BRITISH MEDICAL JOURNAL

LONDON SATURDAY MAY 15 1954

MANAGEMENT OF RHEUMATOID ARTHRITIS WITH PROLONGED CORTISONE ADMINISTRATION*

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After three years' experience at the West London Hospital in the treatment of a series of cases of rheumatoid arthritis with cortisone, we feel that it may be of interest to summarize our results to date. In a previous publication (Copeman *et al.*, 1950) we reported a short study of the effect of cortisone and other steroids in rheumatoid arthritis, and described certain methods for clinical assessment. We later published a longer study of the effects of continuous cortisone administration in the same disease (Copeman *et al.*, 1952). The present paper is a continuation of those studies.

This report is on 20 cases of rheumatoid arthritis, 14 of which have received cortisone for more than two years, and all for at least a year continuously (Table I).

TABLE I.—Duration of Cortisone Treatment

Months:	36	35	34	33	32	31	30	29	25	22	18	17	16	Total
No. of cases	2	3	1	2	1	1	2	1	1	1	2	1	2	20

All the patients selected had previously suffered from active rheumatoid arthritis for at least two and a half years, and the majority for much longer, the average duration of the disease before cortisone treatment being 6.8 years. None of them were able to carry out their normal occupations, and all were regarded as severe cases. They had lost their independence, and described themselves as "crippled." These patients had been under observation and treatment for some time, and the more standard methods, such as adequate rest, salicylates, and gold salt injections, had failed to suppress the progress of their disease.

From this series of 20 cases 17 have now been returned to a working life in their various spheres, although, as the analysis in this report will show, the actual degree of functional improvement varies from case to case.

*This work has been aided by grants from the Dan Mason Research Foundation of the West London Hospital Medical School, the Empire Rheumatism Council, and the Medical Research Council.

Realizing that a real cure in any case was unlikely, we decided to assess our results on a practical functional basis. Accordingly, if the disease was suppressed sufficiently to enable normal work to be resumed and maintained we regarded the result as satisfactory ; if the patient was able to return to work but still complained of considerable pain we termed the result moderate ; and if the patient could not resume work it was held to be unsatisfactory.

Analysis of Results

Any opinion concerning the value of a particular form of treatment must depend on whether the emphasis is placed

on its ability to cure the disease or on its power to relieve symptoms enough to enable the patient to regain functional or social independence. No cure has yet been found for rheumatoid arthritis, and the present study stresses the fact that cortisone must be continuously administered in order to retain improvement. Of our 20 patients who were initially unable to work, however, 17 have returned to their occupations and have continued to carry them out. The

practical value of such improvement obtained through cortisone must, however, be weighed against the possible dangers resulting from long-term treatment with this drug.

Chart showing the effect of long-term cortisone administration on the different components of rheumatoid arthritis (Case 7). Note the marked improvement in functional capacity, moderate improvement in signs of activity of the disease, and deterioration in radiological involvement.

