to the chiefs of a large number of selected clinics in the United States and Canada, of whom the following joined the project:

Dr. Arthur W. Bagnall, Vancouver General Hospital, Vancouver, B.C., Canada.

Dr. Walter Bauer and Dr. Charles L. Short, Massachusetts General Hospital, Boston, Mass.
Dr. Theodore B. Bayles, Robert B. Brigham Hospital, Boston, Mass.
Dr. Paul J. Bilka, University of Minnesota Hospital, Minneapolis, Minn.
Dr. Gideon K. deForest, Grace-New Haven Community Hospital, New Haven, Conn.
Dr. Ephraim P. Engleman, Veterans Administration Hospital and Regional Office, San Francisco, Cal.
Dr. Dwight C. Ensign, Henry Ford Hospital, Detroit, Mich.
Dr. Richard Freyberg, Hospital for Special Surgery, New York, N.Y.
Dr. Wallace Graham, Sunnybrook Hospital, St. Michael’s Hospital, and Toronto General Hospital, Toronto, Canada.
Dr. Edward Hartung, Fourth (N.Y.U.) Division, Bellevue Hospital, New York, N.Y.
Dr. Philip Hench and Dr. Charles Slocumb, Mayo Clinic, Rochester, Minn.
Dr. W. Paul Holbrook, Southwestern C. & R.I., Tucson, Ariz.
Dr. Joseph L. Hollander, Hospital of the University of Pennsylvania, Philadelphia, Pa.
Dr. William Kammerer, New York Hospital, New York, N.Y.
Dr. John Lansbury, Temple University Hospital, Philadelphia, Pa.
Dr. Melvin Levin, Veterans Administration Hospital, Los Angeles, Cal.
Dr. James J. Lightbody, The Harper Hospital, Detroit, Mich.
Dr. L. Maxwell Lockie, Buffalo General Hospital, Buffalo, N.Y.
Dr. Currier McEwen and Dr. Morris Ziff, Third (N.Y.U.) Division, Bellevue Hospital, New York, N.Y.
Dr. Charles Ragan, Faulkner Clinic, Columbia Presbyterian Medical Center, New York, N.Y.
Dr. William Robinson, University Hospital, Rackham Arthritis Research Unit, Ann Arbor, Mich.
Dr. Edward F. Rosenberg, Michael Reese Hospital, Chicago, Ill.
Dr. Richard T. Smith, Benjamin Franklin Clinic, Philadelphia, Pa.
Dr. Charley J. Smyth, Colorado General Hospital, Denver, Col.
Dr. Robert M. Stecher and Dr. Anita Ausenbachs, Cleveland City Hospital, Cleveland, Ohio.
Dr. Otto Steinbrocker, Lenox Hill Hospital, and Hospital for Joint Diseases, New York, N.Y.

* This study was supported by a grant from the Arthritis and Rheumatism Foundation.
† The Committee responsible for preparing the report consisted of: Dr. Currier McEwen (Chairman), Dr. Richard Freyberg, Dr. William Kammerer, Miss Claire Lingg, Dr. Donald Mainland, Dr. Charles Ragan, Dr. Charles Short, and Dr. Morris Ziff.
Objectives

1. To obtain information that would enable the American Rheumatism Association (or other group) to decide whether a controlled comparison of various treatments of rheumatoid arthritis is feasible, and if so, how it could best be planned;
2. To ascertain the experience of certain clinics, during a certain time period, in the treatment of rheumatoid arthritis with cortisone;
3. To look for differences in response that might appear to be related to certain features in the patients or to the mode of treatment;
4. To look for differences between the reports of different clinics regarding outcome and to seek for hints of possible explanations;
5. To form an impression of the facilities of the clinics and of their suitability for possible co-operation in a subsequent controlled comparison of different treatments.

Method

Early in the study the following criteria for admitting patients to the project were agreed on:
1. Patients must have straightforward rheumatoid arthritis of peripheral joints.
2. Cortisone must have been the main therapeutic agent used.
3. The arthritis must have been present for at least 6 months before the administration of cortisone.
4. Only patients would be included who had been observed by the participating physician for a period of at least one year since the initiation of cortisone, and the patient must have received cortisone continuously,* in doses not smaller than 15 mg. daily, with the following exceptions:
   a. dosage stopped because of sustained remission;
   b. dosage stopped because of toxicity;
   c. dosage reduced or discontinued temporarily for observation of patient's response;
   d. dosage discontinued because of inadequate benefit to the patient.

The criteria adopted by the American Rheumatism Association (Steinbrocker, Traeger, and Batterman, 1949) were used:

<table>
<thead>
<tr>
<th>Stage of Disease</th>
<th>Class of Functional Capacity</th>
<th>Grade of Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>I—Early (osteoporosis, but no destructive radiological changes; no nodules or tenosynovitis).</td>
<td>I—Completely normal.</td>
<td>I—Complete remission (no positive laboratory or systemic signs of rheumatoid activity; irreversible anatomical changes may persist).</td>
</tr>
<tr>
<td>II—Moderate (slight cartilage or bone destruction; nodules and tenosynovitis may be present in this and more advanced stages).</td>
<td>II—Limited (performs few or none of the duties of usual occupation or self-care).</td>
<td>II—Major improvement (minimal residual joint swelling and activity may persist).</td>
</tr>
<tr>
<td>III—Severe (cartilage and bone destruction, extensive muscle atrophy, subluxation, ulnar deviation).</td>
<td>III—Incapacitated (little or no self-care).</td>
<td>III—Minor improvement (joint inflammation only partially resolved).</td>
</tr>
<tr>
<td>IV—Terminal (Stage III plus ankylosis).</td>
<td></td>
<td>IV—No improvement or worse (laboratory and clinical data same or worse).</td>
</tr>
</tbody>
</table>

* For the purposes of the study, "continuously" includes those patients who may have stopped cortisone temporarily, but in whom the intent was continuous treatment.

In order to make the collection of data as comparable as possible, special printed forms were adopted for the recording of information (opposite).

Limitations of the Method.—From the outset it was clear that a retrospective analysis of this sort would have certain drawbacks; and other limitations became apparent as the study progressed. Such an analysis, for example, does not permit detailed recording of new observations during the study, but must make use of data already recorded by clinicians who made their original entries with no idea that they would subsequently become part of a statistical investigation. Furthermore, many of the data had been recorded on the original clinic charts several years before the study began and the workers who transferred these data to the official forms (Figure 4) were not in many instances those who had recorded the original observations. This difficulty was made greater by the fact that the stage and class of disease and the grade of response were recorded at clinic visits in only a few clinics, so that observers who knew the patients only slightly, if at all, often had to translate clinical notes into terms of the official criteria.

