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TREATMENT OF ACUTE RHEUMATIC FEVER IN CHILDREN

A Co-operative Clinical Trial of A.C.T.H., Cortisone, and Aspirin

A JOINT REPORT* BY

THE RHEUMATIC FEVER WORKING PARTY OF THE MEDICAL RESEARCH COUNCIL OF GREAT BRITAIN

AND

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Starting in 1949, encouraging reports of A.C.T.H.† and cortisone in the treatment of acute rheumatic fever aroused hope that a more effective therapy had at last become available. Conclusions of the early and uncontrolled studies were, however, somewhat contradictory, in that some investigators reported that the hormones altered the course of acute rheumatic fever while others suggested that they merely suppressed its clinical manifestations (see bibliographies in Thorn *et al.* (1950) and Massell (1954)). At that time no data were available concerning the prevention of rheumatic heart disease by these agents, a question which could be answered only by a long follow-up study.

By early 1950 it became evident to both the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association and the Medical Research Council of Great Britain that there was need for a controlled study of the efficacy of these hormones in comparison with the previously accepted therapy. It was also clear that no single research centre could provide, in a short period of time, enough cases to give a definitive answer. It was therefore proposed that a group of research centres should collaborate. The co-operative clinical trials of the streptomycin treatment of tuberculosis in Great Britain under the Medical Research Council and similar studies in the United States under the Veterans Administration pointed the way. Planning funds were soon made available.

There were several advantages in the establishment of a co-operative study on an international basis. It was possible that the general availability of A.C.T.H. and cortisone in the United States might seriously interfere with a strictly controlled clinical trial. Large numbers of cases would be collected rapidly. Much-needed information on the natural history of the disease in two different parts of the world would be made available.

The Committee on Criteria and Standards of the Council on Rheumatic Fever and Congenital Heart Disease, together with a group of American and Canadian rheumatic fever research workers, set up a subcommittee of principal investigators for American planning. It also established liaison with the Working Party on Rheumatic Fever of the Medical Research Council of Great Britain. Joint planning of the United Kingdom–United States Co-operative Rheumatic Fever Study was begun and the design of the study completed in a six months' period.

The trial was designed to compare the therapeutic effects of the hormones, A.C.T.H. and cortisone, with the usual treatment of rheumatic fever at the time—namely, aspirin—all patients to be treated in hospital on bed rest and protected against beta-haemolytic streptococcal

*This report is being published simultaneously in the *British Medical Journal* in the United Kingdom and in *Circulation* in the United States.

†Throughout this paper A.C.T.H. will be used to indicate corticotropin, *N.N.R.*

infection. Within the limitations imposed by the design of the study, answers were sought to two questions:

(1) What is the relative effectiveness of each of these hormones and of aspirin in altering the course of the acute disease or in suppressing its clinical manifestations?

(2) What is the relative effectiveness of these three agents in preventing rheumatic heart disease?

Information was also collected on the side-effects of the two hormones and of aspirin.

The design created and agreed upon by the principal investigators in both countries, in co-operation with the co-ordinating staff and statistical consultants, provided for diagnostic criteria, random allocation of patients to treatment groups, a uniform six-weeks therapeutic regimen, and a fixed time-pattern for observation and follow-up. It prescribed the type and frequency of clinical and laboratory observations during hospital stay and follow-up period and required reporting on specially prepared forms (see Appendix) to the co-ordinating centres in London and New York City.

This report compares the effects of the three drugs—A.C.T.H., cortisone, and aspirin—on the acute course of rheumatic fever, in children under the age of 16, through 13 weeks from the start of treatment, and on the persistence and development of rheumatic heart disease through one year.* Subsequent reports will include a similar analysis of adult patients and, after longer follow-up, of the relative effectiveness of the three drugs in the prevention of rheumatic heart disease. These extensive data should also provide much information on the natural history of the disease.

Diagnostic Criteria for Admission of a Patient to the Study

To ensure, so far as possible, that in all centres patients admitted to the trial were unquestionable cases of rheumatic fever, and of no other illness, it was necessary to specify precise diagnostic criteria. Since there are no specific diagnostic clinical symptoms or signs or laboratory tests, such criteria must be arbitrary. The criteria had to be broad enough not to exclude many genuine early cases, and yet sufficiently rigid that there should be, among competent clinicians, no reasonable doubt regarding the diagnosis.

The diagnostic criteria were based on those of T. Duckett Jones (1944), modified for the purposes of this study with his advice and assistance.† They divide the manifestations of rheumatic fever into two groups, major and minor. There were five major and five minor manifestations, defined as follows.

Major Manifestations

(1) CARDITIS, *as shown by any one of the following: (a) the development of an organic apical systolic murmur or an aortic diastolic murmur under acceptable observation‡; (b) a change of heart size of more than 15% on standard x-ray film by any standard method of measurement; (c) pericarditis revealed by a definite friction rub or by pericardial effusion; (d) congestive failure, in a patient under 25 years and in the absence of other causes, and shown by one or more of the following: (1) dyspnoea, (2) orthopnoea, (3) enlargement of the liver, (4) basal pulmonary rales, (5) increased jugular venous pressure, or (6) oedema.*

In the assessment of carditis as a criterion for entry to the trial, it was assumed in patients with no known pre-existing rheumatic heart disease or history of an attack of acute rheumatic fever, that previous to the current illness the patient's heart was of normal size and that there were no rheumatic murmurs. In other patients, observations of changes in heart size and murmurs were used in determining carditis, and recorded.

(2) POLYARTHRITIS, *as shown by pain and either limitation of active motion or tenderness, in two or more joints.*

(3) CHOREA, *with movements of at least moderate severity.*

(4) SUBCUTANEOUS NODULES.

(5) ERYTHEMA MARGINATUM (or ANNULARE).

Minor Manifestations

(1) FEVER, *defined as any temperature above 99.3° F. (37.4° C.) by mouth or 100.3° F. (38° C.) rectally, occurring at least twice in one period of 24 hours, or above 100.3° F. (38° C.) by mouth or 101.3° F. (38.5° C.) rectally, observed on any one occasion.*

(2) ELEVATED SEDIMENTATION RATE, *defined as 15 mm./hr. or above (Wintrobe (1935), corrected by the Whitby and Hines chart to a haematocrit of 45%).*

(3) EVIDENCE OF PREVIOUS STREPTOCOCCAL INFECTION, *as shown by a culture in which beta-haemolytic streptococcus predominated, or by an antistreptolysin O titre of 200 units or greater, or by a reliable history of sore throat with fever preceding the onset of illness by an interval of one week to one month.*

(4) AN INCREASED P–R INTERVAL, *defined as a value at least 0.04 sec. beyond those given in the Ashman and Hull (1947) tables for ages under 16.*

(5) A RELIABLE HISTORY OF RHEUMATIC FEVER, *as defined in these criteria or* EVIDENCE OF PRE-EXISTING RHEUMATIC HEART DISEASE—*namely, an apical organic systolic murmur, an apical diastolic or a basal diastolic murmur.*

These criteria having been specified, it was ruled that to be admitted to the study the patient must (*a*) at some time during the illness which brought him to the centre have exhibited at least two major manifestations *or* one major and two minor manifestations, and (*b*) on the first day of the allotted therapy show evidence of any one major manifestation *or* of any two of the three following minor manifestations—fever, elevated sedimentation rate, increased P–R interval.

It was arbitrarily decided that an interval of at least three months with no rheumatic activity must have preceded the present illness to justify its being called a new attack. With any shorter interval of time between the present and a previous illness, the present illness was held to be an exacerbation of symptoms of the previous attack and not a new attack. In such instances, the date of onset was referred back to the beginning of the illness.§

Patients who had had previous hormone therapy were excluded from the trial (a single test dose previously administered was not regarded as therapy). If a patient was receiving salicylate therapy, that treatment was discontinued upon admission to the hospital, before the patient was considered for inclusion. If such a patient subsequently satisfied the criteria he was eligible and admitted in the ordinary way.

*The one year follow-up data represent observations made at a calendar year from the end of the nine-weeks period of treatment and observation (61 weeks from the start of therapy).

†These modified criteria are not necessarily applicable for general use by the practising physician, particularly in questionable cases where continued observation of patients may be necessary for definitive diagnosis.

‡The development of an apical mid-diastolic murmur was also used for the diagnosis of carditis in U.K. centres, but there was only one case in which the diagnosis of carditis rested solely on this murmur, and this case was eligible under other criteria.

§"Onset" was defined as the date of the first observation of any major manifestation or any minor manifestation that appeared to be related in a continuous time sequence to the development of any major manifestation.

Treatment Plan

Dosage Schedules

The dosage schedules of A.C.T.H., cortisone, and aspirin were based (in 1950) on published studies, modified by reports from investigators to Armour Laboratories and Merck and Company. From such information, a dosage was selected to be effective for a period of administration short enough to indicate whether the acute attack had been differentially shortened by any one of the three drugs. Provision was made for decreasing the dosage if toxic manifestations appeared and for "tapering off" so that cessation of therapy would not be abrupt.

While the same hormone dosage was used for all patients, the dosage schedule of aspirin was calculated on the basis of body weight. Cortisone and A.C.T.H. were administered intramuscularly, while aspirin was given by mouth.

The dosage schedules were:

*A.C.T.H.**—All cases U.K. and eight cases U.S.†: a total daily dosage of 80 U.S.P. units for the first four days, 60 units for the next three days, 40 units for the second and third weeks, 30 units for the fourth and fifth weeks, and 20 units for the sixth week, administered every six hours.

All but eight cases U.S.: a total daily dosage of 120 U.S.P. units for the first four days, 100 units for the next three days, 80 units for the second week, 60 units for the third week, 40 units for the fourth and fifth weeks, 20 units for the sixth week, administered every six hours.

The A.C.T.H. dosage in the U.S. was increased early in the study, because with the relatively poor methods available for lot standardization and the lack of dramatic response in the first few cases treated, it was held possible that optimum dosage was not being administered. In regard to the question of "adequacy" of hormone dosage, it is of interest that practically all cases receiving A.C.T.H. or cortisone had side-effects, the details of which are presented later.

Cortisone.‡—A total daily dosage of 300 mg. for the first day, 200 mg. for the next four days, 100 mg. for the remainder of the first three weeks, 75 mg. for the fourth and fifth weeks, 50 mg. for the sixth week.

In the few cases where the hormone dosage was reduced because of undesirable side-effects, the percentage stepwise reduction in dosage thereafter remained unchanged.

Aspirin (acetylsalicylic acid, U.S.P. or B.P., 0.3 g. (5 gr.) tablets).—A total daily dosage of 60 mg. (1 gr.) per lb. of body weight (140 mg. per kg.) or 10 g. (150 gr.) total dosage, whichever was less, for the first two days; 40 mg. (⅔ gr.) per lb. (100 mg. per kg.), or 10 g. (150 gr.), whichever was less, for the next five days; 30 mg. (½ gr.) per lb. (70 mg. per kg.) for the remainder of the six weeks. Administered every four hours for 48 hours, every six hours thereafter. Aspirin was administered without bicarbonate of soda.

Patients unable to tolerate aspirin in the scheduled dosage received the largest amounts that they could tolerate as determined by the investigator. This occurred mainly in the older patients where the body-weight dosage produced side-effects. Conversely, because of the weight-dosage formula, small children did not receive aspirin up to the limit of tolerance.§

During the three-weeks observation period following the six-weeks course of therapy, none of these drugs was administered unless the investigator believed that the patient's condition was so poor as to endanger life or the polyarthritis so painful that it could not otherwise be controlled. In such cases, re-treatment was given for a period of four weeks, using the same drug and dosage as in the first four weeks of initial therapy; it was followed by a three-weeks observation period as before.

If re-treatment was necessary at any time during the three months following the original course of therapy, then the above four-weeks re-treatment scheme was followed. No patient was re-treated unless he demonstrated rheumatic activity sufficient to have brought him into the study initially.

If after three months without activity the patient developed a new attack of rheumatic fever, he was treated as in the original course—that is, for six weeks on the same drug and dosage, followed by a three-weeks period of observation.