TABLE II.—Results

Case No.	Description	Condition Before Treatment	Present Condition	Time on Cortisone	Daily Maintenance Dose of Cortisone	Results as Assessed by Functional Improvement
1	Housewife aged 48. R.A. 8 years	Doing only very light housework	Working. Cooking and housework	36 months	100 mg.; or 60 mg. hydrocortisone	Satisfactory
2	Army officer aged 33. R.A. 5½ years	Partly bedridden; could walk 30 yards	Full-time clerical work. Drives invalid chair. Considerable pain from secondary osteoarthritis of hips	36 "	100 mg.	Moderate. Walks with difficulty
3	Housewife aged 40. R.A. 4½ years	Unable to dress herself or do housework	Working, and leading a normal life	35 "	50 "	Satisfactory
4	Housewife aged 36. R.A. 12½ years	Unable to dress herself or run her home	Working. Can do housework with difficulty. Only partial suppression	35 "	62.5 "	Moderate. Oedema and some pain
5	Housewife aged 43. R.A. 5 years	Unable to do housework, lift anything, do her hair, or get out of a bath	Working. Leading a busy social life entertaining for her husband; much hampered by her knees	35 "	100 "	Moderate. Much pain
6	Superintendent water inspector aged 45. R.A. 14 years	Unable to work	Working full-time with much travelling	34 "	62.5 "	Satisfactory
7	Treasury official aged 35. R.A. 7 years	Just managing to work with long periods of sick leave. Unable to dress himself	Working full-time without difficulty	33 "	37.5 "	"
8	Clerk aged 34. R.A. 8 years	Unable to work or do housework	Working. Has completed training as a dressmaker. Arthrodiesis of left wrist	33 "	75 "	"
9	Housewife aged 36. R.A. 5½ years	Able to do light cooking only	Working. Able to do much more in her home, but hampered by her knees from walking any distance	32 "	50 mg., plus fortnightly injections of 50 mg. hydrocortisone into both knees	"
10	Housewife aged 31. R.A. 11 years	Unable to do housework or look after children. Walked with a stick	Working and leading a normal life, hindered only by deformed feet	31 "	62.5 mg.	"
11	Typist aged 21. R.A. 3½ years	Unable to work	Working full-time and leading a normal life	30 "	62.5 "	"
12	Chiropodist aged 54. R.A. 10½ years	Unable to work and permanently in hospital	Full-time clerical work in spite of much permanent damage	30 "	87.5 "	"
13	Railway maintenance worker aged 44. R.A. 4½ years	Bedridden. Much muscle-wasting and joint effusion	Not working, though mobile and independent and capable of light employment	29 "	75 "	"
14	Housewife aged 51. R.A. 4½ years	Unable to do housework or shopping	Working and leading a normal life. Some tenderness and swelling of right wrist and left knee	25 "	75 "	"
15	Gold blocker aged 50. R.A. 2½ years	Unable to work	Working full-time	22 "	37.5 "	"
16	Housewife aged 49. R.A. 8 years	Unable to look after herself	Not working. Can do only light housework. Marked depression on a higher dose	19 "	75 "	Unsatisfactory
17	Schoolteacher aged 41. R.A. 5 years	Unable to work	Working, but has much stiffness in ankles and knees	19 "	62.5 "	Moderate. Acne and moonface on higher dose
18	Housewife aged 52. R.A. 4½ years	Unable to run her home or carry anything	Working. Leading a normal life, but has some pain in hands and feet	17 "	62.5 "	Satisfactory
19	Children's nurse aged 52. R.A. 5 years	Unable to look after herself	Not working. Unsatisfactory response with hypertension	16 "	75 "	Unsatisfactory
20	Housewife aged 23. R.A. 5 years	Unable to do housework or look after child	Working and leading a normal life	16 "	75 "	Satisfactory

In order, therefore, to assess the true value of this therapy we have analysed in each case the effect of cortisone on various important components of the disease process, such as the objective joint changes, the patient's functional capacity, clinical and laboratory evidence of activity, and the radiological changes. Table II shows the results of this analysis in the whole series, and the Chart gives a graphic representation of the changes in a particular case.

These cases have been examined in detail every few weeks since the start of treatment, and the various components of the disease process assessed according to the following categories (Table III).

TABLE III

	Joint Involvement	Activities of Daily Life	Functional Tests	Systemic Signs and Lab. Tests	Radiological
Marked improvement	—	7	8	—	—
Moderate improvement	14	11	7	15	—
Unchanged	1	1	3	3	12
Deterioration	5	1	2	2	8
Total No. of cases	20	20	20	20	20

Objective Joint Involvement.—This was measured by examination of the joints for swelling, tenderness, and range of movement; the recordings were charted each month.

Activities of Daily Life (Functional Capacity).—At the outset of this trial a set of test questions was drawn up to estimate the patients' chief limitations in the conduct of their everyday life—for example, ability to dress, speed of dressing, ability to shave or do hair, ability to bath themselves, ability to walk, speed of walking, ability to climb stairs, ability to work, number of analgesics needed daily, how often awakened by pain.

Functional Tests.—Ten functional tests were adapted for each patient, depending on the joints involved. Among these were the power of grip, using a baumanometer cuff, starting at 30 mm. Hg (normal 260 mm. Hg +). Certain common functions, such as taking off a jacket, jumping, or standing on the toes, were also timed. These tests can be arranged to give a composite picture of the patient's functional abilities and can be carried out in a few minutes.

Systemic Signs and Laboratory Tests.—The clinical signs of activity apart from joint changes are fever, loss of weight, and muscle-wasting. The laboratory tests we have used consistently are the sedimentation rate (Westergren) and estimation of the haemoglobin level.