It should constantly be borne in mind that the study was primarily designed to ascertain the amount and kind of information that was available. It did not, therefore, meet the requirements of a definitive study. These requirements and a discussion of the limitations of the survey method are presented in a companion article (Mainland, 1955) which immediately follows this report. In the analysis, attention was confined to those statements and figures that had the appearance of being most reliable. If, however, it had been possible to make, at each clinic, a proper study of the numerous factors influencing the figures and other statements that were received, some of the estimates and inferences presented here might have been different.

The Sample

Forms were collected for a total of 608 patients from the various clinics, of which 62 had to be eliminated because of incompleteness or obvious unreliability, leaving 546 which form the basis of this analysis. The question of bias in selection of patients was obviated by including only patients from those clinics which submitted data on their total patient population which met the criteria. The patients all had been under observation for at least one year since the start of cortisone therapy and many had been under treatment and observation for longer periods between 1949, when cortisone first became available, and May 1, 1953, the closing date for submitting forms for inclusion in the analysis. Some patients had been under treatment throughout this period, but others only during the early or later parts of it. Clearly, it was a period of change in methods of selecting patients for cortisone and in schedules of dosage.
<table>
<thead>
<tr>
<th>Name</th>
<th>Sex</th>
<th>Date of birth (month - day - year)</th>
<th>Institution</th>
<th>Patient's Chart No.</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

**A.R.A. COOPERATIVE STUDY OF CORTISONE THERAPY IN RHEUMATOID ARTHRITIS**

### 1. DIAGNOSIS
- Rheumatoid arthritis (peripheral) Y N
- Spondylitis (spine and sacro-iliac only) Y N
- Spondylitis with hip and/or shoulder involvement Y N
- Spondylitis with peripheral joints Y N
- Psoriasis present Y N
- Psoriasis with terminal I-P involvement Y N

### 2. START OF CORTISONE THERAPY *
- (Encircle which)
  - Before Menopause
  - During Menopause
  - After Menopause

### 3. DOSAGE - Mgs. (approximate daily average by months)

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<th>8</th>
<th>9</th>
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<th>12</th>
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<th>19</th>
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<td>32</td>
<td>33</td>
<td>34</td>
<td>35</td>
<td>36</td>
</tr>
</tbody>
</table>

### 4. Result of Treatment
- Before Cortisone XXXX
- After 2 weeks
  - 1 month
  - 3 months
  - 6 months
  - 9 months
  - 12 months
  - 15 months
  - 18 months
  - 21 months
  - 24 months
  - 27 months
  - 30 months
  - 33 months
  - 36 months

### 5. CORTISONE STOPPED PERMANENTLY
- Date stopped month day year
- Reason (encircle which)
  - Remission
  - Partial remission
  - Inadequate benefit
  - Worse
  - Toxicity**
  - Other**

### 6. NODULES at start of Cortisone*
- Present Y N
- Change during treatment (encircle which)
  - Unchanged
  - Increased
  - Decreased
  - Disappeared

### 7. PSORIASIS at start of Cortisone*
- Present Y N
- Change during treatment (encircle which)
  - Unchanged
  - Increased
  - Decreased
  - Disappeared

### 8. ONSET OF DISEASE

<table>
<thead>
<tr>
<th>Result</th>
<th>month</th>
<th>year</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

### 9. ONSET OF THIS ATTACK

<table>
<thead>
<tr>
<th>Result</th>
<th>month</th>
<th>year</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

### 10. OTHER DISEASES - at start of Cortisone*
- Tuberculosis** Y N
- Diabetes mellitus** Y N
- Hypertension Y N
- Peptic ulcer** Y N
- Psychoneurosis** Y N
- Other** Y N

### 11. JOINTS INVOLVED at start of Cortisone*
- Hand
- Wrist
- Elbow
- Shoulder
- Foot
- Ankle
- Knee
- Hip
- Spine
- Jaw

### 12. PREVIOUS THERAPY
- Gold Y N
- Cortisone Y N
- Corticotropin Y N
- Other** Y N

### 13. CONCOMITANT THERAPY
- Helpful (yes, no, doubtful)

<table>
<thead>
<tr>
<th>Result</th>
<th>Date appeared</th>
<th>Duration</th>
<th>Cortisone (continued, reduced, stopped)</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
</tbody>
</table>

### 14. SIDE EFFECTS
- Glycosuria
- Fluid retention**
- Psychosis**
- Peptic ulcer**
- Thrombosis**
- Pathological fracture
- Infection**
- Masking of infection**

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Result</th>
<th>Date appeared</th>
<th>Duration</th>
<th>Cortisone (continued, reduced, stopped)</th>
</tr>
</thead>
<tbody>
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<td></td>
</tr>
</tbody>
</table>

### 15. FOLLOW UP
- Patient still under observation Y N
- Patient died Y N month day year
- Cause of death
- Patient left study Y N month day year
- Reason

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* By participating clinic. ** Amplify on reverse side.

(Signed) __________________________ M. D.

Date: __________________________

Answer every question. Leave no blanks. Where the answer is unknown, write “NR” (No Record).
All patients, of course, met the requirements noted above (p. 326). These were considered essential to ensure the inclusion of only genuine cases of rheumatoid arthritis. However, the requirements themselves introduced several difficulties. For example, a patient in whom cortisone had been tried previously and found either ineffective or "toxic" would probably not get into the series.

Age at Onset of Disease.—Four patients were under 5 years of age at the onset of their disease, and three patients were over 80. In only slightly more than 4 per cent. was the age at onset of disease under 15. The frequency of first episodes rose rapidly from age 15 to age 30, remained high to age 60, and then fell rapidly. Fully three-quarters of the patients had experienced the onset of disease between the ages of 25 and 60 years.

It is not possible to determine accurately the age incidence of a disease from data such as these, because one does not know the number of persons at a given age in the general population from which these patients were drawn who might have attended these clinics had they been attacked. Therefore, we have chosen not to show the foregoing figures, and those in the following paragraphs, in graph form lest they appear to possess an accuracy which would be unwarranted.

Age at Start of Cortisone Therapy.—Three patients were under 5 years of age at the start of treatment and four were over 80. Only 3 per cent. of the males and 5 per cent. of the females were under 20 and most of them were between 35 and 60 years of age. This doubtless reflects in part the relative rarity of the disease before maturity, but probably also the rarity of children in many of the clinics.

Sex.—Of the 546 patients, 37 per cent. were males and 63 per cent. females.

Duration of Disease at Start of Cortisone Therapy.—The duration of disease ranged from less than one to more than 24 years. Duration was less than 4 years in roughly 25 per cent., less than 8 in roughly 50 per cent., and more than 12 in roughly 25 per cent.