Auxiliary Therapy

Sodium and Potassium Intake.—To minimize salt retention in hormone-treated patients, and to maintain comparability among the three treatment groups, the dietary intake of sodium was restricted to less than 2 g. per day for all patients for at least four weeks. All patients received added potassium chloride by mouth daily, 2 g. for those weighing less than 60 lb. (27.2 kg.) and 3 g. for those 60 lb. (27.2 kg.) or more, except that those few who developed oliguria due to congestive failure received no added potassium. Serum potassium levels were estimated weekly.

Streptococcal Prophylaxis.—Every effort was made through streptococcal prophylaxis to prevent recurrent attacks of rheumatic fever which would introduce an additional variable in the study. All patients, upon admission to the study and on the fourth, seventh, and tenth days of treatment, received procaine penicillin G in aluminium monostearate intramuscularly, 300,000 units for those weighing less than 60 lb. (27.2 kg.), 600,000 units for those 60 lb. (27.2 kg.) or more.‖ On the 14th day after admission to the study, and continuously thereafter, sulphadiazine was administered in a dose of ½ g. per day to those weighing less than 60 lb. (27.2 kg.) and 1 g. per day to those weighing 60 lb. (27.2 kg.) or more. (In a few patients, oral penicillin in a dose of 100,000 units twice a day was substituted when sensitivity to sulphadiazine developed.) Sera were drawn for determination of antistreptolysin-O titres (Massell and Miller's unpublished technique modified from Hodge and Swift, 1933) at weeks 0, 5, 9, and 13, and at each follow-up examination, to detect intercurrent streptococcal infection.

In addition to this routine, throat cultures were made on all patients on admission to hospital, and thereafter whenever there was indication of a throat infection. Those with positive cultures received penicillin therapy, as prescribed by the investigator.

Other Therapy.—All but a few patients were kept at bed rest for the nine weeks of therapy and observation. In a few cases of chorea, sedatives were necessary. No antirheumatic drugs other than those allocated for the study were given. Therapy necessary for any complicating illness was recorded.

Allocation of Patients to Treatment

Patients on admission to the study were divided into two age groups, 0 to 15 years and 16 and over, and into three groups according to the length of time in each case between the date of onset of the attack and the date at which therapy began. The three duration-from-onset groups were (1) 14 days or less; (2) 15 to 42 days; (3) 43 days and over.

For each of these three duration groups, within each age group, and separately for each treatment centre, the three treatments, A.C.T.H., cortisone, and aspirin, were listed in

*A.C.T.H., donated by Armour Laboratories, was in three lots of water-soluble material standardized on both animals and human beings. All the U.K. cases were treated with one lot (K-50601R), while most of the U.S. cases received a second lot (J-24109R), although a few were treated with a third lot (L-56702). The U.S.P. unit is expressed as a milligram equivalent of A.C.T.H. lot number LA-IA.

†One Canadian centre took part in the trial, but for easy reference the term "U.S." is used to include all North American centres.

‡Cortisone, donated by Merck and Company, was the regular commercial preparation for intramuscular use—namely, the acetate of 17-hydroxy-11-dehydrocorticosterone, suspended in a vehicle consisting of sodium carboxymethyl cellulose, Tween 80, and 1.5% benzyl alcohol in isotonic saline.

§Salicylate blood levels determined in two U.S. centres showed a positive correlation with body weight; lower blood levels found in one U.K. centre revealed no such relationship.

‖At the House of the Good Samaritan (Boston) a variable dosage schedule was used.

TABLE 1.—*Details of 15 Cases Admitted to the Study in Which the Treatment and Observation Schedule was not Followed, with Reference to Their Inclusion or Exclusion From the Analysis.*

Treatment Group	Treatment Stopped (5 Cases)	Treatment Changed (5 Cases)	Re-treatment (4 Cases)	Treatment Incomplete (1 Case)
A.C.T.H. (4 cases) ..	(1) U.S. gastric haemorrhage 6th day. Excluded (2) U.S. renal haemorrhage 21st day. Included (3) U.S. toxicity[1] 27th day. Included (4) U.K. toxicity[2] 32nd day. Included			
Cortisone (3 cases) ..			(11) U.S. re-treated 48th day. Included (12) U.S. re-treated 50th day. Included	(15) U.S. patient left hospital 12th day.[3] Excluded
Aspirin (8 cases) ..	(5) U.S. discharged from hospital 41st day.[4] Included	(6) U.S. in failure. Changed to A.C.T.H. 8th day. Excluded (7) U.S. carditis and failure. Changed to A.C.T.H. 28th day. Included under aspirin (8) U.S. carditis. Changed to A.C.T.H. 28th day. Included under aspirin (9) U.S. carditis. Changed to cortisone 50th day. Included under aspirin (10) U.K. pericarditis and failure. Changed to cortisone 51st day. Included under aspirin	(13) U.S. re-treated 45th day. Included (14) U.S. re-treated 58th day. Included	

[1] Unusually rapid weight gain and enlargement of liver not responding to mercurial diuretics. [2] Too rapid development of moonface. [3] Family moved to another city. [4] Child was an unmanageable behaviour problem.

random order for as many patients as were likely to be admitted, using random sampling numbers and keeping the numbers of patients on the three treatments approximately equal in each centre. The co-ordinating centre in each country issued serially numbered and sealed envelopes to the treatment centres. Thus, on admission of a patient of given age and specified duration-from-onset group, the investigator at the treatment centre had merely to open the next available envelope for that particular group to find a statement of the treatment to be applied. He was therefore unable to predict the treatment for his next case. The allocation was both "blind" and random.*

The admission report on the patient, and the assignment envelope, were then sent to the co-ordinating centre. If for any special reason the investigator decided in advance that a patient fulfilling the criteria should not be admitted to the study, no envelope was opened. In every such case, however, an admission report was required, together with an explanation as to why the patient had not been admitted. Six such cases were reported in the U.S.; none in the U.K.†

The Study Sample

In all, 505 children under 16 years of age were admitted to the study—242 in the U.K. between March 2, 1951, and October 6, 1952, and 263 in the U.S. between January 15, 1951, and June 15, 1952. Four of these cases were subsequently excluded when their illness proved to be a disease other than rheumatic fever. These were a case on cortisone (U.K.) of Henoch–Schönlein purpura, a case on aspirin (U.K.) of tuberculous meningitis, a case on A.C.T.H. (U.S.) of lupus erythematosus disseminatus, and a case on A.C.T.H. (U.S.) of salmonella infection. In another case on A.C.T.H. (U.S.) there was *x*-ray evidence of tuberculous infection superimposed upon the rheumatic fever, and hormone treatment was therefore withheld. These five exclusions present no problem.

In the remaining 500 patients (240 U.K., 260 U.S.) there was only the small number of 15, or 3%, in whom the prescribed treatment and observation schedule was not fully carried out (2 U.K., 13 U.S.). Table 1 shows their nature and the action taken with regard to them. Only three (Cases 1, 6, and 15) have been wholly excluded from the statistical analysis of the trial, since their treatment with the allotted drug was very brief (6, 8, and 12 days). All other cases had been treated for three weeks or longer. Three of them (Cases 2, 3, and 4) fall within the original provision for a reduction of dosage when essential, and four (Cases 11, 12, 13, and 14) within the provisions for re-treatment in active cases. Such patients, together with one (Case 5) that left the hospital after the six weeks of therapy, can be included under the allotted therapy without any difficulty.

There remain four aspirin cases in which, on account of the severity of the illness, the investigator administered hormone treatment. In two (Cases 7 and 8) a change to A.C.T.H. was made during the treatment period (on the 28th day); in two, treatment with cortisone was instituted during the observation period (on the 50th and 51st days), after completion of the aspirin treatment. It was thought better to continue these cases in the aspirin group in spite of the change of treatment, since the exclusion of these four cases from the analysis at these points of time would make the picture of the aspirin group somewhat too favourable, since severely ill cases were being artificially removed from it.

Altogether, it is clear that these three exclusions, four changes of the allotted treatment, and eight variations of the treatment schedule can have had no appreciable effect upon the results of the trial.

Two U.S. and four U.K. patients died during the first year and are included in the analysis.

Taken as a whole, the 497 cases under age 16 show the following features. There were, altogether, 14 cases (3%) aged 3 or 4 years, 200 (40%) aged 5 to 9 years, and 283 (57%) aged 10 to 15 years. In just over one-half (255) the allotted therapy was begun within 14 days of the onset of the attack, and a more detailed analysis shows that 149, or 60%, of these "early" cases were treated within one week of onset. In nearly two-thirds (327 cases) there was neither history of a previous attack of rheumatic fever nor evidence of pre-existing rheumatic heart disease. Only 128,

*In a few centres, for varying durations of time, the investigators wished to withhold some patients for other studies. In these instances a predetermined proportion of the envelopes contained, as an instruction, "free case." Such exclusions, therefore, were also "blind" and randomly determined, and could not bias the group brought into the study.

†These six cases were: one, with schizoid personality, considered unsuitable for the trial; one, excluded because his private physician insisted upon cortisone therapy; and four severe cases excluded in one centre under provision of the protocol—namely, "If in the opinion of the principal investigator, the patient is severely ill to the point where his life is in danger, that patient may be removed from any group and given therapy at the discretion of the investigator." These four cases were treated with A.C.T.H. as follows: (1) a 12-year-old boy in a sixth attack with acute carditis, mitral insufficiency, and congestive failure made a smooth recovery without residual heart disease; (2) a 9-year-old girl in a second attack with residual heart disease, mitral insufficiency, and congestive failure made a gradual but unremarkable recovery; (3) a 12-year-old girl in a second attack, with residual heart disease, acute carditis, mitral insufficiency, and congestive failure, made, after a stormy course, a slow recovery with persistence of chronic heart disease with increasing cardiac enlargement; and (4) a 9-year-old boy in a first attack with mitral insufficiency, pericarditis, and congestive failure died after seven days of treatment.

or approximately one-quarter, of the 497 cases were in fact definitely diagnosed as having pre-existing rheumatic heart disease at the start of therapy. Mitral stenosis as shown by an apical pre-systolic murmur was reported in only 16 cases. In general, therefore, the group contained a large proportion of cases still in the early stages of the disease.

Comparability of Treatment Groups at Start of Therapy

The method of allocation ensured that in each treatment group there was approximately the same number of cases with regard to the duration from onset of attack to start of therapy. Thus, there were on A.C.T.H., cortisone, and aspirin, respectively, 86, 85, and 84 "early" cases (0 to 14 days); 47, 45, and 46 "medium" cases (15 to 42 days); and 29, 37, and 38 "late" cases (43 days or more) (Table 2).

TABLE 2.—*Comparison of Treatment Groups at Start of Therapy: Duration of Illness from Onset, Sex, Mean Age, and Mean Weight*

Treatment Group	Total Cases	Duration from Onset			Sex		Mean Age (Years)	Mean Weight (lb.)
		0–14 Days	15–42 Days	43+ Days	M	F		
U.K.:								
A.C.T.H.	80	39	27	14	40	40	10·0	66·0
Cortisone	80	38	25	17	34	46	9·9	63·6
Aspirin ..	80	32	27	21	40	40	9·6	64·4
Total ..	240	109	79	52	114	126	9·8	64·7
U.S.:								
A.C.T.H.	82	47	20	15	51	31	9·9	71·4
Cortisone	87	47	20	20	45	42	10·1	71·7
Aspirin ..	88	52	19	17	49	39	10·2	73·6
Total ..	257	146	59	52	145	112	10·1	72·2
U.K. and U.S.:								
A.C.T.H.	**162**	**86**	**47**	**29**	**91**	**71**	**10·0**	**68·8**
Cortisone	**167**	**85**	**45**	**37**	**79**	**88**	**10·0**	**67·9**
Aspirin ..	**168**	**84**	**46**	**38**	**89**	**79**	**9·9**	**69·2**
Total ..	**497**	**255**	**138**	**104**	**259**	**238**	**10·0**	**68·6**

The average age and mean body weight in the three treatment groups were almost identical, and the sex distribution was reasonably alike. In general, it is clear that the balance produced by the design of the study permits amalgamation of the duration-from-onset groups and of the data for the two countries.