Radiological.—X-ray films taken before treatment included all the main joints involved at that time. The points particularly observed for change subsequently were soft-tissue swelling, osteoporosis, cartilage and joint erosions, and loss of joint space. A number of our cases have shown evidence of radiological progression in spite of the fact that their functional ability has none the less improved with cortisone.

Dosage Schedule

To find the optimum maintenance dose it is necessary to employ some method of assessing the clinical activity of the disease, and we have found that by measuring joint tenderness and function, together with the patient's own account of his pain and mobility, at regular intervals this can be achieved with reasonable accuracy. The patients in this series were seen and assessed weekly or fortnightly in the early stages, and once there was evidence that the symptoms and signs were being adequately suppressed the maintenance dose was found by reducing the initial dose by small amounts at intervals of not less than five days. A maintenance dose of 50 mg. a day or less was aimed at, but could by no means always be achieved. When the maintenance dose had been established the patients reported as out-patients every four or six weeks for observation.

In some cases a low maintenance dose will successfully suppress the inflammatory signs in all but one or two joints, often knees. We have found that by the use of hydrocortisone (compound F) as an intra-articular injection every few weeks, or occasionally at longer intervals, we can suppress this residual inflammation, and we have in addition sometimes been able to lower the patient's oral dose of cortisone.

In our early cases we adopted the scheme of dosage originally suggested by Hench *et al.* (1949), in which on successive days 300, 200, 100 mg. were used. We soon found, however, that the response provoked in this way tended to be too dramatic, and so led to subsequent disappointment on the part of the patient if this rate of progress did not continue. We therefore adopted a routine initial dose of 100 mg. daily, and with this it proved possible to measure the patient's response after about five days. In more recent cases in this series we have lowered the initial dose still further to 75 mg. daily; a level which has proved to be equally satisfactory in most cases.

Variation of Maintenance Dosage

The maintenance dose may have to be increased temporarily when conditions of extra stress occur, but should be lowered again as soon as possible. The average maintenance dose by the oral route in this series has been 69 mg. a day, which is the same as that reported by Fischer and Brøchner-Mortensen (1953) in Denmark.

Fourteen of our patients have received cortisone continuously for over two years, and during this period their dose requirements have not altered to any large extent, although in two cases the dose had to be increased somewhat. In Cases 6 and 8 the dose was progressively reduced during the first few months of treatment to 25 mg. cortisone a day, and was maintained satisfactorily at that level for some months. It was then thought probable that patients who need such a low dose might be able to dispense altogether with the drug, so it was stopped, with the unfortunate result that the disease relapsed at once. In neither of these cases were we ever able to lower the maintenance dose down to 25 mg. a day again.

We believe that the dose of cortisone should never be altered on account of surgery. Healing has proceeded normally after all operative procedures undertaken on our patients, notably in emergencies such as strangulated hernia (Case 12) and evacuation of a haematoma (Case 1), and in planned surgery such as an arthrodesis (Case 8). In the three cases of peptic ulceration which occurred (Cases 4, 7, and 12) the dose of cortisone was lowered slightly, but in each instance the lesion healed normally with ordinary medical treatment.

Side-effects

It is important to try to estimate the likelihood of the occurrence of side-effects in each case. Such an assessment often fails because the maintenance dose required cannot be accurately foretold. Experience has shown that in general men can tolerate a higher dose than women with-

out developing side-effects, and that obesity and "moon-face" are particularly apt to occur in women near the menopause. Most of the side-effects we have encountered were mild and could be controlled by merely lowering the dosage and supervising the diet, or adjusting the sodium or potassium intake; but over a long period they may sometimes become troublesome enough to offset the functional improvement gained.

We have divided the side-effects observed in this series into two groups: (1) those which were serious in the sense that they might endanger the patient's life; and (2) those which were merely inconvenient, aesthetically displeasing, or transitory.

Group 1. Side-effects Dangerous to Life

Depression.—The most serious reported complication of hormone treatment is psychosis. We have taken particular trouble in our series to exclude patients with psychological incidents in their history, and we have not encountered this complication. We have, however, one patient (Case 16) who suffers such severe depression on the minimal dose needed to control her arthritis that, although she has no family or previous history of psychological disturbances, we have decided to withdraw the drug.