Previous and Concomitant Therapy.—The question forms provided space for the clinic physicians to record previous and concomitant therapy as well as their own and the patient's appraisal of benefit induced. All patients had received some form of drug therapy before entering the study. Gold compounds had been used in roughly 60 per cent. and short courses of corticotropin or cortisone in about 30 per cent. Most had received salicylates. Similarly, during the present period of study, gold compounds were given concurrently to about 20 per cent. of the patients, phenylbutazone to about 20 per cent., and salicylates to about 70 per cent. The information obtained regarding the apparent effects of these agents was too incomplete to justify presentation, except that the great majority of patients and physicians considered concomitant salicylates helpful.

Analysis of the Data

Disposition of Patients at End of Study.—At the end of the study, 432 patients were still under observation, of whom approximately 60 per cent. were still receiving cortisone. The remaining 114 patients of the original 546 were no longer available. Of these, 29 (5 per cent. of the total) had died, and 85 (16 per cent. of the total) had been lost to the study for a variety of reasons: about one-quarter because of dissatisfaction resulting from "toxicity" or lack of benefit, about one-third because of transfer to care by other physicians or movement to another community, and about one-fifth because of failure to co-operate. It is probably safe to assume that, saving for the ten who moved to other communities, most of these patients were not satisfied with the results.

Table I (opposite) shows certain data on the 29 patients who died. Probably some of these deaths were related to the cortisone therapy, whereas such a relationship appears most unlikely in others. However, information regarding all possible untoward effects of cortisone is still too meagre to decide which of these deaths were and which were not influenced by therapy.

Dosage.—During the first few weeks or months of cortisone therapy, the dose used is relatively large in many clinics and rather wide variations in the amount given are frequent from week to week. In analysing the dosage schedules employed, therefore, the first 3 months of treatment were excluded. In 43 per cent. of the patients the average daily dose after the third month of treatment was not more than 50 mg.; conversely, in 57 per cent. it was more than 50 mg. Since the more seriously ill patients would be expected to require the larger doses, it was not surprising to find that those taking more than 50 mg. daily tended to receive cortisone longer than those taking 50 mg. or less. Conversely, it was not unexpected to find that considerably more of the patients receiving the smaller doses went into remission (23 per cent.) than of those receiving the larger doses (7 per cent.).

Undesirable Occurrences during Cortisone Therapy.—The untoward events in patients receiving cortisone are usually referred to as "effects" of treatment. For the purposes of this report it has seemed preferable to call these "occurrences", because it is not always possible to be certain whether or not the hormone was the cause. In most instances, however, it is reasonable to suppose that these undesirable occurrences were, in fact, related to the therapy.

For purposes of this discussion the undesirable occurrences were separated into those considered of major significance and those of minor importance. This is, of course, an arbitrary distinction and not all readers will agree on the category into which the
CORTISONE IN THE MANAGEMENT OF RHEUMATOID ARTHRITIS

TABLE I
DEATHS WHILE UNDER OBSERVATION
(29 Patients)

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Sex</th>
<th>Age at Death</th>
<th>Cause of Death</th>
<th>Age at Death</th>
<th>Cause of Death</th>
<th>Age at Death</th>
<th>Cause of Death</th>
<th>Age at Death</th>
<th>Cause of Death</th>
<th>Age at Death</th>
<th>Duration of Cortisone Therapy (mths)</th>
<th>Reason for Stopping Cortisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant rheumatoid arthritis</td>
<td>F</td>
<td>48</td>
<td>x</td>
<td>4</td>
<td>20</td>
<td>Worse</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Disseminated lupus erythematosus and cerebral thrombosis</td>
<td>M</td>
<td>49</td>
<td>2½</td>
<td>1</td>
<td>Inadequate benefit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute bacterial endocarditis</td>
<td>M</td>
<td>60</td>
<td>x</td>
<td>19</td>
<td></td>
<td>Operation for cancer</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>F</td>
<td>50</td>
<td>1</td>
<td>26</td>
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<td></td>
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<tr>
<td>Transverse colon</td>
<td>M</td>
<td>42</td>
<td>x</td>
<td>22</td>
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<td></td>
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<tr>
<td>Myocardial infarction</td>
<td>M</td>
<td>56</td>
<td>x</td>
<td>3</td>
<td>Fluid retention—probably myocardial failure</td>
<td></td>
<td></td>
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<tr>
<td>Cardiac decompensation</td>
<td>M</td>
<td>80</td>
<td>1</td>
<td>8</td>
<td>Inadequate benefit</td>
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<td></td>
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<tr>
<td>Cerebral haemorrhage</td>
<td>M</td>
<td>64</td>
<td>2</td>
<td>11</td>
<td>Phlebitis, pathological fracture</td>
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<td></td>
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<tr>
<td>Pneumonia</td>
<td>F</td>
<td>72</td>
<td>4</td>
<td>26</td>
<td>Congestive failure, collapsed vertebra</td>
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<tr>
<td>*Tuberculosis</td>
<td>M</td>
<td>58</td>
<td>3</td>
<td>1</td>
<td>Pulmonary tuberculosis</td>
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<td></td>
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<tr>
<td>Pancreatitis</td>
<td>F</td>
<td>68</td>
<td>4 days</td>
<td>26</td>
<td>Pancreatitis</td>
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<tr>
<td>Bowel infarction secondary to diffuse periarthritis nodosa</td>
<td>M</td>
<td>56</td>
<td>1½</td>
<td>3</td>
<td>Acute manic-depressive psychosis</td>
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<tr>
<td>Infarcted ileum with peritonitis</td>
<td>M</td>
<td>54</td>
<td>x</td>
<td>10</td>
<td>Haematemesis</td>
<td></td>
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<tr>
<td>Bacteremia</td>
<td>F</td>
<td>48</td>
<td>4</td>
<td>16</td>
<td>Bleeding duodenal ulcer; pathological fracture of vertebra</td>
<td></td>
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<tr>
<td>Anaesthetic death with shock</td>
<td>M</td>
<td>50</td>
<td>2 days</td>
<td>14</td>
<td>Haematemesis</td>
<td></td>
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</tr>
<tr>
<td>Accident—fire</td>
<td>F</td>
<td>72</td>
<td>3</td>
<td>11</td>
<td>Haematemesis—neoplasm stomach</td>
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<tr>
<td>Suicide</td>
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<td>x</td>
<td>8</td>
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<tr>
<td>Unknown or no record</td>
<td>F</td>
<td>42</td>
<td>x</td>
<td>5</td>
<td>No further record</td>
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* No history of tuberculosis at start of cortisone.