Clinical features of the three treatment groups at the start of therapy are compared in Table 3. With regard to the first item, temperature, it should be noted that oral temperatures were taken in the U.K. (except at one centre) and rectal temperatures in the U.S. (except at one centre). An arbitrary correction of each oral reading was made by the addition of 1° F., and the tabulations are of the maximum "rectal temperature" recorded on each day. As the distribution of patients in each centre was evenly divided among the three treatment groups, the comparison between treatments should not be biased, even though the arbitrary temperature correction may be imperfect. It will be seen that at the start of therapy there was a larger proportion of U.S. cases (57.6%) with a rectal temperature of 100.4° F. (38° C.) or above than of U.K. cases (45.4%). This difference may be real, but it is possible that the addition of 1° F. to the oral temperature may not make the latter entirely equivalent to the rectal temperatures taken in the U.S.

The proportion of cases initially febrile (those with a temperature of 100.4° F. or greater) among the three treatment groups is dependent upon whether comparison is made on the first day of treatment or on the day before treatment was begun. On the first day of treatment there was a smaller proportion of cases febrile in the aspirin group (40.5%) than in the cortisone (61.1%) or the A.C.T.H. (53.7%) group. These differences were in part due to the more immediate antipyretic effect of aspirin in comparison with A.C.T.H. and the slowly absorbed intramuscular cortisone. This is borne out by the proportions of cases febrile on the day before therapy was started in the A.C.T.H. (61.7%), cortisone (58.1%), and aspirin (53.0%) groups.

The pulse during sleep and the erythrocyte sedimentation rates reveal no material difference (Table 3). Their mean values also showed no real differences, the average pulse during sleep being 93, 93, and 90, and the average E.S.R. 46.7, 46.2, and 45.1, for the A.C.T.H., cortisone, and aspirin groups respectively.

Within each country, the treatment groups do not differ appreciably in their incidence of joint involvement, subcutaneous nodules, and erythema marginatum, but there appears to be some difference in these respects between the two countries. The proportion of cases showing these signs (Table 3) were: joint involvement U.K. 36.7%, U.S. 49.4%; subcutaneous nodules U.K. 21.7%, U.S. 7.4%; erythema marginatum U.K. 7.9%, U.S. 3.9%. The last difference might well be due to chance, but the first two (joint involvement and subcutaneous nodules) are statistically significant ($P<0.05$). On the other hand, subdivision of these cases into early, medium, or late (Tables 10 and 15) suggests that there is no real difference between the two countries in the incidence of joint involvement. Nodules were observed more frequently in the U.K. at each stage, and particularly in the late cases.

TABLE 3.—*Comparison of Treatment Groups at Start of Therapy: Percentage with Specified Symptoms*

		Treatment Group			Total
		A.C.T.H.	Cortisone	Aspirin	
Number of cases	U.K.	80	80	80	240
	U.S.	82	87	88	257
	U.K. and U.S.	**162**	**167**	**168**	**497**
Temperature 100·4° F. (38° C.) or more (rectal)	U.K.	47·5	51·2	37·5	**45·4**
	U.S.	59·8	70·1	43·2	**57·6**
	U.K. and U.S.	**53·7**	**61·1**	**40·5**	**51·7**
Pulse during sleep 100 or more per minute	U.K.	41·8	33·3	34·6	**36·6**
	U.S.	29·2	36·0	26·1	**30·6**
	U.K. and U.S.	**35·8**	**34·6**	**30·6**	**33·7**
E.S.R. 20 mm./hr. or more	U.K.	87·5	86·2	88·8	**87·5**
	U.S.	96·3	93·8	94·1	**94·7**
	U.K. and U.S.	**91·9**	**90·0**	**91·5**	**91·2**
Joint involvement	U.K.	33·8	36·2	40·0	**36·7**
	U.S.	43·9	56·3	47·7	**49·4**
	U.K. and U.S.	**38·9**	**46·7**	**44·0**	**43·3**
Subcutaneous nodules	U.K.	22·5	23·8	18·8	**21·7**
	U.S.	9·8	6·9	5·7	**7·4**
	U.K. and U.S.	**16·0**	**15·0**	**11·9**	**14·3**
Chorea	U.K.	8·8	13·8	22·5	**15·0**
	U.S.	2·4	9·2	9·1	**7·0**
	U.K. and U.S.	**5·6**	**11·4**	**15·5**	**10·9**
Erythema marginatum	U.K.	10·0	8·8	5·0	**7·9**
	U.S.	4·9	4·6	2·3	**3·9**
	U.K. and U.S.	**7·4**	**6·6**	**3·6**	**5·8**
Pre-existing rheumatic heart disease	U.K.	31·2	32·5	31·2	**31·7**
	U.S.	28·0	14·9	18·2	**20·2**
	U.K. and U.S.	**29·6**	**23·4**	**24·4**	**25·8**
Pericarditis	U.K.	10·0	16·2	5·0	**10·4**
	U.S.	6·1	3·4	5·7	**5·1**
	U.K. and U.S.	**8·0**	**9·6**	**5·4**	**7·6**
Congestive failure	U.K.	12·5	10·0	3·8	**8·8**
	U.S.	15·9	8·0	8·0	**10·5**
	U.K. and U.S.	**14·2**	**9·0**	**6·0**	**9·7**
Cardiothoracic ratio of 0·55 or more	U.K.	21·5	26·0	13·3	**20·3**
	U.S.	22·5	11·8	10·5	**14·7**
	U.K. and U.S.	**22·0**	**18·5**	**11·8**	**17·4**
Atrioventricular conduction time of 0·18 sec. or more	U.K.	32·5	30·1	24·4	**28·9**
	U.S.	34·2	38·3	32·1	**34·9**
	U.K. and U.S.	**33·3**	**34·4**	**28·3**	**32·0**
No organic murmur	U.K.	20 0	13·8	17·5	**17·1**
	U.S.	26·8	33·3	36·4	**32·3**
	U.K. and U.S.	**23·5**	**24·0**	**27·4**	**24·9**
Apical systolic murmur	U.K.	75·0	77·5	73·8	**75·4**
	U.S.	69·5	64·4	59·1	**64·2**
	U.K. and U.S.	**72·2**	**70·7**	**66·1**	**69·6**
Apical mid-diastolic murmur	U.K.	48·8	46·2	45·0	**46·7**
	U.S.	34·1	23·0	25·0	**27·2**
	U.K. and U.S.	**41·4**	**34·1**	**34·5**	**36·6**
Basal diastolic murmur	U.K.	38·8	35·0	33·8	**35·8**
	U.S.	12·2	12·6	11·4	**12·1**
	U.K. and U.S.	**25·3**	**23·4**	**22·0**	**23·5**
Apical presystolic murmur	U.K.	5·0	2·5	1·3	**2·9**
	U.S.	4·9	3·4	2·3	**3·5**
	U.K. and U.S.	**4·9**	**3·0**	**1·8**	**3·2**

Returning to Table 3, chorea was recorded more frequently in the U.K.; in both countries chance factors brought fewer cases into the A.C.T.H. group and more into the aspirin. Thus in the total group of 162 on A.C.T.H., 167 on cortisone, and 168 on aspirin there were 9, 19, and 26 cases with chorea as a presenting symptom. Severe cases, however, numbered only four, two, and five.

For a general picture of the status of the heart at start of therapy, the 497 cases have been divided (Table 4) into groups depending on the presence or absence of pre-existing rheumatic heart disease and carditis (as defined in the diagnostic criteria). Groups A and B contain all the cases without evidence of pre-existing heart disease at the time of admission. Group A includes: (1) cases with no carditis; (2) cases with murmurs of questionable significance (doubtful carditis); (3) cases with no, or doubtful, carditis but with a prolonged P–R interval. Group B includes cases with definite carditis at the start of therapy. Within both these groups, the number of cases with a definite previous history of rheumatic fever was negligible. Group C contains all those with definite or doubtful pre-existing rheumatic heart disease, whether or not carditis was also present. Both groups B and C are further subdivided into (1) cases with and (2) cases without pericarditis and/or failure at start of therapy.

Table 4 shows that the cases analysed in this way have in general fallen equally into the three treatment groups. The main departure lies in a somewhat lower number of cases on A.C.T.H. in group B (no pre-existing heart disease, carditis present at start of treatment). In the less important C group, in which the course of the disease is difficult to analyse because of pre-existing rheumatic heart disease, there is some predominance of cases with pericarditis and/or failure in the A.C.T.H. group.

TABLE 4.—*Condition of the Heart at Start of Therapy, by Duration from Onset. U.K. and U.S., all Cases*

Cardiac Group and Treatment Group	Total	Duration from Onset		
		0–14 Days	15–42 Days	43+ Days
Cardiac Group A—no or questionable carditis;* no pre-existing heart disease:				
A.C.T.H.	40	30	6	4
Cortisone	39	29	6	4
Aspirin	38	26	10	2
Total Group A	117	85	22	10
Cardiac Group B—carditis present; no pre-existing heart disease:				
A.C.T.H.	74	34	29	11
Cortisone	89	38	29	22
Aspirin	89	44	24	21
Total Group B	252	116	82	54
Cardiac Group C—with definite or questionable pre-existing heart disease:				
A.C.T.H.	48	22	12	14
Cortisone	39	18	10	11
Aspirin	41	14	12	15
Total Group C	128	54	34	40
Cases with failure and/or pericarditis included in Cardiac Group B:				
A.C.T.H.	13	4	6	3
Cortisone	14	3	7	4
Aspirin	10	7	—	3
Total	37	14	13	10
Cases with failure and/or pericarditis included in Cardiac Group C:				
A.C.T.H.	14	5	4	5
Cortisone	10	5	3	2
Aspirin	7	3	—	4
Total	31	13	7	11

* Questionable carditis includes 8 A.C.T.H., 6 cortisone, and 7 aspirin cases with a grade P murmur and 13 A.C.T.H., 12 cortisone, and 10 aspirin cases with a prolonged P–R interval and either no murmur or grade P murmur. (For definition of grade P murmur, see footnote to section on Murmurs.)

Returning to the incidence of the individual signs of involvement of the heart at start of therapy, Table 3 shows, for A.C.T.H., cortisone, and aspirin respectively, no appreciable differences for apical systolic murmurs (72.2%, 70.7%, and 66.1%), basal diastolic murmurs (25.3%, 23.4%, and 22.0%), and the proportion of cases with atrio-ventricular conduction time of 0.18 sec. or more (33.3%, 34.4%, and 28.3%). The proportions with a cardio-thoracic ratio of 0.55 or more were not equal, there being a smaller proportion in the aspirin group (22.0%, 18.5%, and 11.8%), but, as will be seen in the section on heart size (Table 20), this is largely due to the unequal distribution of cases with pre-existing heart disease (Group C). There was also a somewhat larger number of cases in failure at the start of therapy in the A.C.T.H. group, compared with the cortisone and aspirin groups (14.2%, 9.0%, and 6.0%).

Between the two countries, the individual signs of cardiac involvement were equally reported except for basal diastolic murmurs. These were more often reported in the U.K. (35.8%) than in the U.S. (12.1%), but this difference came from one U.K. centre only. Ninety-three of the 240 U.K. cases came from this centre, where the incidence of basal diastolic murmurs was 73.1%. In the remainder of the U.K. centres the incidence was 12.2%.

In short, these comparisons show that in many respects the three treatment groups were very similar—namely, in the duration-from-onset, age, sex, body weight, temperature, pulse during sleep, erythrocyte sedimentation rate, frequency of polyarthritis,* subcutaneous nodules, erythema marginatum, and in the P–R interval. There are, however, a few differences. The group on aspirin included an undue proportion with chorea as a presenting symptom, although the few severe cases of chorea fell fairly equally in the three treatment groups. The A.C.T.H. group contained a larger proportion of cases with pericarditis and/or failure (particularly in the U.S.), and the aspirin group contained rather fewer (particularly in the U.K.). These differences are not large, but must be borne in mind in the study of the response of the illness to the different treatments.

Results

The course of rheumatic fever was followed in each case after admission to the study during the six-weeks period of treatment, three-weeks period of observation, at monthly intervals for six months following the end of the observation period, and at two-months intervals until the end of the first year (quarterly thereafter). This report includes an analysis of each symptom, sign, and laboratory test considered as evidence of active rheumatic fever or of rheumatic heart disease through a period of one year following the end of the observation period.