Hypertension.—In all but three of our cases the blood pressure remained unaffected by treatment; in one (Case 19), however, hypertension became evident early in treatment and the blood pressure rose from 120/80 to 200/105 on the eighteenth day. The condition was symptomless, but, as it has so far proved impossible to find a dose which will control arthritis without further increasing the hypertension, cortisone is being withdrawn. In the other two cases the blood pressure rose slightly at the onset of treatment, but has not increased during the past year. Both these patients are working full time, and we have not felt it necessary to withdraw the hormone (Cases 2 and 15).

Gastric Complications.—There have been three gastric complications in the present series. Case 7 developed a duodenal ulcer after thirteen months on cortisone. This healed normally on medical treatment with slight reduction of the cortisone dosage whilst in hospital, and he has now been symptom-free for fifteen months. Case 4, who had a previous history of gastric ulcer, complained of retrosternal pain referred to the back. On investigation this was found to be due to an oesophagitis associated with a hiatus hernia, which responded to ordinary medical treatment with slight reduction in cortisone dosage. Continued medical treatment keeps her free from oesophageal pain. Case 12, after two years' continuous cortisone, complained of exhaustion, which was found to be due to anaemia secondary to melaena. On admission to hospital the haemoglobin had fallen to 4.23 g. Without alteration in the dose of cortisone she became symptom-free after transfusion and medical treatment. There was no x-ray evidence of peptic ulcer three weeks after the melaena stopped, but she has continued on an ulcer dietary regime.

Miscellaneous.—In the earlier cases, before the drug could be given by mouth, we encountered a great deal of trouble with injection abscesses. We have not encountered any intestinal intolerance to administration by the oral route. One case (No. 2), which has been reported fully elsewhere (Bishop and Glyn, 1952), has concurrent diabetes. He has been satisfactorily maintained on continuous cortisone therapy, however, whilst his diabetes has been controlled by insulin. We have already reported (Copeman *et al.*, 1952) the death from cerebral haemorrhage of one of our long-term patients. This was not, however, thought to be attributable to cortisone, and as she received the drug for only nine months her case is not included in the present series.

Group 2. Less Important Side-effects

Obesity.—The most common side-effect in female patients on cortisone has been a tendency to accumulate fat, both local and general. In nine cases there has been some rounding of the face; in two the development of localized

deposits of fat over the lower cervical vertebrae ("buffalo hump"), and in six cases some weight increase, due partly to fluid retention as evidenced by peripheral oedema, and partly to the voracious appetite which such patients occasionally develop. These effects were controlled with difficulty in some cases, by reduction of dosage, a salt-free diet, and fluid restriction.

Miscellaneous.—Minor skin abnormalities have occurred on high dosage: acne in three cases, excess sweating and hypertrichosis in two, and pigmentation in a single case. All these have disappeared on dose reduction. Minor psychiatric symptoms were occasionally noted, and were fairly evenly divided between those who showed apathy and exhaustion and those who complained of tension and irritation. In no case were they severe or disabling, and it seems that in such cases the drug merely tends to accentuate the normal personality trends.

Discussion

It is universally agreed that cortisone in adequate dosage will suppress the symptoms and signs of rheumatoid arthritis in a relatively short period, and it is recognized that when the drug is withdrawn a rapid relapse generally follows. It is, however, argued by some that because of this necessity for prolonged or even indefinite administration cortisone does not constitute practical therapy, and that owing to the danger of side-effects its use is not justified in practice.

Published reports of long-term treatment with cortisone and A.C.T.H. have now appeared from various parts of the world. Holbrook (1953), reporting on a group of 36 patients with rheumatoid arthritis treated with cortisone, found that at the end of twenty-four months only 10 of these were still getting worth-while improvement, and that all showed some clinical and x-ray advance in their disease. West and Newns (1953) reported a study of 27 patients with rheumatoid arthritis treated for an average of nineteen months with a maintenance dose between 50 and 75 mg. a day. They compared their series with other patients who had not received cortisone, and concluded that this drug does not have a favourable effect on the course of rheumatoid arthritis, and because of the danger of complications do not recommend its administration on a long-term basis.

In New York Freyberg *et al.* (1951) studied 44 patients who received cortisone uninterruptedly for more than a hundred days. In many patients a good partial remission could be maintained with 50–75 mg. daily. These authors none the less point out that prolonged use of cortisone is not practical treatment for all patients with rheumatoid arthritis. They advocate its use mainly for definite purposes, such as to check rapidly worsening disease or to facilitate certain stages in physical therapy or rehabilitation.