TABLE II
MAJOR UNDESIRABLE OCCURRENCES

<table>
<thead>
<tr>
<th>Major Undesirable Occurrences</th>
<th>Per cent. of 546 Patients</th>
<th>Per cent. of 232 Patients receiving 50 mg. or less</th>
<th>Per cent. of 314 Patients receiving more than 50 mg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycosuria</td>
<td>8-6</td>
<td>8-2</td>
<td>8-9</td>
</tr>
<tr>
<td>Fluid retention</td>
<td>24-3</td>
<td>19-8</td>
<td>27-7</td>
</tr>
<tr>
<td>Psychosis</td>
<td>2-4</td>
<td>2-2</td>
<td>2-3</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>6-6</td>
<td>4-4</td>
<td>8-3</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>5-5</td>
<td>2-7</td>
<td>7-6</td>
</tr>
<tr>
<td>Pathological fracture</td>
<td>3-3</td>
<td>0-9</td>
<td>5-1</td>
</tr>
<tr>
<td>Infarction</td>
<td>11-0</td>
<td>7-7</td>
<td>13-4</td>
</tr>
<tr>
<td>Masking of infection</td>
<td>0-9</td>
<td>0-4</td>
<td>1-3</td>
</tr>
<tr>
<td>None</td>
<td>54-1</td>
<td>63-3</td>
<td>47-4</td>
</tr>
</tbody>
</table>

specific occurrences are placed. Notably, for example, many would include glycosuria among the minor incidents, and others might consider excessive fatigability a major symptom of danger.

Table II lists the "major" undesirable occurrences. It will be noted that almost half of the patients exhibited one or more and that, as would be expected, the incidence was greater in patients receiving more than 50 mg. cortisone daily.

Table III lists the "minor" undesirable occurrences. Again, the incidence was greater in the group receiving more than 50 mg. cortisone daily, but, as in the case of the "major" occurrences, some
appeared to be as apt to occur with the smaller as with the larger doses.

Two cautionary comments must be made regarding the data in Tables II and III. First, it is probable that the rates of, at least, the major untoward incidents are lower than they would have been if only patients who had never previously taken cortisone had been included in the study; because those who had previously manifested severe undesirable changes would be less likely to appear in the survey than those who had used cortisone without difficulty. Second, because of the varied lengths of time of treatment and observation, the percentages of undesirable occurrences can be taken as greater than would have been found in patients treated and observed for exactly 12 months, but less than if treatment of all patients had continued to 24 months or longer.

An attempt was made to analyse the effects of duration of treatment and of age on the rates of major undesirable occurrences. It was the opinion of the committee that the data probably were not sufficiently reliable to warrant presentation in tabular form; however, certain comments may be made. There appeared to be no consistent relationship between duration of treatment and the appearance of major undesirable occurrences, with the possible exception of pathological fractures which occurred more frequently in the patients treated longer. As regards the age of the patient at the time of treatment, there was only one instance each of glycosuria and of spread of infection among 23 patients under the age of 20 years, and none of the other major untoward incidents. Because of the small number of patients in that group these figures cannot be considered statistically significant. They are, however, in agreement with the usual experience that untoward occurrences are relatively infrequent in children. After the age of 20, the patient’s age appeared to have little bearing on the rates of occurrences with the exception of pathological fractures and, possibly, of peptic ulcer. Pathological fractures, as would be expected in view of the increase in osteoporosis in post-menopausal women and in elderly males, were found more often in the older patients (the actual figures being none under age 20, 0-6 per cent. in the 20 to 44 year age group, 3-3 per cent. in the 45 to 64 year age group, and 9-8 per cent. in the 51 patients over 65). Conversely, peptic ulcer was noted in 9-3 per cent. of patients between 20 and 44 years of age, in 6-3 per cent. of those between 45 and 64, and in only 2 per cent. of those over the age of 64. These figures do not necessarily represent the true incidence of such occurrences in patients receiving cortisone.

Taking the major undesirable occurrences as a whole, it is of interest to note that, save for the patients below the age of 20 (only 4 per cent. affected), the rates among the patients in the three older age groups were almost identical—50, 46, and 49 per cent. respectively.

**Effect of Treatment on Nodules and Psoriasis.**

Rheumatoid subcutaneous nodules were recorded as present in 159 patients (29 per cent.). These increased in number or size or both during treatment in 21, and remained unchanged in 79; they decreased in 37 patients, but disappeared in only nine. There was no record of the result in the remaining thirteen patients. Thus, there appeared to be no relationship between the course of the nodules and the administration of cortisone.

Psoriasis was reported in 27 (5 per cent.) of the 546 patients. As in the case of nodules, there appeared to be no relationship between cortisone therapy and the course of the cutaneous lesions.

**Effect of Treatment on Arthritis.**

The motivating purpose of the entire study, of course, was to see what might be learned from the various clinics regarding the effects of cortisone on the articular and systemic manifestations of rheumatoid arthritis.

Table IV (opposite) summarizes the grade of improvement in 546 patients at the end of observation if they were still on cortisone, or at the time cortisone was stopped. The time that cortisone was stopped was taken for purposes of recording as the last date before stopping cortisone on which observations of grade of improvement were reported on the survey form. Since the latter was done at 3-monthly intervals, this length of time would be the maximum possible interval between the date of the observation of grade of improvement and the date of stopping cortisone.

<table>
<thead>
<tr>
<th>Minor Undesirable Occurrences</th>
<th>Per cent. of 546 Patients</th>
<th>Per cent. of 222 Patients receiving 50 mg. or less</th>
<th>Per cent. of 314 Patients receiving more than 50 mg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moonface</td>
<td>57.7</td>
<td>40.5</td>
<td>70.5</td>
</tr>
<tr>
<td>Acne</td>
<td>10.8</td>
<td>9.5</td>
<td>11.8</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>15.7</td>
<td>15.5</td>
<td>15.9</td>
</tr>
<tr>
<td>Striae</td>
<td>5.6</td>
<td>5.2</td>
<td>6.0</td>
</tr>
<tr>
<td>Emotional instability</td>
<td>20.1</td>
<td>14.6</td>
<td>24.2</td>
</tr>
<tr>
<td>Redistribution of fat</td>
<td>21.6</td>
<td>9.9</td>
<td>30.2</td>
</tr>
<tr>
<td>Menstrual irregularity*</td>
<td>37.6</td>
<td>30.0</td>
<td>43.6</td>
</tr>
<tr>
<td>Excess fatigability</td>
<td>17.9</td>
<td>12.4</td>
<td>21.3</td>
</tr>
<tr>
<td>None</td>
<td>28.0</td>
<td>40.5</td>
<td>18.8</td>
</tr>
</tbody>
</table>

* Per cent. of 138 pre-menopausal patients.
CORTISONE IN THE MANAGEMENT OF RHEUMATOID ARTHRITIS

Table IV
GRADE OF IMPROVEMENT AT END OF OBSERVATION IF STILL ON CORTISONE, OR AT TIME CORTISONE WAS STOPPED

<table>
<thead>
<tr>
<th>Stage</th>
<th>Class</th>
<th>Number of Cases</th>
<th>Grade of Improvement (Per cent.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>I or II</td>
<td>I or II</td>
<td>110</td>
<td>13</td>
</tr>
<tr>
<td>I or II</td>
<td>III or IV</td>
<td>108</td>
<td>12</td>
</tr>
<tr>
<td>III or IV</td>
<td>I, II, III or IV</td>
<td>328</td>
<td>3</td>
</tr>
</tbody>
</table>

* No record.