Each manifestation is considered at specified points of time and discussed individually. The methods of analysis include: comparison of averages; the proportion with a change greater than an arbitrary maximum amount: the proportion with a manifestation present or absent; the number, or percentage, above or below an arbitrary limit of normal. (With this last method of analysis, a constant number or percentage over a period of time does not indicate that the same cases continue abnormal but that of all the cases at risk the number abnormal remains the same.) In general, when several such indices yielded the same results, the simplest is reported; when two methods yielded differing results, both are reported. When a difference between treatment groups in one of these measurements is significant the probability value is reported; otherwise differences in results between treatments are not significant.

Temperature

Temperatures were measured four times a day throughout the nine-weeks period of treatment and observation. The maximum reading for each day is used in this analysis,

and cases are considered febrile if that reading (rectal) was 100.4° F. (38° C.) or above. The three groups were comparable on the day before treatment (Chart I). Following start of treatment, the proportion of febrile cases decreased rapidly in all three groups, although it was most rapid on the first day in the aspirin group (Chart I, Table 5). During the latter part of the first week the proportion febrile in the A.C.T.H. group was lower than that of the other two groups, but at the end of the week all three groups were in the same range, the aspirin group lagging slightly behind. In the main this lag in the aspirin group persisted throughout the six-weeks period of treatment, and was more prominent among the cases febrile than among those afebrile at start of treatment.

At the end of the sixth week of treatment there was a rise in the proportion of febrile cases in the A.C.T.H. group, persisting into the eighth week and then slowly decreasing. A similar rise occurred in the cortisone group, beginning in the seventh week, reaching a peak in the eighth, and decreasing slowly during the ninth week. The aspirin group showed a smaller rise with its peak in the seventh week, and decreasing during the eighth and ninth weeks. At the end of the ninth week all three groups had about the same proportion of febrile and afebrile cases (Table 6).

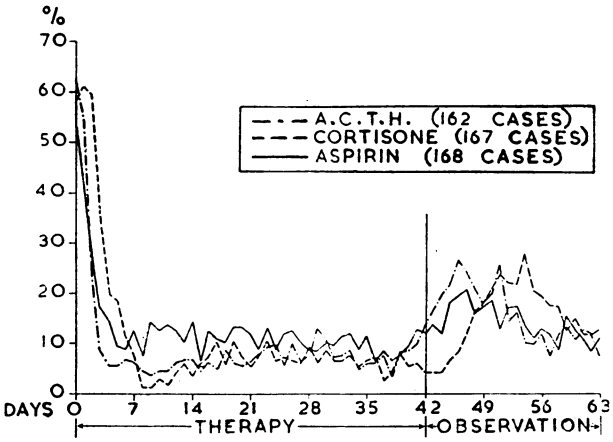

CHART I.—Temperature. Percentage of cases on each day with a rectal temperature of 100.4° F. (38° C.) or above

TABLE 5.—*Temperature: Percentage of Cases with a Rectal Temperature of 100.4° F. (38° C.) or Above at Specified Times.* U.K. and U.S., all Cases*

Treatment Group	No. of Cases	Start of Therapy	Week of Therapy 1	2	3	4	5	6	Week of Observation 7	8	9
All Cases											
A.C.T.H.	162	53·7	5·8	6·0	6·6	8·9	5·8	13·4	19·3	9·7	9·6
Cortisone	167	61·1	6·8	5·2	6·8	7·0	6·4	4·8	18·2	19·1	12·2
Aspirin	168	40·5	9·7	10·3	11·3	9·1	8·9	12·8	17·0	11·9	9·5
Febrile Cases at Start of Treatment											
A.C.T.H.	87	100·0	5·8	7·7	6·9	10·0	6·5	14·1	21·8	9·6	6·7
Cortisone	102	100·0	6·5	6·2	7·0	7·6	5·6	4·3	20·6	20·9	12·0
Aspirin	68	100·0	12·7	15·7	16·7	14·3	8·3	13·7	20·2	13·6	12·5
Afebrile Cases at Start of Treatment											
A.C.T.H.	75	0·0	5·8	4·0	6·2	7·6	4·9	12·5	16·4	9·9	12·9
Cortisone	65	0·0	7·3	3·6	6·7	6·2	7·7	5·6	14·5	16·4	12·5
Aspirin	100	0·0	7·7	6·7	7·7	5·7	9·4	12·1	14·9	10·7	7·4

* To reduce irregularities, the values given for the end of the weeks are based upon all the observations made on *three* days centred at the end of the week—i.e., 6, 7, and 8 for week 1; 13, 14, and 15 for week 2; and so on up to days 62 and 63 for week 9.

TABLE 6.—*Temperature: Distribution at End of Ninth Week. U.K. and U.S., all Cases*

Rectal Temperature	No. with given Temperature at the End of the Ninth Week A.C.T.H.	Cortisone	Aspirin
97·4° F. (36·3° C.)-	3	4	5
98·4° F. (36·9° C.)-	33	47	41
99·4° F. (37·4° C.)-	104	92	101
100·4° F. (38·0° C.)-	18	18	12
101·4° F. (38·6° C.)+	1	1	1
Not stated	3	5	8
Total	162	167	168

Pulse Rate During Sleep

The pulse rate was taken during sleep, between the hours of 12 midnight and 5 a.m. At start of treatment (Table 7), 31% to 36% of the patients in each group had a pulse rate of 100 per minute or more (tachycardia), while less than 5% had a rate of less than 60 per minute (bradycardia).

TABLE 7.—*Pulse Rate During Sleep: Percentage of Cases with Bradycardia (under 60) and Tachycardia (100 and over) at Specified Times.* U.K. and U.S., all Cases*

Treatment Group	No. of Cases	Start of Therapy	Week of Therapy 1	2	3	4	5	6	Week of Observation 7	8	9
Percentage with Bradycardia											
A.C.T.H.	162	4·6	14·7	10·9	7·4	6·1	3·8	2·5	0·0	0·6	0·7
Cortisone	167	2·0	18·3	24·7	13·7	12·0	8·3	6·9	2·0	0·4	0·3
Aspirin	168	4·1	4·8	10·0	9·3	7·1	4·3	1·6	3·8	1·5	4·3
Percentage with Tachycardia											
A.C.T.H.	162	35·8	13·9	10·7	9·6	13·9	12·7	13·3	24·6	21·4	21·3
Cortisone	167	34·6	10·1	6·5	7·2	7·5	6·3	5·9	13·2	22·7	20·1
Aspirin	168	30·6	10·1	7·9	6·9	7·3	5·3	6·8	10·7	8·8	6·7

* See footnote to Table 5.

Following start of treatment there was a slight rise in the proportion with tachycardia among the cortisone cases during the first two days. Apart from this, the proportion decreased at approximately the same rate in all three groups, reaching the same level in cortisone and aspirin at the end of the first week, the A.C.T.H. group having a slightly higher figure. These relative proportions remained unchanged throughout the treatment period. When therapy was stopped there was a sharp rise in the A.C.T.H. group and a slower rise to the same level in the cortisone group. At the end of the observation period one-fifth of the cases in both groups still had tachycardia. On the other hand, the proportion with tachycardia in the aspirin group remained almost unchanged when treatment ended and throughout the observation period (Table 7 and Chart II).

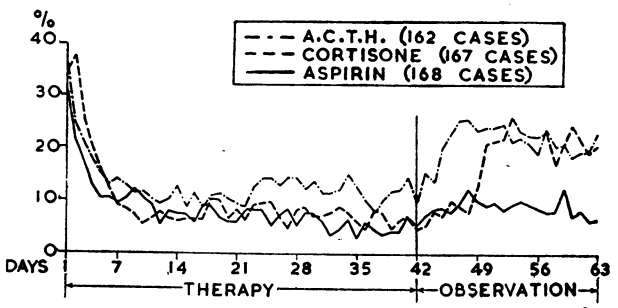

CHART II.—Tachycardia Percentage of cases on each day with a pulse rate of 100 or more.

Detailed analysis showed that in all treatment groups there was the same rapid fall in the proportion with tachycardia among the cases of short duration (0–14 days), while in those of longer duration (15+ days) it fell more slowly. Thus, starting from the same level of 30% to 40% with tachycardia, there was a fall at the end of the first week to only 1% to 8% among the cases of short duration, in comparison with 13% to 22% among those of longer duration. This latter group lagged behind until the fourth or fifth week.

TABLE 8.—*Erythrocyte Sedimentation Rate: Percentage of Cases with a Rate of 20 mm./hour or higher (uncorrected) at Specified Times,* U.K. and U.S., all Cases.*

Treatment Group	No. of Cases	Start of Therapy	Week of Therapy						Week of Observation			Follow-up	
			1	2	3	4	5	6	7	8	9	13 Wks.	1 Year
A.C.T.H. ..	162	91·9	64·3	28·1	17·1	20·3	22·8	20·6	47·2	43·0	32·2	11·6	10·3
Cortisone ..	167	90·0	87·3	46·1	38·8	28·2	23·0	19·1	24·8	44·1	41·8	16·1	12·8
Aspirin	168	91·5	79·0	66·7	49·4	39·6	32·9	22·0	24·8	23·6	21·4	13·5	12·8

* The observations were not always made on the final day of the week, but were in most cases made at weekly intervals. A margin of ±3 days was allowed in deriving weekly values.

The proportion with bradycardia increased sharply after the start of treatment in both hormone groups, reaching 14.7% in the A.C.T.H. group at the end of the first week and almost 25% in the cortisone group at the end of the second week. From this point the proportion with bradycardia decreased to approximately the starting level by the end of the treatment period. In contrast, bradycardia occurred later in the aspirin group, reaching a peak of a little over 10% in the second to third weeks, and declining thereafter (Table 7 and Chart III).

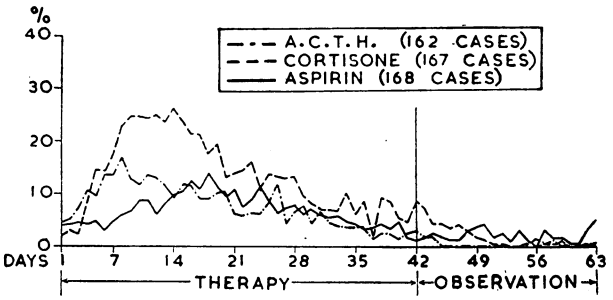

CHART III.—Bradycardia. Percentage of cases on each day with a pulse rate of 60 or less.

Erythrocyte Sedimentation Rate

The erythrocyte sedimentation rate was measured by the Wintrobe method (uncorrected)† at the start of treatment, weekly throughout the treatment and observation period, and at each follow-up examination. Its course was followed by tabulation of the proportion of cases with a rate of 20 mm. per hour at specified times.

At the start of treatment, approximately 90% of the cases in each treatment group had an elevated sedimentation rate. This proportion decreased rapidly in the hormone groups, with the A.C.T.H. group showing the sharpest drop, levelling off at the third week, in contrast to the cortisone group, which reached roughly this same level about the fifth week (Chart IV, Table 8). The proportion of those with an elevated rate in the aspirin group lagged distinctly behind that of both hormone groups, not reaching the same level until the last week of treatment. When treatment was stopped, however, there was a sharp rise in the proportion with a raised rate in the A.C.T.H. group, and a slower rise to the same level in the cortisone group, while there was no change in the aspirin group. By the 13th week the proportion in all three groups had reached the same low level of 12–16%. The very similar distribution of values at this point is shown in Table 9; at one year the proportions were relatively unchanged from the 13th-week figures. Separate analysis showed that these trends were the same for all three duration-from-onset groups.

†A corrected sedimentation rate of 15 mm./hr. or above was established as a minor diagnostic criterion for admission to the study, and was so used. In analysing the course of the disease for the first 13 weeks, an uncorrected rate of 20 mm./hr. or above was used, because (1) the centrifuges used in the haematocrit determinations were not standardized, with resulting variations from centre to centre, and (2) analysis of uncorrected and corrected readings for each of the drugs showed the same trends, and it seemed undesirable to introduce an unnecessary variable.

To summarize, during treatment the proportion with an elevated sedimentation rate decreased much more rapidly in the hormone groups than in the aspirin group, but it increased sharply, though temporarily, in both hormone groups after treatment was stopped, in contrast to a negligible change in the aspirin group. It finally reached the same low level in all three groups at 13 weeks, and this equal level was maintained at one year.