In Copenhagen Fischer and Brøchner-Mortensen (1953, 1954) have treated 50 patients suffering from rheumatoid arthritis with both cortisone and A.C.T.H. In their first report on 24 patients these authors were unwilling to commit themselves on the practicability of this form of treatment. In their second paper they report the study of 50 cases. In five cases treatment was abandoned because of an unsatisfactory response, whilst in another five cases complications necessitated stopping these drugs. In four cases treatment was stopped after five to twelve months because remission had occurred. The remaining 36 were maintained with an average dose of 69 mg. of cortisone a day from five to thirty-three months. Measurement of the joint-movement index and the general functional ability showed an improvement in 84% of the group when compared with the pretreatment values. Of the group in remission or continuing treatment only two had been capable of work before treatment started, compared with 31 during therapy; whilst the number of totally disabled subjects in this series was reduced from nine to one. Those authors now conclude, therefore, that this form of treatment is of practical value in the therapeutic management of selected cases of rheumatoid arthritis.

From Paris, Coste *et al.* (1953) reported 20 cases of rheumatoid arthritis treated continuously for many months. In three cases remissions occurred and they were able to stop treatment without relapse; in a further three cases the results were poor and cortisone was discontinued; whilst in the remaining 14 patients the results were satisfactory enough to make continued therapy worth while. Like most recent workers they preferred continuous to intermittent courses of treatment, and they believe that this method can be used as a practical therapeutic measure in this disease, save perhaps in early cases which might anyhow be expected to go into remission spontaneously. They estimated the risk of psychotic side-effects at 1% in their series.

Clark *et al.* (1953) reported on 35 patients with this disease treated with cortisone for from three to twenty-four months. Major subjective improvement was obtained in 74% and major objective improvement in 38%, although minor complications were common. They did not consider that hormone therapy should be employed until maximum benefit from conservative measures has been established, and that it should always be combined with such measures.

A study of long-term cortisone treatment was reported by Ward *et al.* (1953) in which 65 patients were treated. In 57 (88%) of these cortisone controlled the symptoms adequately, and in 8 (12%) the drug was stopped because the dose required for significant relief of symptoms also produced side-effects. In 46 patients the drug was given continuously for from eight to twenty-four months. In 44 of these patients there was moderate to great improvement; in the remaining two cases the relief was only mild. Nine cases showed mild side-effects. These authors concluded that long-term cortisone is a practical and useful method of treatment in rheumatoid arthritis, and is the treatment of choice in certain phases.

Conclusion

As the result of our experience with a well-observed group of 20 cases of rheumatoid arthritis, we consider that cortisone therapy is a practical addition to treatment in selected cases.

As cortisone is not actually curative, and since we have seen radiological progression of joint damage in patients in whom the symptoms were being suppressed, we consider that more conservative methods of treatment, such as adequate rest, salicylates, gold salts, and physiotherapy, should generally be tried first, as these will themselves in some cases produce adequate remission of the disease.

Absolute contraindications to cortisone therapy are recent or active tuberculosis, present or past psychosis or psycho-neurosis, diabetes, hypertension, and severe osteoporosis; while long-standing cases with much permanent irreversible deformity and joint damage are also unsuitable for cortisone therapy.

Evidence is adduced to show that the functional improvement of the patient under cortisone treatment is greater than the actual degree of suppression of the activity of the disease. The most suitable cases are therefore those in which the functional disability exceeds the anatomical joint damage.

It is our experience that, although previously incapacitated, a number of patients can be restored to and maintained in relatively normal activity by long-term cortisone treatment. Such patients, however, require careful and constant supervision if this result is to be achieved.

Summary

Twenty cases of rheumatoid arthritis have been treated with cortisone; 14 of them received this drug for over two years.

All were previously incapacitated, but 17 have been able to return to their occupations with the help of this treatment, as the result of varying degrees of functional improvement, the extent and nature of which have been analysed.

The dosage and management of these cases, and the side-effects seen in the course of their treatment, are discussed.