It should be pointed out that the grades of improvement noted correspond to different periods of treatment for different individuals, these intervals being in some cases as short as a few weeks and in other cases as long as 36 months. Also, since cortisone was stopped because of toxicity in the case of some patients, the grades of improvement given apply in a proportion of the cases to patients who at the time of evaluation were exhibiting toxic reactions to cortisone serious enough to require stopping the drug. This, however, would not be expected to influence the grade of improvement. Finally, it is likely that at the time of the last evaluation before stopping cortisone, the dosage was being tapered off in a number of the patients; so that even though cortisone had not been stopped, it has been reduced in dosage sufficiently to render these patients susceptible to relapse of symptoms.

It is readily apparent from the Table that the greatest improvement occurred in those patients whose disease was less far advanced.

Interclinic Variations.—It has been intended to subject the data from the total group of patients to more detailed analysis. However, appraisal of the forms submitted for the individual patients revealed such wide variations for the different clinics that such an approach was invalid. Table V illustrates the differences in the distribution of patients by grade of therapeutic response at the end of 12 months of treatment with cortisone in thirteen of the clinics. These clinics were selected by excluding those that presented data for fewer than ten patients in stages 3 and 4 at the beginning of treatment and also those from which the data were in any other respect unsatisfactory. Patients in Stages 3 and 4 were selected for this detailed analysis because they were more numerous than those in the milder stages of disease. The number of patients varied from 53 in Clinic C to ten in Clinics E and Z. Percentages in Grades I and 2 are shown separately in Table V to illustrate the rarity with which Grade I was assigned, but the percentage in these two grades are then pooled to show the proportion of more favourable results. These varied from none to 71 per cent. in the thirteen clinics (mean 30 per cent.). Conversely, the proportion of patients with unsatisfactory results (Grades 3 and 4 and those in whom cortisone was stopped because of inadequate benefit) varied from 22 to 93 per cent. in the different clinics (mean 60 per cent.). If to these are added those patients whose cortisone was stopped because of undesirable occurrences, the unsatisfactory results increase to 29 to 100 per cent. in the various clinics (mean 70 per cent.). The number of undesirable occurrences considered sufficiently serious to require stopping cortisone ranged from none among 53 patients in three clinics to 30 per cent. in another clinic (mean 10 per cent.).

Even when allowance is made for the relatively small numbers in some of the clinics, the differences are highly significant, the probability of chance

Table V
DIFFERENCES IN DISTRIBUTION OF PATIENTS BY GRADE OF IMPROVEMENT 12 MONTHS AFTER START OF CORTISONE IN THIRTEEN CLINICS
INITIAL STATUS—STAGES 3 AND 4 IN ALL CLASSES
(The values are percentages rounded to the nearest 1 per cent.)

<table>
<thead>
<tr>
<th>Clinic</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>G</th>
<th>H</th>
<th>L</th>
<th>M</th>
<th>N</th>
<th>P</th>
<th>Q</th>
<th>Z</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>16</td>
<td>9</td>
<td>53</td>
<td>30</td>
<td>10</td>
<td>13</td>
<td>34</td>
<td>14</td>
<td>18</td>
<td>24</td>
<td>13</td>
<td>23</td>
<td>10</td>
<td>—</td>
</tr>
<tr>
<td>Grade 1</td>
<td>6</td>
<td>2</td>
<td>34</td>
<td>7</td>
<td>30</td>
<td>31</td>
<td>26</td>
<td>71</td>
<td>39</td>
<td>8</td>
<td>38</td>
<td>—</td>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td>Grade 2</td>
<td>19</td>
<td>34</td>
<td>36</td>
<td>7</td>
<td>30</td>
<td>31</td>
<td>32</td>
<td>71</td>
<td>39</td>
<td>46</td>
<td>—</td>
<td>17</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>34</td>
<td>36</td>
<td>7</td>
<td>30</td>
<td>31</td>
<td>32</td>
<td>71</td>
<td>39</td>
<td>46</td>
<td>—</td>
<td>17</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Grades 3 and 4</td>
<td>56</td>
<td>54</td>
<td>55</td>
<td>93</td>
<td>70</td>
<td>69</td>
<td>65</td>
<td>22</td>
<td>44</td>
<td>50</td>
<td>85</td>
<td>65</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>+ Inadequate Benefit*</td>
<td>19</td>
<td>12</td>
<td>9</td>
<td>—</td>
<td>—</td>
<td>3</td>
<td>7</td>
<td>17</td>
<td>4</td>
<td>15</td>
<td>18</td>
<td>30</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>66</td>
<td>64</td>
<td>93</td>
<td>70</td>
<td>69</td>
<td>68</td>
<td>29</td>
<td>61</td>
<td>54</td>
<td>100</td>
<td>83</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

* Inadequate Benefit = Cortisone stopped permanently because it was judged to confer inadequate benefit, or patient became worse.
† Toxic = Cortisone stopped permanently because of undesirable occurrences.
occurrence being only slightly greater than 0.001 (by the \( \chi^2 \) contingency test). In order to learn whether there was any obvious factor that might help account for these differences, the data in Table V were analysed from the following standpoints:

1. Percentage of female patients at each clinic;
2. Percentage of private patients;
3. Average age at onset of the attack of rheumatoid arthritis that formed the subject of this survey;
4. Average interval between original onset of disease and start of cortisone therapy;
5. Average date of start of cortisone therapy (this factor was examined because of the possibility of changing therapeutic customs or types of patients selected over the 3-year period);
6. Average number of joints involved at the start of treatment;
7. Percentage of patients in Stage 3 at start of treatment;
8. Percentage of patients in Classes 1 and 2 at start of treatment;
9. Average number of specified forms of concomitant therapy per patient;
10. Percentage of patients given gold as concomitant therapy;
11. Percentage of patients treated with salicylates in addition to cortisone.

For each of these eleven items a relationship with the performance index (percentages in Grades 1 and 2) of the same clinic at 12 months was sought by dot diagram, and if the diagram showed any possibility of a relationship a correlation coefficient was calculated. The method is crude, but, with one exception, there was no suggestion of a correlation. The one exception was a negative correlation (rank correlation coefficient \(-0.53\)) between the percentage in Grades 1 and 2 and the average number of joints involved at the start of cortisone therapy. That is, the smaller the average number of joints involved per patient, the higher was the percentage of patients in the more favourable groups.