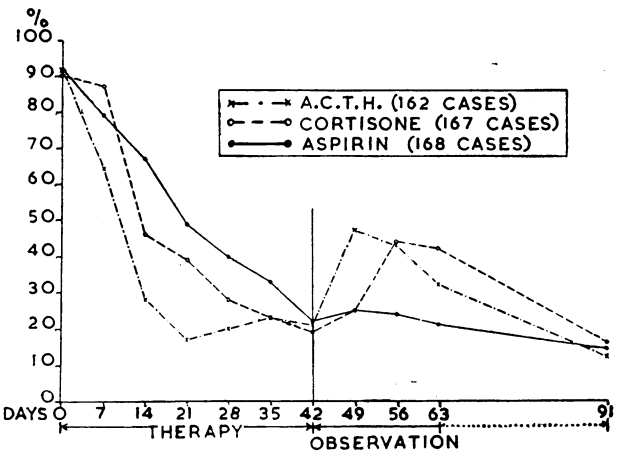

CHART IV.—Erythrocyte sedimentation rate. Percentage of cases with a rate of 20 mm./hr. or above (uncorrected Wintrobe).

TABLE 9.—*Erythrocyte Sedimentation Rate: Distribution at 13 Weeks. U.K. and U.S., all Cases*

Erythrocyte Sedimentation Rate (mm./hr. Uncorrected)	No. with Given Rate at 13 Weeks		
	A.C.T.H.	Cortisone	Aspirin
0–19	137	130	134
20–29	13	20	14
30–39	2	4	3
40–49	3	1	2
50–59	—	—	2
Not stated	7	12	13
Total	162	167	168

Joint Involvement‡

At start of therapy there was a greater proportion of cases with joint involvement in the U.S. centres (49.4%) than in the U.K. (36.7%), the difference occurring entirely among the early cases (Table 10). In both countries the percentages were about the same in each treatment group.

In each treatment group, cases with joint involvement on admission rapidly lost this symptom. Thus on the third day of therapy joint involvement was still present in 28.6% of A.C.T.H., 56.4% of cortisone, and 36.5% of aspirin cases.

‡Polyarthritis as a major manifestation for diagnosis of rheumatic fever was defined as "pain and either limitation of active motion, or tenderness in two or more joints." For following the course of this manifestation after start of treatment, a system of grading was adopted in which the lowest grade was defined as joint pain without objective joint findings. Since this lowest grade is less than that required for the definition of polyarthritis, the course of the manifestation is referred to as "joint involvement."

TABLE 10.—*Joint Involvement: Comparison of U.K. and U.S. Cases at Start of Therapy*

Duration from Onset at Start of Therapy (in Days)	U.K.			U.S.		
	Total Cases	With Joint Involvement		Total Cases	With Joint Involvement	
		No.	%		No.	%
0–14	109	57	52·3	146	101	69·2
15–42	79	20	25·3	59	13	22·0
43+	52	11	21·2	52	13	25·0
Total ..	240	88	36·7	257	127	49·4

By the eighth day it remained in less than 10% in each treatment group. Throughout the rest of the treatment period joint involvement was present in none of the cortisone cases, in only a rare case in the A.C.T.H. group, and in a few cases in the aspirin group (Table 11). After treatment was stopped there was an insignificant increase of cases with joint involvement in the A.C.T.H. group, and these had disappeared by the 13th week; in the cortisone group there was an immediate rise to 10.3%, followed by complete disappearance at the ninth week and one recurrence at the 13th week; in the aspirin group two cases continued up to the 13th week. Among cases in which joint involvement disappeared it later reappeared in only a few cases (A.C.T.H. 5, cortisone 15, and aspirin 8).

TABLE 11.—*Cases with Joint Involvement at Start of Therapy: Number and Percentage with Joint Involvement at Specified Times. U.K. and U.S., all Cases*

Time from Start of Therapy	A.C.T.H.		Cortisone		Aspirin	
	No. of Cases	%	No. of Cases	%	No. of Cases	%
1 day	63	100·0	78	100·0	74	100·0
2 days	41	65·1	59	75·6	52	70·3
3 ,, ...	18	28·6	44	56·4	27	36·5
4 ,, ...	12	19·0	27	34·6	11	14·9
5 ,, ...	5	7·9	17	21·8	9	12·2
6 ,, ...	7	11·1	13	16·7	9	12·2
7 ,, ...	5	7·9	8	10·3	9	12·2
8 ,, ...	4	6·3	6	7·7	6	8·1
15 ,, ...	1	1·6	—	0·0	6	8·1
22 ,, ...	2	3·2	—	0·0	5	6·8
29 ,, ...	1	1·6	—	0·0	6	8·1
36 ,, ...	2	3·2	—	0·0	2	2·7
43 ,, ...	2	3·2	—	0·0	4	5·4
50 ,, ...	3	4·8	8	10·3	6	8·1
57 ,, ...	2	3·2	7	9·0	5	6·8
63 ,, ...	1	1·6	—	0·0	2	2·7
13th week ..	—	0·0	1	1·3	2	2·7

TABLE 12.—*Cases without Joint Involvement at Start of Therapy: Development of Joint Involvement During Specified Intervals. U.K. and U.S., all Cases*

Treatment Group	No. of Cases Without Joint Involvement at Start of Therapy	No. Developing Joint Involvement		
		1–42 Days	43–63 Days	At 13 Weeks
A.C.T.H.	99	4	5	—
Cortisone	89	5	4	—
Aspirin	94	—	4	—

In the aspirin group, although the number with nodules was fairly small, the nodules tended to persist to the end of the sixth week. This tendency was even more apparent among the chronic cases (43+ days), although the rate of disappearance in these cases was perhaps lower with all three drugs. These differences in response came from the U.K. cases, since at the end of six weeks only two, and at 13 weeks only one, with nodules still remaining were U.S. cases.

Among cases *without* joint involvement at start of therapy (Table 12), a few developed it during the 13-weeks period (A.C.T.H. 9, cortisone 9, aspirin 4). In five A.C.T.H., four cortisone, and the four aspirin cases the joint involvement appeared for the first time after the end of treatment.

There is little to choose between the three drugs in their effect on joint involvement, apart from some delay in response to cortisone administered intramuscularly.

Chorea

At the start of therapy there was a larger proportion of cases with chorea in the aspirin group than in either of the hormone groups. Chorea seemed to persist longer in the aspirin than in the hormone groups, but this difference is not significant (Table 13). The persistence of this symptom was strikingly more pronounced in the U.K. than in the U.S. cases, since at 13 weeks nearly all were in U.K. centres (the A.C.T.H. case, one of three cortisone, and eight of nine aspirin cases).

Among the cases *without* chorea at the start of therapy, a few in all three treatment groups developed this symptom at some time during the 13-weeks period (Table 14).

The persistence of chorea, as well as its appearance for the first time, was not significantly different between the treatment groups.

TABLE 13.—*Cases with Chorea at Start of Therapy: Subsequent Course. U.K. and U.S., all Cases*

Treatment Group	No. of Cases with Chorea at Start of Therapy	No. with Chorea at		
		End of Therapy (Week 6)	End of Observation (Week 9)	Follow-up (13 Weeks)
A.C.T.H.	9	1	—	1
Cortisone ..	19	2	1	3
Aspirin	26	9	5	9

TABLE 14.—*Cases without Chorea at Start of Therapy: Development of Chorea During Specified Time Intervals. U.K. and U.S., all Cases*

Treatment Group	No. of Cases Without Chorea at Start of Therapy	No. Developing Chorea		
		1–42 Days	43–63 Days	At 13 Weeks
A.C.T.H.	153	3	—	—
Cortisone	148	3	—	2
Aspirin	142	4	—	1

Subcutaneous Nodules

At the start of therapy there was a significantly larger proportion of cases with subcutaneous nodules in the U.K. (21.7%) than in the U.S. (7.4%), most of the difference occurring in the group of late cases (Table 15). Among the three treatment groups in the two countries, however, such cases were fairly evenly distributed except for slightly fewer in the aspirin group.

TABLE 15.—*Nodules: Comparison of U.K. and U.S. Cases at Start of Therapy*

Duration from Onset at Start of Therapy (in Days)	U.K.			U.S.		
	Total Cases	With Nodules		Total Cases	With Nodules	
		No.	%		No.	%
0–14	109	6	5·5	146	2	1·4
15–42	79	14	17·7	59	7	11·9
43+	52	32	61·5	52	10	19·2
Total ..	240	52	21·7	257	19	7·4

In most of the early and medium-duration cases (0–42 days) receiving A.C.T.H. or cortisone, subcutaneous nodules had disappeared by the end of treatment (Table 16). In the aspirin group, although the number with nodules was fairly small, the nodules tended to persist to the end of the sixth week. This tendency was even more apparent among the chronic cases (43+ days), although the rate of disappearance in these cases was perhaps lower with all three drugs. These differences in response came from the U.K. cases, since at the end of six weeks only two, and at 13 weeks only one, with nodules still remaining were U.S. cases.

New subcutaneous nodules developed in some cases during the treatment period in all treatment groups, and particularly among cases with nodules at the start of therapy (Tables 16 and 17). During the treatment period there was a slightly greater tendency for cases in the aspirin group to develop new nodules than among those in the hormone groups. Of the 36 cases in all treatment groups in which new nodules developed during therapy, 25 were U.K. cases.

Thus it may be concluded that new nodules appeared on all treatments and that nodules persisted longer in the aspirin- than in the A.C.T.H.- and cortisone-treated cases.

TABLE 16.—*Cases with Nodules at Start of Therapy: Subsequent Course. U.K. and U.S., all Cases*

Treatment Group and Duration from Onset	No. with Nodules at Start of Therapy	No. with Nodules Persisting to: End of Therapy (Week 6)	End of Observation (Week 9)	Follow-up (13 Weeks)
0–42 days:				
A.C.T.H. ..	13	4	1	—
Cortisone ..	12	4	2	1
Aspirin ..	4	3	2	1
43 days+:				
A.C.T.H. ..	13	6	4	3
Cortisone ..	13	7	4	1
Aspirin ..	16	12	12	10

		No. in which *Fresh* Nodules Appeared: 1–42 Days	43–63 Days	At 13th Week
All duration groups:				
A.C.T.H. ..	26	5	2	1
Cortisone ..	25	3	—	—
Aspirin ..	20	9	2	1

TABLE 17.—*Cases without Nodules at Start of Therapy: Development of Nodules During Specified Time Intervals. U.K. and U.S., all Cases*

Treatment Group	No. of Cases Without Nodules at Start of Therapy	No. Developing Nodules: 1–42 Days	43–63 Days	At 13 Weeks
A.C.T.H. ..	136	7	—	1
Cortisone ..	142	2	—	—
Aspirin ..	148	10	1	1

Erythema Marginatum

At the start of therapy there were 29 cases with erythema marginatum (A.C.T.H. 12, cortisone 11, aspirin 6). The proportion with new episodes developing during treatment and observation was similar for all treatment groups (Table 18). At 13 weeks, erythema marginatum had persisted in two A.C.T.H. cases and one aspirin case.

Among the cases *without* erythema marginatum at start of treatment, the number developing episodes for the first time during treatment or observation was also similar for all treatment groups (A.C.T.H. 10, cortisone 15, and aspirin 11). Among these cases only one remained at 13 weeks—a cortisone case which first manifested erythema marginatum during the observation period. In addition there was one aspirin case in which erythema marginatum appeared for the first time at the 13th week (Table 19).

Thus the rate of appearance or disappearance of episodes of erythema marginatum seemed to be unrelated to therapy.

TABLE 18.—*Cases with Erythema Marginatum at Start of Therapy: New Episodes of Erythema Marginatum. U.K. and U.S., all Cases*

Treatment Group	No. of Cases with Erythema Marginatum at Start of Therapy	New Episodes Developing: 1–42 Days	43–63 Days	At 13 Weeks
A.C.T.H. ..	12	5	1	—
Cortisone ..	11	2	2	—
Aspirin ..	6	2	1	—

TABLE 19.—*Cases without Erythema Marginatum at Start of Therapy: Development of Erythema Marginatum During Specified Time Intervals. U.K. and U.S., all Cases*

Treatment Group	No. of Cases without Erythema Marginatum at Start of Therapy	No. Developing Erythema Marginatum: 1–42 Days	43–63 Days	At 13 Weeks
A.C.T.H. ..	150	9	1	—
Cortisone ..	156	10	5	—
Aspirin ..	162	9	1	1

Heart Size

Variations in heart size were analysed by three methods:

1. The proportion in each treatment group with a cardiothoracic ratio of 0.55 or more; this method described extreme grades of cardiac enlargement.