The cortisone used in this study was partly provided from a generous gift made jointly to the Medical Research Council and the Nuffield Foundation by Messrs. Merck & Co. Inc., and partly from the Ministry of Health. We wish to acknowledge the valuable assistance given to us by Dr. B. Gottlieb, consultant physician, St. Mary Abbots Hospital, and his assistants, and by the following pathologists and biochemists and their assistants: Dr. H. E. Archer, Dr. J. D. Robertson, and Dr. R. G. L. Waller, West London Hospital; Dr. A. G. Signy, St. Mary Abbots Hospital; and Dr. A. E. Kellie, Middlesex Hospital.

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AN APPRECIATION OF MITRAL STENOSIS*

PART II. INVESTIGATIONS AND RESULTS

BY

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THE ELECTROCARDIOGRAM P Mitrale

The P mitrale may be defined as a widened P wave of normal or only slightly increased voltage, usually notched, bifid, or flat-topped. It was present in all but four of the surgical cases with normal rhythm. The exceptions included three instances of the P pulmonale (due to extreme pulmonary hypertension in two and to tricuspid stenosis in one); there was only one instance in which the P wave was normal, and this was the mildest in the series. In 10 cases the auricular complex was a mixture of the P mitrale and the P pulmonale: the pulmonary vascular resistance was in the extreme grade in two of these, between 6 and 9 units in three of them, and relatively normal in three; tricuspid stenosis was responsible in the other two. The P mitrale was at least 0.12 second wide in 79% of the whole surgical group.

In the medical series with normal rhythm, the P mitrale was absent in three-quarters of the trivial cases of mitral stenosis and in 10% of the relatively mild cases in the sense that they were not severe enough to warrant valvotomy. It was present in all

the cases in which mitral incompetence was associated with stenosis, although usually of only moderate degree; there was no presystolic murmur in 80% of these cases. A P pulmonale was present in the most extreme example of pulmonary hypertension and in two cases of tricuspid stenosis, but in only one other. Excluding the trivial cases, a well-developed P mitrale, at least 0.12 second in duration, occurred in half of all the medical cases with normal rhythm.

In the group with almost pure mitral incompetence the P wave was normal in all trivial and mild cases; it was present in relatively mild degree (0.10 to 0.11 second) in half of those of moderate grade. It was seen, also in relatively mild degree, in 80% of the severe cases (grade 3 or 4).

A conspicuous P mitrale (grade 3 or 4) could not be correlated with a dominant a wave in the left atrial pressure tracing: thus only one-third of the cases showing such a waves had a grade 3 or 4 P mitrale; conversely, only a similar proportion of cases having a conspicuous P mitrale had an a wave higher than v in the left atrial tracing. The grade of the P mitrale could not be correlated with the size of the left atrium, this fact being best illustrated by the relatively mild grades found in mitral incompetence, which favours left atrial dilatation. Nor could it be correlated closely with the size of the mitral orifice found at operation, the great majority of those with conspicuous P mitrales having an orifice either in the average grade (1 by 0.5 cm.) or in the slightly tighter grade (0.75 by 0.4 cm.); in only one was the stenosis extreme (0.5 by 0.3 cm.).

It is concluded that the P mitrale is a good sign of well-developed mitral valve disease, and that if it is well marked (grade 3 or 4) it strongly favours stenosis rather than incompetence; also that it should be present in all cases of stenosis that are severe enough to warrant valvotomy.

Right Ventricular Preponderance

The degree of right ventricular preponderance in mitral stenosis based on a conventional interpretation of the six routine V chest leads was closely related to the pulmonary vascular resistance (Fig. 7). An important practical fact noticed in the analysis was that any degree of right ventricular preponderance in mitral stenosis meant that the case was severe enough to warrant valvotomy: the converse, of course, was not true.

Left Ventricular Preponderance

Left ventricular preponderance was very rare in pure mitral stenosis, and when present was only of slight degree. In the mitral incompetent group, on the other hand, it occurred in 82%, excluding trivial cases, and in degree averaged slightly over grade 2. Grade 3 left ventricular preponderance always meant severe mitral incompetence in the absence of aortic valve disease. In the medical group with significant mitral incompetence, left ventricular preponderance, averaging a little under grade 2, occurred in one-third, ventricular balance being normal in half and

FIG. 7.—Relationship between right ventricular preponderance and pulmonary vascular resistance.

*The second part of a lecture delivered before the San Francisco Heart Association on October 29, 1953, and modified for the Strickland Goodall lecture of the Society of Apothecaries of London, March 24, 1954. Part I appeared in last week's issue (p. 1051).