The possibility was also borne in mind that in some clinics the patients may have had more "active" rheumatoid arthritis, or arthritis less susceptible to change by any form of therapy. For example, some clinics may have chosen for cortisone therapy chiefly patients who had responded poorly to other forms of treatment, whereas in other clinics cortisone may have been the first therapeutic agent selected. Unfortunately, differences of this type are not necessarily reflected in stage and class of disease and hence are not readily distinguished in the forms from which the statistical analyses were derived.

In spite of these possible factors, no simple explanations were found which would satisfactorily account for all the variations between clinics. A very plausible suggestion is that the differences lay largely in the interpretations of the various clinic physicians—differences in interpretation of the criteria of stage and class of disease and of grade of response, in judgment as to severity of disability, undesired occurrences, and the like. The incidence of unsatisfactory benefit plus "toxic effects" sufficient to require stopping cortisone reported by the various clinics illustrates this point well. As shown in Table V, it varied between 29 per cent. in one clinic and 100 per cent. in another. It would appear probable that such variations represented differences in the judgment of the physicians rather than in the reactions of the patients.

**Status of Patients at Intervals after Start of Cortisone**

*More Seriously Affected.*—One consequence of the significant differences between clinics was that simple summation of the patients from all the clinics to produce overall percentages would distort the picture by giving weight according to the numbers of patients contributed to the survey by the respective clinics. In the preparation of material for the subsequent Tables, therefore, the unweighted averages were used. For example, in Table V, the thirteen percentages for Grade 2 were summed and divided by thirteen to give the mean (28 per cent.) in the last column; and this was entered in the 12-months column of Table VI (opposite). The other columns of that Table and those which follow were produced in the same way.*

Table VI shows the distribution of patients by grade of response at intervals after the start of cortisone treatment for those patients from the thirteen clinics who had an initial status of Stages 3 and 4 (all classes) at the start of the study. Regarding the number of patients, the deficiency at 2 weeks as compared with 6 months is due to the absence of a record of grade in fifteen patients, but the record for this group at the next observation time (one month) was almost identical with the record of those patients from the same clinic whose records were complete; therefore, there is no reason to suspect that bias has been introduced. The decrease in numbers after 12 months is due chiefly to the stipulation that 12 months be the minimum period for observation. Fewer patients had been under observation for 18 months, fewer still for 24 months, and so on. The diminishing totals, therefore, are for the most part not true losses; *i.e.* patients who started treatment early enough to contribute to the 18-, 24-, or 30-month data but who failed to continue under observation. Although there were eighteen

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* Some further details of calculation are discussed by Mainland (1955).
true losses after 24 months, examination showed that no reasonable disposition of these patients, if their status at 24 months had been known, would have had much effect on the conclusions to be drawn from the Tables. The same was not true regarding losses among the less severe cases, discussed later.

Table VI shows that, if we may assume that Grades 1 and 2 indicate a favourable response and the other grades an unfavourable response, the responses in terms of averages of the thirteen clinics appear to be favourable and unfavourable in about equal proportions at 2 weeks, and then in a fairly steady ratio of 3:7 for the next 2 years. The data at the end of 30 months showed some decrease in the average percentage in the "favourable" group. However, the number of contributions from many of the clinics had become so small by that time that it would be unwise to draw conclusions from the 30-month data, which are not included in Table VI.

As regards the fairly steady ratio of 3:7 during the 2-year period, inspection of the raw data revealed that this was not due to any two-way flow between the favourable and unfavourable groups, but mostly to a tendency for patients to remain in one or the other of these broad groups.

Table VII presents a similar analysis of the same patients as those in Table VI, but in terms of their functional class. A marked improvement is seen by the end of the second week of treatment compared with the status immediately before the start of cortisone. At 6 months the ratio of more favourable outcome (Classes 1 and 2) to less favourable outcome is about 1:1, and thereafter there appears to be a slight but fairly steady decline to about 2:3 at the end of 2 years. The data are not broken down for the individual thirteen clinics as was done for grades in Table V. At the end of 30 months the percentages were essentially the same as at 24 months. Again, however, the number of patients contributed by some clinics by that time was too small to warrant drawing conclusions. As with grades, the interclinic variation was large; for example, at 12 months the percentage in the favourable group varied from 20 per cent. in one clinic to 75 per cent. in another.

Less Seriously Affected.—The data for patients

### Table VI

**DISTRIBUTION OF PATIENTS BY GRADE OF RESPONSE AT INTERVALS AFTER START OF CORTISONE TREATMENT**

**INITIAL STATUS—STAGES 3 AND 4, ALL CLASSES**

<table>
<thead>
<tr>
<th>Time after Starting Cortisone (months)</th>
<th>0.5</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>254</td>
<td>269</td>
<td>267</td>
<td>222</td>
<td>186</td>
</tr>
<tr>
<td>Range per clinic</td>
<td>9-53</td>
<td>10-53</td>
<td>9-53</td>
<td>3-50</td>
<td>3-48</td>
</tr>
<tr>
<td>Grade 1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Grade 2</td>
<td>49</td>
<td>30</td>
<td>28</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td>Total</td>
<td>51</td>
<td>31</td>
<td>30</td>
<td>31</td>
<td>28</td>
</tr>
<tr>
<td>Grades 3 and 4 and Inadequate Benefit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxic</td>
<td>48</td>
<td>63</td>
<td>60</td>
<td>55</td>
<td>51</td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
<td>70</td>
<td>69</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

### Table VII

**DISTRIBUTION OF PATIENTS BY FUNCTIONAL CLASS AT INTERVALS AFTER START OF CORTISONE TREATMENT**

**INITIAL STATUS—STAGES 3 AND 4, ALL CLASSES**

<table>
<thead>
<tr>
<th>Time after Starting Cortisone (months)</th>
<th>At Start of Treatment</th>
<th>0.5</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>254</td>
<td>269</td>
<td>267</td>
<td>222</td>
<td>186</td>
<td></td>
</tr>
<tr>
<td>Functional Class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class 1</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Class 2</td>
<td>19</td>
<td>53</td>
<td>47</td>
<td>41</td>
<td>41</td>
<td>35</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>58</td>
<td>52</td>
<td>48</td>
<td>46</td>
<td>40</td>
</tr>
<tr>
<td>Classes 3 and 4, Inadequate Benefit, Tox</td>
<td>80</td>
<td>42</td>
<td>48</td>
<td>52</td>
<td>54</td>
<td>60</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
less seriously affected (those in Stages 1 and 2 at the start of the study) were divided into two groups according to their initial functional class: i.e. those in Classes 1 and 2, and those in Classes 3 and 4. Unweighted averages, obtained as in Table VI, are shown in Table VIII. Reliable conclusions were scanty, however, because:

(i) The numbers of patients per clinic were small, varying from two to eleven;

(ii) The true losses, as defined above, amounted to eleven out of 92 patients by the end of 24 months and cast doubt on the validity of conclusions drawn from the patients who remained under observation.