2. The frequency of change in transverse cardiac diameter of 0.6 cm. or more, between 0–3, and 3–6, and 6–9 weeks and 0–1 year; this method, although starting from an abnormal base line, was more sensitive than method 1 to temporary changes of a lesser degree.

3. The proportion of cases with a cardiothoracic ratio of 0.50 or more; this method yielded no additional information and will not be further discussed.

In Cardiac Group A the proportion with a cardiothoracic ratio of 0.55 or more in any treatment group at any time was insignificant (Table 20). In Cardiac Group B (excluding those with failure or pericarditis or both) the approximately equal distribution among the three treatment groups persists throughout. In Cardiac Group C (excluding those with failure or pericarditis or both) there was a smaller proportion of cases initially in the aspirin group with extreme grades of cardiac enlargement. This inequality persists at three, six, and nine weeks, but disappears at one year. In the group of cases with failure or pericarditis or both, the relative inequality persists throughout.

Using the more sensitive index of change in heart size of 0.6 cm. or more, a larger proportion showed an increase over the 0–9 weeks period in each hormone compared with the aspirin group. This difference appeared early, since analysis of the 0–3 and 3–6 weeks intervals showed the same result, but at one year it had disappeared (Chart V). In contrast, the proportion showing a decrease in heart size was similar for all treatment groups. Cardiac groups A, B, and C all showed this difference between each of the hormones and aspirin early in treatment and the same equality at the end of one year. Among cases with failure and/or pericarditis (in which the proportion of enlarged hearts was

TABLE 20.—*Cardiothoracic Ratio: Percentage of Cases in Cardiac Groups with T.D./I.D. Ratio of 0.55 or More at Specified Times. U.K. and U.S., all Cases**

Cardiac Group and Treatment Group	No. of Cases	Start of Therapy	Week 3	End of Therapy Week 6	End of Observation Week 9	Follow-up One Year
Cardiac Group A: No or questionable carditis, no pre-existing heart disease:						
A.C.T.H.	40	2·6	0·0	0·0	2·7	2·9
Cortisone	39	2·7	2·9	0·0	0·0	0·0
Aspirin ..	38	0·0	0·0	0·0	0·0	0·0
Cardiac Group B†: Carditis present, no pre-existing heart disease:						
A.C.T.H.	61	5·0	8·3	12·1	8·6	10·2
Cortisone	75	10·7	7·1	10·3	8·4	6·0
Aspirin ..	79	9·2	13·9	6·4	7·8	5·8
Cardiac Group C†: With definite or questionable pre-existing heart disease:						
A.C.T.H.	34	27·3	30·3	28·1	29·0	13·8
Cortisone	29	29·6	28·6	31·0	37·0	17·4
Aspirin ..	34	15·2	15·2	15·2	9·4	16·0
Congestive failure and/or pericarditis:						
A.C.T.H. ..	27	81·5	66·7	68·0	64·0	47·8
Cortisone ..	24	56·5	50·0	52·2	31·8	19·0
Aspirin ..	17	43·8	58·8	41·2	31·2	27·3
All groups:						
A.C.T.H. ..	162	22·0	20·8	21·6	20·5	15·6
Cortisone ..	167	18·5	16·1	17·9	14·8	8·5
Aspirin ..	168	11·8	15·7	10·2	8·9	8·0

* At the specified times there were sometimes one or two observations missing. The percentages are based upon the numbers available.
† Excluding cases with failure and/or pericarditis at start of therapy.

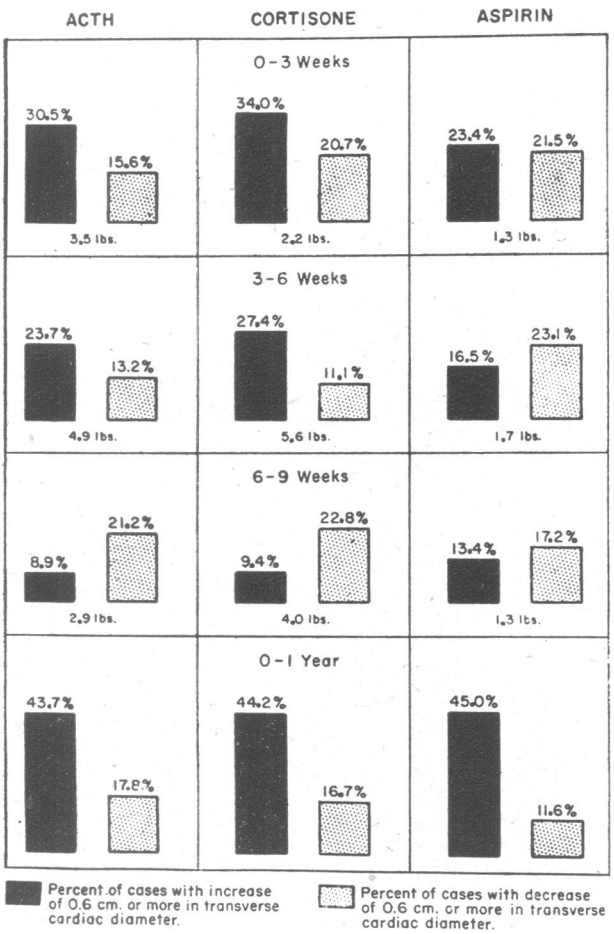

CHART V.—Changes in heart size and average weight gain in specified time intervals.

high at start of therapy), approximately one-third showed an early decrease regardless of therapy, and few (16%) showed an increase during treatment.

Considering gains in body weight, increases in heart size were more frequent in each hormone group than in the aspirin group during 0–3 and 3–6 weeks, but not during 6–9 weeks. In each period, however, both hormone groups had an average weight gain two to three times as great as the aspirin group; in other words, there was no clear relationship between weight gain and increase in heart size.

In summary, when heart size is measured by the proportion with a cardiothoracic ratio of 0.55 or more, the cardiac subgroups and the total cases reveal no differences between treatments. Using the more sensitive index of change in heart size of 0.6 cm. or more, there is a tendency for cases treated with A.C.T.H. or cortisone to show a temporary increase in heart size.

Atrioventricular Conduction Time

The course of the atrioventricular conduction time* (measured by the P–R interval in the electrocardiogram) was analysed, using:

1. The percentage with a P–R interval of 0.18 sec. or longer.
2. The percentage with a P–R interval of 0.16 sec. or longer.
3. The average P–R interval.
4. The percentage with an increase or decrease in the P–R interval of 0.03 sec. or more during the interval of 0–3, 0–6, 6–9, and 0–9 weeks.

The four methods led to the same conclusions, and only the percentages with a P–R interval of 0.18 second or longer are presented here.

The proportions of cases with a P–R interval of 0.18 second or longer are distributed fairly equally at start of therapy in each of the treatment and each of the cardiac groups (Chart VI, Table 21). They decreased initially more

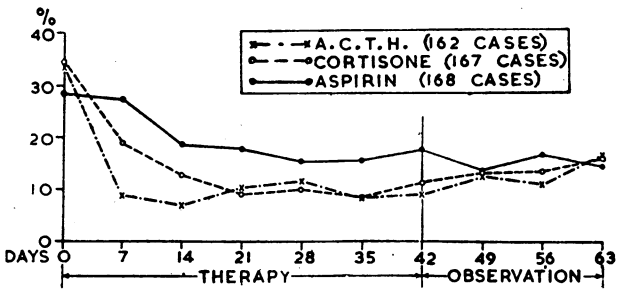

CHART VI.—Atrioventricular conduction time. Percentage of cases with P–R interval of 0.18 second or more.

TABLE 21.—*Atrioventricular Conduction Time: Percentage of Cases in Cardiac Groups with P–R Interval of 0.18 sec. or Above at Specified Times. U.K. and U.S., all Cases**

Cardiac Group and Treatment Group	No. of Cases	Start of Therapy	Week 3	End of Therapy Week 6	End of Observation Week 9	Follow-up One Year
Cardiac Group A: No or questionable carditis, no pre-existing heart disease:						
A.C.T.H.	40	36·8	5·3	5·7	7·1	6·5
Cortisone	39	40·5	8·1	11·1	13·6	18·5
Aspirin ..	38	30·6	13·3	15·2	20·0	0·0
Cardiac Group B†: Carditis present, no pre-existing heart disease:						
A.C.T.H.	74	28·2	6·1	6·0	14·3	14·3
Cortisone	89	29·3	7·3	11·4	12·7	22·5
Aspirin ..	89	25·6	14·5	13·8	10·0	12·3
Cardiac Group C†: With definite or questionable pre-existing heart disease:						
A.C.T.H.	48	38·3	20·5	15·9	25·6	30·8
Cortisone	39	40·0	13·9	10·8	24·2	11·1
Aspirin ..	41	32·4	28·2	27·5	20·0	25·9
All groups:						
A.C.T.H. ..	162	33·3	10·1	8·9	16·4	17·5
Cortisone ..	167	34·4	9·0	11·2	15·9	19·2
Aspirin ..	168	28·3	17·8	17·6	14·4	12·5

* See footnote to Table 20.
† Includes cases with failure and/or pericarditis at start of therapy.

rapidly among those receiving A.C.T.H. or cortisone than among those receiving aspirin, with the A.C.T.H. group showing a very rapid fall at the end of the first week from 33.3% to 8.7% and in the second week to 6.9%. At the third week the A.C.T.H. and cortisone groups were at the same level, with the aspirin group clearly lagging behind. This difference was maintained to the end of the treatment period, after which, at 9 weeks and at one year, all three groups were in the same range (13% to 19%). This decrease during treatment in the hormone-treated cases occurred in all cardiac groups, but was less marked in cardiac group C.

The hormones appear to decrease the P–R interval to values below those at 9 weeks and at one year. The values at these later times might well be expected to be closer to normal than those recorded during the acute illness. It may be questioned, therefore, whether the early decrease in P–R intervals is an effect of the hormones on the disease or merely a direct effect on the atrioventricular conduction time.

*The diagnostic criteria for admission of patients to the study defined normal P–R intervals as corrected for age and heart rate according to the Ashman-Hull tables. These corrections were not used in evaluating the course of the disease because the P–R intervals were unduly influenced by marked pulse rate changes, and because recent unpublished studies of the P–R interval in normal children by the Child Research Council of Denver question the corrections proposed by Ashman and Hull.

TABLE 23.—*Cardiac Group B* (with carditis, no pre-existing heart disease): Apical Systolic Murmurs, Grades at Start of Therapy and at Specified Times. U.K. and U.S., all Cases*

Grade at Start of Therapy and Treatment Group	Total Cases	Grade at end of Therapy (Week 6)				Grade at end of Observation (Week 9)				Grade at Follow-up (13 Weeks)					Grade at Follow-up (One Year)				
		0	1	2	3	0	1	2	3	0	1	2	3	Not Known	0	1	2	3	Not Known
Grade O:																			
A.C.T.H. ..	5	4	–	1	–	4	–	1	–	4	–	1	–	–	5	–	–	–	–
Cortisone ..	8	8	–	–	–	8	–	–	–	7	–	–	–	1	7	–	–	–	1
Aspirin ..	12	10	2	–	–	11	1	–	–	11	–	–	–	1	11	–	–	–	1
Grade 1:																			
A.C.T.H. ..	14	10	2	1	1	11	2	–	1	11	2	1	–	–	12	1	1	–	–
Cortisone ..	27	19	7	1	–	14	11	1	1	20	5	–	2	–	17	7	3	–	–
Aspirin ..	18	4	10	4	–	6	8	4	–	7	7	3	–	1	10	5	3	–	–
Grade 2:																			
A.C.T.H. ..	35	9	9	15	2	7	11	15	2	6	11	14	3	1	10	9	10	3	3†
Cortisone ..	36	8	14	14	–	11	12	13	–	12	13	10	1	–	19	7	7	2	1
Aspirin ..	49	5	17	24	3	12	13	19	5	10	14	18	5	2	24	9	9	6	1†
Grade 3:																			
A.C.T.H. ..	20	1	3	9	7	1	2	8	9	3	1	8	8	–	4	3	6	7	–
Cortisone ..	16	1	–	6	9	–	1	6	9	–	3	3	9	1	2	2	2	9	1
Aspirin ..	10	–	2	3	5	1	1	4	4	1	2	4	3	–	2	1	5	1	1
Grade not Stated:																			
Cortisone ..	2	1	–	–	1	1	–	1	–	1	–	1	–	–	1	–	–	1	–

*Includes cases with failure and/or pericarditis at start of therapy. †Includes one death.