Therefore, in order to minimize the effect of lost patients, attention in Table VIII is confined to the first 12 months. As would be expected, it appears that the percentage of favourable results varies inversely as the initial status. It is seen also that by the end of 12 months of cortisone treatment the average percentage of favourable results in all three groups is between 30 and 45 per cent.

Table IX presents a similar comparison of milder and more severe cases with respect to functional class. The familiar improvement immediately after the start of treatment is followed by a decline, but even at the end of 12 months there was an average of close to 75 per cent. of favourable results in the milder cases, and of close to 50 per cent. in the more severe cases.

Changes in Individual Patients.—In the discussion of Table VI, it was mentioned that the degree of improvement remained fairly steady after 6 months, and that this steadiness was due chiefly to the tendency for individual patients to remain at the same level of improvement, rather than to a two-way flow of deterioration and improvement. This was fairly obvious from inspection of the individual data sheets, and was confirmed by more precise examination.

In one clinic from which the data appeared very reliable, 38 patients initially in Stages 3 and 4 provided data for 24 months. None of them showed a better grade of response at 24 months than at 12. 66 per cent. were in the same grade, and 34 per cent. had deteriorated. When the same patients were analysed by functional class, the same relationships were found, except that 8 per cent. of the patients had been assigned a more favourable class at 24 months than at 12.

In a similar analysis of 61 milder cases (initial Stages 1 and 2) from twelve clinics, 3 per cent. showed a better grade at 24 months than at 12, 72 per cent. remained in the same grade, and 25 per cent. deteriorated. There were no significant differences between the various clinics in these figures.

These data suggest that improvement attained by the end of 12 months may be expected to continue for at least another year in 60 to 70 per cent. of

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**Table VIII**

PERCENTAGES OF PATIENTS SHOWING A FAVOURABLE (GRADE 1 OR 2) RESPONSE AT INTERVALS AFTER START OF CORTISONE TREATMENT

<table>
<thead>
<tr>
<th>Initial Status</th>
<th>Time after Starting Cortisone (months)</th>
<th>Interclinic Variations at 12 mths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5</td>
<td>6</td>
</tr>
<tr>
<td>Stages 1 and 2, Classes 1 and 2</td>
<td>76</td>
<td>57</td>
</tr>
<tr>
<td>Stages 1 and 2, Classes 3 and 4</td>
<td>61</td>
<td>45</td>
</tr>
<tr>
<td>Stages 3 and 4 (from Table VI)</td>
<td>51</td>
<td>31</td>
</tr>
</tbody>
</table>

Data for Stages 1 and 2, Classes 1 and 2, are from twelve clinics; total patients, 73 (3-11 per clinic).

Data for Stages 1 and 2, Classes 3 and 4 are from ten clinics; total patients, 63 (2-10 per clinic).

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**Table IX**

PERCENTAGES OF PATIENTS SHOWING A FAVOURABLE (CLASS 1 OR 2) RESPONSE AT INTERVALS AFTER START OF CORTISONE TREATMENT

<table>
<thead>
<tr>
<th>Initial Status</th>
<th>Time after Starting Cortisone (months)</th>
<th>Interclinic Variations at 12 mths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At Start of Treatment</td>
<td>0.5</td>
</tr>
<tr>
<td>Stages 1 and 2, All Classes</td>
<td>57</td>
<td>85</td>
</tr>
<tr>
<td>Stages 3 and 4, All Classes (from Table VI)</td>
<td>20</td>
<td>58</td>
</tr>
</tbody>
</table>

Data for Stages 1 and 2 are from twelve clinics; total patients, 125 (4-21 per clinic).
patients. However, the limitations of the method of study and the small number of patients do not justify a firm conclusion.

Discussion

In addition to the aim of obtaining information about the course of rheumatoid arthritis in patients under treatment with cortisone, an important purpose of this study was to learn whether a controlled comparison of various forms of treatment of this disease is feasible. In this connexion the most important feature was probably the revelation of the great differences in the data of the different clinics. For evaluation of cortisone therapy it has sometimes been proposed that a comparison be made of a cortisone-treated series of patients with a series treated before the days of cortisone. This "previous series" method is always perilous, and how perilous it may be is well illustrated by the present survey, where large differences between cortisone-treated series are revealed.

A co-operative scheme of a "forward-moving" clinical trial, e.g. comparison of cortisone and salicylates, for example, would doubtless reduce the interclinic differences by standardization of methods and criteria; but it is improbable that it would remove serious interclinic differences entirely. Therefore, it would be unrealistic to expect that direct pooling of the data from all the participating clinics would be permissible. Samples of the present size might well be adequate to show the superiority of one or another treatment; but even the largest individual samples in the present series would not give precise estimates of the benefits of any one treatment in any one clinic.

The large number of patients in this survey who received other agents as concomitant therapy, and the urgent desire of many patients to receive cortisone, suggests that there might be considerable difficulty in obtaining sufficient participants for an adequate co-operative, standardized, controlled trial in clinics in the United States. From the quality of the data, however, it appears probable that it would be possible to select certain clinics or physicians as appropriate participants in a controlled clinical trial or in some other type of study.

Summary and Conclusions

A statistical analysis has been made of the course of rheumatoid arthritis in a group of patients treated with cortisone in 29 co-operating clinics and observed for 1 to 3 years between 1949 and 1953. Certain of the data reported were derived from the entire sample of 546 patients, whereas others which required more detailed analysis were derived from a smaller sample of approximately half that number from thirteen clinics which submitted the largest individual samples.

The survey was designed primarily to reveal the amount and kind of information available throughout the country and did not meet the requirements of a definitive study, but the estimates and inferences are based on those statements and figures that had the appearance of being the most reliable.

In three-quarters of the patients the onset of disease had occurred between the ages of 25 and 60 years. Females comprised 63 per cent. of the group and males 37 per cent.

In roughly 25 per cent. of the patients, rheumatoid arthritis had been present for less than 4 years, in 50 per cent. less than 8 years, and in 25 per cent. more than 12 years.

Most of the patients had received therapy before the study began, and some also received concomitant therapy with agents other than cortisone during the period of the study; but valid conclusions as to the benefit of such treatments could not be drawn.

At the end of the period of study, 432 of the 546 patients were still under observation, and of these 60 per cent. were still receiving cortisone. Of the other 114 patients, 29 (5 per cent.) had died, and 85 (16 per cent.) had been lost to the study.

Undesirable occurrences of major significance were seen in 46 per cent. of the 546 patients, and minor undesirable occurrences in 72 per cent.

Rheumatoid subcutaneous nodules were present in 29 per cent., and psoriasis in 5 per cent. No significant relationship was found between the course of these lesions and treatment with cortisone.

Wide differences in the progress of patients under cortisone were reported by the various clinics. These great differences which appeared to arise chiefly from differences in interpretation and judgment on the part of the various clinic physicians, made necessary special statistical treatment of the data in order to arrive at justifiable conclusions.

Among the patients more severely affected by the disease (Stages 3 and 4 when the study began), the ratio of favourable to unfavourable results at the end of 2 years was 3:7 in terms of grade of response, and 4:6 in terms of improvement in functional class. In the more mildly affected patients (Stages 1 and 2 when the study began), the proportion of favourable results was larger. In all groups improvement was more favourable in terms of functional class than in terms of grade of response (as defined by the American Rheumatism Association; Steinbrocker and others, 1949).

The limitations of this type of therapeutic survey are discussed more fully by Mainland (1955).
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**REFERENCES**


**Expérience avec la cortisone dans le traitement de l’arthrite rhumatismale**

Rapport d’une enquête collective dirigée par un comité de l’American Rheumatism Association

**RÉSUMÉ**

On a procédé à une enquête statistique sur l’évolution de l’arthrite rhumatismale chez un groupe de malades traités par la cortisone et suivis pendant 1 à 3 ans entre 1949 et 1953 dans 29 cliniques participant à l’enquête. Ont été soumis à une analyse détaillée, des résultats de la moitié de ce nombre et se basent sur des renseignements fournis par 13 cliniques disposant de plus grands lots de cas.

Cette enquête a été entreprise avant tout pour connaître le genre et la quantité des renseignements disponibles dans le pays, sans donc créer des conditions requises pour une analyse précise, mais les calculs et les déductions se basent ici sur ces constatations et chiffres qui ont la meilleure appareance d’exactitude.

Ces trois quarts des sujets de l’étude a débuté entre l’âge de 25 et de 60 ans. Le groupe comprenait 63% de femmes et 37% d’hommes.

Chez environ 25% des sujets, l’arthrite rhumatismale était présente depuis moins de 4 ans, chez 50% moins de 8 ans et chez 25% moins de 12 ans.

La plupart des malades a été traitée avant le commencement de cette enquête, et certains d’entre eux ont été traités, en plus de la cortisone, par d’autres moyens au cours de la période d’enquête, mais on ne peut pas tirer de conclusions valables sur le bénéfice de tel traitement.

A la fin de l’enquête, sur les 546 malades, 432 se trouvaient encore sous observation et 60% d’entre eux recevaient toujours de la cortisone. D’entre les 114 restants, 25 (5%) étaient morts et 85 (16%) se sont trouvés dans des conclusions de diverses raisons variées.

On a observé des effets secondaires majeurs chez 46% des 546 malades et des mineurs chez 72%.

Des nodules rhumatismaux sous-cutanés étaient présents chez 29% et le psoriasis chez 5%. On n’a pas trouvé de rapport significatif entre l’évolution de ces lésions et le traitement de la cortisone.

En comparant les rapports de diverses cliniques on a trouvé de grandes différences dans le progrès des malades traités par la cortisone. Ces différences, attribuables surtout à l’interprétation et au jugement des médecins des cliniques, ont demandé une élaboration statistique spéciale des données pour pouvoir arriver à des conclusions justifiables.

**Méthodes grevées** (stade 3 et 4 au temps du commencement de l’enquête) au bout de 2 ans les résultats favorables et défavorables étaient en proportion de 3 : 7 du point de vue de la réaction thérapeutique gradée et de 4 : 6 du point de vue fonctionnel. Chez les malades benins (stade 1 et 2 au début de l’enquête) la proportion des résultats favorables était plus grande. Dans le groupe des malades majeurs, un espoir d’amélioration plus prononcée que le critère de la réaction thérapeutique (selon la définition de l’American Rheumatism Association; Steinbrocker et coll., 1949).

On discute plus amplement les limitations d’une enquête thérapeutique de ce type dans une maladie de genre d’arthrite rhumatismale dans l’article suivant (Mainland, 1955).

**Experiencia con la cortisona en el tratamiento de la artritis reumatoide**

Informe de un estudio cooperativo dirigido por una comisión de la American Rheumatism Association

**SUMARIO**

Se procedió a un análisis estadístico respecto a la evolución de la artritis reumatoide en un grupo de enfermos tratados con cortisona en 29 clínicas participantes y seguidos durante uno a tres años entre 1949 y 1953. De los datos presentados aquí, algunos proceden del grupo entero de 546 enfermos; otros, habiendo necesitado un análisis más detallado, vienen de un número aproximadamente dos veces menor, ofrecidos por 13 clínicas con los mayores lotes de casos.

El primer objeto de esta investigación fue el averiguar el tipo y la cantidad de información disponible en el país y se requirió una experiencia más detallada de lo que en este estudio efectuado en el año 1953. Nos acabamos basando sobre informes y cifras que ofrecen mayor apariencia de exactitud.

En los tres cuartos de los sujetos la enfermedad había empezado entre la edad de 25 y 60 años. El grupo comprendió un 63% de mujeres y un 37% de hombres. En cerca de 25% de los enfermos la artritis reumatoide había existido desde menos de 4 años, un 30% desde menos de 8 años y en un 25% desde menos de 12 años.

La mayoría de los enfermos obtuvo tratamiento antes de empezar esta investigación; algunos recibieron además de la cortisona, otra terapia durante el periodo de investigación; no se puede decir con seguridad que los resultados de mejora fueran en beneficio de tal tratamiento.

Al cabo de la investigación, de los 546 enfermos considerados, 432 encontrabanse todavía bajo observación y el 60% de ellos seguía recibiendo cortisona. De los demás 114, 25 (5%) murieron y 85 (16%) encontráronse por varias razones fuera de la investigación.

Ocurrieron novedades mayores se observaron en el 46% y menores en el 72%.

Nódulos reumáticos subcutáneos se vieron en un 29% y psoriasis en un 5%. No se notó relación significativa entre la evolución de estas lesiones y el tratamiento con la cortisona.

Al comparar los informes de varias clínicas se observaron grandes diferencias en el progreso de los enfermos tratados con cortisona. Estas diferencias debidas principalmente a la interpretación y al juicio de los médicos de las clínicas, exigieron una elaboración estadística especial de los datos para poder llegar a conclusiones justificables.

En los enfermos graves (período 3 y 4 al tiempo de empezar la investigación) al cabo de 2 años la proporción de los resultados favorables y desfavorables fue de 3 : 7 según los criterios de la respuesta terapéutica graduada y de 4 : 6 desde el punto de vista de la mejoría funcional. En los enfermos benignos (período 1 y 2 al empezar la investigación) la proporción de los resultados favorables fue mayor. En todos los grupos el criterio funcional indicó resultados más favorables que el criterio de la reacción terapéutica graduada (definida por la American Rheumatism Association; Steinbrocker y col., 1949).

Se discuten más detalladamente las limitaciones de tal investigación terapéutica en enfermedades del tipo de artritis reumatoide en el artículo siguiente (Mainland, 1955).