Apical Systolic and Basal Diastolic Murmurs‡

The development and course of significant heart murmurs are among the most important aspects of rheumatic fever. They are analysed during the acute attack (0–13 weeks) and at one year, according to the status of the heart at the start of treatment—that is, Cardiac Group A, those without pre-existing heart disease or carditis; Cardiac Group B, those with carditis and without pre-existing heart disease; and Cardiac Group C, those with pre-existing heart disease.

Cardiac Group A

Each treatment group included approximately the same number of cases without carditis or pre-existing heart disease. None of these had an apical systolic or basal diastolic murmur on admission to the study. During the nine-weeks period of treatment and observation it was unusual for either of these murmurs to appear, and at 13 weeks few cases had either an apical systolic or a basal diastolic murmur or both, regardless of the type of therapy (Table 22). At 13 weeks,

TABLE 22.—*Cardiac Group A (no Carditis, no Pre-existing Heart Disease): Murmurs Present at Specified Times. U.K. and U.S., all Cases*

	Total Cases	No. with Murmurs at			
		End of Therapy (Week 6)	End of Observation (Week 9)	Follow-up (13 Weeks)	Follow-up One Year
A.C.T.H. ..	40	3	5	5	5
Cortisone ..	39	2	1	3	4
Aspirin	38	3	2	2	5

among 40 A.C.T.H. cases there were five with apical systolic murmurs; among 39 cortisone cases there was one with an apical systolic murmur, one with a basal diastolic murmur, and one with both; and among the 38 aspirin cases there were two with apical systolic murmurs. At one year apical systolic murmurs were still few: five A.C.T.H., four cortisone, and five aspirin. One of the cortisone cases also had a basal diastolic murmur. In other words, if a case of rheumatic fever meeting the criteria for admission to this study had no apical systolic or basal diastolic murmur at that time the chance of developing either murmur during the acute attack or at one year was only approximately 1 in 8, regardless of treatment.

Cardiac Group B

Among the cases with carditis without pre-existing heart disease, the distribution of apical systolic murmurs by grades was not the same in the three treatment groups at start of therapy; there were relatively more Grade O and Grade 2 murmurs among the aspirin, Grade 1 among the cortisone, and Grade 3 among the A.C.T.H. cases. For this reason, analysis of the group as a whole becomes complicated and each grade is analysed separately.

The Group B cases without an apical systolic murmur at start of therapy (included in Group B on account of other murmurs, increase in heart size, failure or pericarditis) behaved much like the cases without carditis (Group A). It was unusual for them to develop an apical systolic murmur during the first 13 weeks following the start of treatment or at one year, regardless of the treatment employed (Table 23).

In Group B cases, Grade 1 apical systolic murmurs at start of treatment appeared to respond differently during the acute attack in hormone-treated cases compared with the aspirin-treated cases. In the majority of the cases treated with A.C.T.H. or cortisone the Grade 1 murmur disappeared by the end of six weeks of treatment. There was a slight increase in their frequency among the cortisone cases at nine weeks, but otherwise there was no appreciable change at the 9th and 13th weeks. By contrast, in only 4 of 18 aspirin cases did the Grade 1 apical systolic murmur disappear at six weeks and in only seven by the 13th week. There were relatively few Grade 1 murmurs that increased to Grade 2 or 3 during the 13-weeks period in any of the treatment groups. At one year following the end of the observation period, the differences between the three treatment groups were no longer significant (Table 23).

Grade 2 apical systolic murmurs in cases with carditis (Group B) presented a somewhat different pattern. These murmurs disappeared in slightly more cortisone than A.C.T.H. or aspirin cases. Thus by the end of 13 weeks they had disappeared in about one-sixth of the A.C.T.H., one-fifth of the aspirin, and one-third of the cortisone cases. Considering murmurs which decreased as well as those which disappeared, the differences among the treatment groups are not so great. At the end of 13 weeks in one-half of the A.C.T.H. and aspirin cases the Grade 2 murmur had diminished or had disappeared, in comparison with five-sevenths of the cortisone cases. With the number of cases studied, none of these differences reached the 5% level of

‡In this study the following grades were adopted for reporting apical systolic murmurs: Grade O—No murmur, or a murmur considered to be "functional" on the basis of its apparent origin at the pulmonic area or along the left sternal border. Grade P—Murmur apparently localized to the apical area, but so faint as not to be transmitted to or toward the axilla. Grade 1—Soft apical systolic murmur transmitted to or toward the axilla. Grade 2—Louder similar murmur. Grade 3—Very loud similar murmur, usually transmitted to the back. In the analysis of the data, the "P" murmurs were included under Grade O.

significance. By the end of one year, only minor differences remained. Thus in the Group B cases there were no striking differences in the effect of A.C.T.H., cortisone, or aspirin on Grade 2 apical systolic murmurs during the acute attack or at one year.

Grade 3 apical systolic murmurs in cases with carditis did not disappear, except in a few instances, during the 13-weeks period or at one year, regardless of the type of treatment (Table 23). Some of these loud murmurs became less intense, particularly in the aspirin group, but this difference again was not significant.

Summarizing, the apical systolic murmurs in Group B cases responded in relatively the same way to the three forms of treatment, except when the apical systolic murmur was of minimum intensity (Grade 1). In these cases a larger proportion of such murmurs disappeared during therapy with A.C.T.H. and cortisone than with aspirin, but there was little difference between treatment groups at the end of one year.

In 11 centres, basal diastolic murmurs in cardiac Group B cases were recorded in 20 of 201 (10%), while in one U.K. centre they were present in 41 cases (80%), absent in 8, and undetermined in 2. Two separate analyses are therefore presented.

In the 11 centres, basal diastolic murmurs were present at the start of therapy in 7 of 58 A.C.T.H., 8 of 70 cortisone, and 5 of 73 aspirin cases (Table 24). At 6, 9, 13 weeks, and one year the disappearance of these murmurs or their appearance in cases originally without them was approximately the same for all treatment groups.

In the one U.K. centre, of eight cases initially without basal diastolic murmurs one developed a transient murmur. In 41 cases where the murmur was initially present it had disappeared by nine weeks more frequently from the A.C.T.H. (14 of 15) than from the cortisone (6 of 13) and aspirin groups (4 of 13). The difference was still present at one year (13 of 15 A.C.T.H., 4 of 12 cortisone, and 5 of 12 aspirin).

Cardiac Group C

These cases with pre-existing heart disease, including those with additional pericarditis or failure or both on admission, are difficult to evaluate.

The disappearance of apical systolic murmurs Grades 1 and 2 during the acute attack was slower in the aspirin group: in 8 of 32 A.C.T.H. and 8 of 23 cortisone cases these murmurs had disappeared at the end of 13 weeks, as compared with 2 of 23 cases in the aspirin group (Table 25). However, at one year there was very little difference between the three treatment groups. None of the 43 Grade 3 apical systolic murmurs had disappeared at 13 weeks after start of therapy, and only two (1 A.C.T.H. and 1 cortisone) had disappeared by the end of one year.

In the Group C cases from 11 centres, the appearance or disappearance of basal diastolic murmurs showed no differences among the treatment groups during the acute attack or at one year (Table 26). A few new basal diastolic murmurs appeared, and an insignificant number of those present disappeared during the 13-weeks period or at one year. In the one U.K. centre, separately considered, there were also no differences between treatment groups. Only 2 of 29 Group C cases had no basal diastolic murmurs initially and none appeared later. Where the murmur was present initially, it persisted to one year in 7 of 10 A.C.T.H., 6 of 6 cortisone, and 9 of 11 aspirin cases.

This analysis of apical systolic and basal diastolic murmurs among Group C cases showed only one difference—a more rapid disappearance of lower grades of apical systolic murmurs in cases receiving A.C.T.H. and cortisone.

Apical Diastolic Murmurs

Mid-diastolic Murmurs

This analysis of mid-diastolic murmurs is limited to the data for the U.K. centres, differing from the pattern of presentation elsewhere in this report. The U.S. data are not included, since a review of the records indicated that varying

TABLE 24.—*Cardiac Group B* (with carditis, no pre-existing heart disease): Basal Diastolic Murmurs at Start of Therapy and at Specified Times. U.K. and U.S. Cases†*

Status at Start of Therapy and Treatment Groups	Total Cases	End of Therapy (Week 6)		End of Observation (Week 9)		Follow-up (13 Weeks)			Follow-up (One Year)		
		Absent	Present	Absent	Present	Absent	Present	Not Known	Absent	Present	Not Known
No Murmur at Start:											
A.C.T.H.	51	48	3	49	2	48	2	1	48	1	2‡
Cortisone	62	60	2	60	2	59	2	1	58	3	1
Aspirin	68	63	5	64	4	63	2	3	62	4	2‡
Murmur Present at Start:											
A.C.T.H.	7	1	6	1	6	2	5	–	1	5	1
Cortisone	8	3	5	3	5	5	3	–	2	5	1
Aspirin	5	2	3	2	3	2	3	–	2	3	–

* Includes cases with failure and/or pericarditis at start of therapy.
† Includes 201 cases in 11 of the 12 centres where basal diastolic murmurs were present at start of therapy in 10% of cases, and excludes 51 cases in one centre where basal diastolic murmurs were present in 41 cases (80%), absent in 8, and undetermined in 2 because of a loud pericardial friction rub.
‡ Includes one death.

TABLE 25.—*Cardiac Group C§ (with definite or questionable pre-existing heart disease): Apical Systolic Murmurs, Grades at Start of Therapy and at Specified Times. U.K. and U.S., all Cases*

Grade at Start of Therapy and Treatment Group	Total Cases	Grade at End of Therapy (Week 6)				Grade at End of Observation (Week 9)				Grade at Follow-up (13 Weeks)					Grade at Follow-up (One Year)				
		0	1	2	3	0	1	2	3	0	1	2	3	Not Known	0	1	2	3	Not Known
Grade 0 at Start:																			
A.C.T.H.	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Cortisone	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Aspirin	7	5	1	1	–	4	2	1	–	4	1	–	–	2	6	1	–	–	–
Grades 1 & 2 at Start:																			
A.C.T.H.	32	5	8	16	3	7	6	15	4	8	3	15	5	1	7	9	12	4	–
Cortisone	23	4	8	11	–	5	8	10	–	8	5	10	–	–	6	7	9	1	–
Aspirin	23	1	2	19	1	2	5	15	1	2	3	15	3	–	6	3	13	–	1‖
Grade 3 at Start:																			
A.C.T.H.	16	–	–	2	14	–	–	3	13	–	1	2	13	–	1	–	3	11	1
Cortisone	16	1	–	5	10	–	1	4	11	–	1	4	10	1‖	1	–	5	8	2‖
Aspirin	11	–	–	4	7	–	–	5	6	–	–	5	6	–	–	1	5	4	1‖

§ Includes cases with failure and/or pericarditis at start of therapy. ‖Includes one death.

TABLE 26.—*Cardiac Group C* (with definite or questionable pre-existing heart disease): Basal Diastolic Murmurs at Start of Therapy and at Specified Times. U.K. and U.S. Cases†*

Status at Start of Therapy and Treatment Group	Total Cases	End of Therapy (Week 6)		End of Observation (Week 9)		Follow-up (13 Weeks)			Follow-up (One Year)		
		Absent	Present	Absent	Present	Absent	Present	Not Known	Absent	Present	Not Known
No Murmur at Start:											
A.C.T.H.	29	26	3	27	2	26	3	–	24	5	–
Cortisone	20	18	2	18	2	18	2	–	18	2	–
Aspirin	21	20	1	19	2	17	2	2	16	3	2‡
Murmur Present at Start:											
A.C.T.H.	9	1	8	3	6	2	7	–	2	6	1
Cortisone	12	1	11	1	11	–	11	1‡	1	10	1‡
Aspirin	8	1	7	1	7	1	7	–	2	6	–

* Includes cases with failure and/or pericarditis at start of therapy.
† Includes 99 cases in 11 of the 12 centres where basal diastolic murmurs were present at start of therapy in 29% of cases, and excludes 29 cases in one centre where basal diastolic murmurs were present in 93% of cases.
‡ Includes one death.

terms—namely, mid-diastolic murmur, third heart sound, and gallop rhythm—were recorded inconsistently from centre to centre and from observer to observer of the same case in the same centre. Further, in acute rheumatic carditis this murmur is rarely heard in the absence of an organic apical systolic murmur, which was consistently recorded. The U.S. investigators therefore agreed that the mid-diastolic murmur in the U.S. cases should not be analysed.

In the U.K. no such murmur developed during the year in Group A cases. In Group B, where the murmur was initially absent it appeared in only a few cases, equally in all treatment groups. Where it was initially present it persisted up to the 13th week to a greater extent in the aspirin group (9 of 17 cases) compared with A.C.T.H. (3 of 19) and cortisone (5 of 18). At one year, however, there was little difference between the three groups (1 of 17 A.C.T.H., 3 of 18 cortisone, and 3 of 16 aspirin). In Group C cases, where the murmur was initially absent it appeared in a few cases in all treatment groups by the end of one year. Where the murmur was initially present it persisted in all treatment groups at the ninth week (13 of 20 A.C.T.H., 12 of 19 cortisone, and 15 of 19 aspirin), becoming slightly less at one year (9, 10, 9 cases, respectively).

Presystolic Murmurs

Apical presystolic murmurs were not included in this analysis, as they result from slowly progressive scarring of the mitral valve and are not evidence of acute carditis. In this study they were present in only 16 of 497 cases (3.2%) on admission, and they appeared for the first time in very few (12 additional cases during the following 13 weeks).

Summary of Murmurs

Summarizing the effects of treatment on murmurs during the acute attack and at the end of the first year, the following conclusions appear justified :

1. The development of an apical systolic murmur among those without such murmurs at start of therapy, regardless of the presence or absence of carditis, was infrequent and was not related to the treatment.

2. The disappearance of softer apical systolic murmurs was more rapid among those receiving A.C.T.H. or cortisone than among those receiving aspirin, but at the end of one year the treatment groups did not differ significantly. Similar results were found for the apical mid-diastolic murmur for the U.K. centres only.

3. The disappearance or diminution of loud apical systolic murmurs rarely occurred, regardless of therapy.

4. The appearance or disappearance of basal diastolic murmurs occurred in a relatively small proportion of cases, and in 11 of 12 centres was not related to therapy.§

5. At the end of one year there was no evidence that the treatment groups differed in the frequency with which murmurs had appeared or disappeared.

§In the one U.K. centre where an abnormally high proportion of basal diastolic murmurs was heard at entry, they disappeared more frequently in the A.C.T.H. group.

Seriously Ill Cases

Cases here described as seriously ill are those with congestive failure, pericarditis, or both, present on admission or occurring during the 13-weeks period of treatment and follow-up, and those cases terminated by death during the one-year period of this report.

Congestive Failure and/or Pericarditis

At the start of treatment, 23 of 162 A.C.T.H., 15 of 167 cortisone, and 10 of 168 aspirin cases had congestive failure (Table 27). Among these cases, failure disappeared

TABLE 27.—*Congestive Failure: U.K. and U.S., all Cases*

Interval from Start of Therapy in Days	Cases with Failure at Start of Therapy			Cases without Failure at Start of Therapy		
	No. with Failure Present on First Day of Interval			No. Developing Failure for First Time During Interval		
	A.C.T.H.	Cortisone	Aspirin	A.C.T.H.	Cortisone	Aspirin
1–7	23	15	10	4	3	2
8–14	18	12	9	—	1	5
15–21	13	10	5	2	1	—
22–28	9	4	3	—	1	1
29–35	6	4	3	1	—	—
36–42	5	4	3	—	—	—
43–49	5	3	1	—	—	1
50–56	3	3	1	—	—	—
57–63	4 (1)	1	1	—	1 (died)	—
64th day	2	1	1	—	—	—
13th week	3 (2)	1	1	—	—	1

N.B.—Figures in parentheses indicate number of cases on given day in which failure had reappeared after previous disappearance.

at about the same rate, regardless of therapy. In all but one case in each treatment group failure disappeared by the 13th week. After initial disappearance it reappeared in only three cases, all in the A.C.T.H. group.

Among the cases *without* congestive failure at the start of therapy, 7 of 139 A.C.T.H., 7 of 152 cortisone, and 10 of 158 aspirin cases developed failure during the 13-weeks period (Table 27). In 21 of these (7 A.C.T.H., 6 cortisone, and 8 aspirin), failure appeared during the treatment period but disappeared in all but five cases during the observation period. One of these, a cortisone case, had a fatal outcome during the observation period, and four (two A.C.T.H., two aspirin) had persistent failure at the ninth week. In three cases (one A.C.T.H., two aspirin) failure was present at the 13th week. In one of these aspirin cases treatment had been changed to A.C.T.H. on the 28th and continued to the 70th day.

Thus among the cases with or without failure at the start of therapy there were no marked differences among the treatment groups in the behaviour of congestive failure.

Pericarditis was present at the start of therapy in 13 of 162 A.C.T.H., 16 of 167 cortisone, and 9 of 168 aspirin cases, and disappeared at approximately the same rate regardless of therapy (Table 28). In only four of these (two cortisone and two aspirin) did the symptom reappear following its disappearance.

Among the cases *without* pericarditis at the start of therapy (Table 28), there were 3 of 149 A.C.T.H., 3 of 151 cortisone, and 5 of 159 aspirin cases which developed pericarditis for

TABLE 28.—*Pericarditis: U.K. and U.S., all Cases*

Interval from Start of Therapy in Days	Cases with Pericarditis at Start of Therapy			Cases without Pericarditis at Start of Therapy		
	No. with Pericarditis Present on First Day of Interval			No. Developing Pericarditis for First Time During Interval		
	A.C.T.H.	Cortisone	Aspirin	A.C.T.H.	Cortisone	Aspirin
1–7 ..	13	16	9	1	1	1
8–14 ..	8	8	7	2	—	2
15–21 ..	3	6	3	—	—	—
22–28 ..	2	5	3 (1)	—	—	—
29–35 ..	1	3	3 (1)	—	—	1
36–42 ..	1	2	1	—	1	—
43–49 ..	1	2	1	—	—	1
50–56 ..	1	—	1	—	1	—
57–63 ..	—	1 (1)	—	—	—	—
64th day ..	—	1 (1)	1 (1)	—	—	—
13th week	—	—	—	—	—	—

N.B.—Figures in parentheses indicate number of cases on given days in which pericarditis had reappeared after previous disappearance.

the first time during the 13-weeks period. In nine of these (three A.C.T.H., two cortisone, and four aspirin) pericarditis appeared during the treatment period. In all 11 cases it was of short duration, persisting in no case until the ninth week, and never reappearing after disappearance.

Thus among cases with or without pericarditis at start of therapy it appeared and disappeared regardless of treatment.

Deaths

Among the 497 cases, 6 deaths occurred during the one year of follow-up. Their case histories were as follows:

Case 1.—A 12-year-old girl was admitted to a U.K. centre in her first attack, with fever, carditis with apical systolic murmur and gallop rhythm, erythema marginatum, and elevated sedimentation rate. She was treated with A.C.T.H. on the 24th day of her disease, with symptomatic improvement but with progressive carditis. A basal diastolic murmur, noted intermittently during the first week of treatment, later was constantly present, becoming associated with a basal systolic murmur. In the fourth week an apical mid-diastolic murmur was heard and nodules appeared, rapidly increasing in number. The acute disease was obviously not controlled by A.C.T.H. No additional symptoms appeared during the three-weeks observation period. The patient was kept in bed thereafter throughout her slow but progressive downhill course, death occurring five months after the beginning of treatment and one day following her removal from the hospital against advice.

Case 2.—A 7-year-old boy with a four-days history of precordial, pleural, and joint pains was admitted to his local hospital, where his sedimentation rate was found to be elevated and a diagnosis of rheumatic fever was made. He was treated with penicillin, sulphonamides, and 60 gr. (4 g.) of aspirin and 30 gr. (2 g.) of sodium bicarbonate a day for 12 days without improvement. During this period he is said to have developed "a murmur" of gradually increasing loudness. He became dyspnoeic and was transferred to a U.S. centre. On admission he was extremely ill, with fever, orthopnoea, dyspnoea, cyanosis, muffled heart sounds, apical systolic murmur, gallop rhythm, and tachycardia (146/min.). Bronchial breathing and rales were heard over both lung fields. A diagnosis of rheumatic pancarditis with mitral valvular disease and congestive heart failure was made and rheumatic pneumonia suspected. The patient was treated with digitalis and mercaptomerin ("thiomerin"), and admitted to the study in the cortisone group. He died 20 hours after admission, having received 300 mg. of cortisone. Necropsy revealed a large flabby heart with verrucae on the mitral valve and left auricular wall.

Case 3.—A 13-year-old girl with a previous history of rheumatic fever and rheumatic heart disease with mitral insufficiency was admitted to a U.S. centre on the fifth day of a recurrent attack, following an upper respiratory infection with sore throat of three weeks' duration. She was moderately ill with fever, polyarthritis, elevated sedimentation rate, and probable carditis. She was treated with cortisone for six weeks with a fairly satisfactory response, although the evidence of underlying rheumatic heart disease was unchanged. Two weeks following end of treatment, she suddenly, for the first time, went into congestive failure associated with raised temperature and erythrocyte sedimentation rate. Retreatment with cortisone was begun immediately, but she became rapidly worse and died one day later, on the 57th day after admission to the study. Necropsy revealed a greatly hypertrophied heart with obliteration of the pericardial cavity and chronic mitral disease without stenosis, bilateral pleural effusions, diffuse pulmonary oedema, and ascites. Microscopical examination showed evidence of diffuse active pancarditis.

Case 4.—A 9-year-old boy was admitted to a U.K. centre with a history of three weeks of polyarthritis with two weeks of rash. He was found to have fever, erythema marginatum, an enlarged heart, and a loud apical systolic murmur. He was admitted to the study and aspirin therapy begun. After slight improvement his temperature rose again, the heart shadow became enlarged, and a basal diastolic murmur was heard intermittently. At the end of nine weeks he was still considered to be seriously ill, and was transferred to another hospital, where he developed increasing congestive failure, which later stabilized and then gradually improved. Four months after start of treatment, while still hospitalized, he became febrile and a group A beta-haemolytic streptococcus was isolated from his throat. He was treated with penicillin but remained febrile for 12 days, after which his temperature returned to normal but signs of congestive failure progressively increased. He died one month after this relapse, five months after start of treatment. Necropsy revealed rheumatic endocarditis, myocarditis, cardiac dilatation, a bicuspid aortic valve (? congenital), and chronic venous congestion of lungs, liver, and spleen.

Case 5.—A 12-year-old boy was admitted to a U.K. centre in his second attack with pre-existing rheumatic heart disease with mitral stenosis. Rheumatic fever had continued without intermission for four months, manifesting itself by nodules, arthritis, erythema marginatum, precordial pain, and fever. Physical findings during that period were enlarged heart, apical systolic, mid-diastolic, pre-systolic, and basal diastolic murmurs, enlarged liver, pulmonary congestion, elevated sedimentation rate, and prolonged P-R interval. The patient was admitted in the aspirin group and received symptomatic benefit; relapse followed at the end of treatment. Four additional courses of aspirin were given, the patient responding in the same way each time. He was then placed on a cortisone schedule but showed no improvement, dying in the fifth week of this treatment, in congestive failure, eight months after admission to the study. Necropsy revealed rheumatic heart disease with enlarged heart, mitral stenosis, acute mitral and tricuspid endocarditis, Aschoff bodies and fibroid changes in the myocardium, congestive failure with pulmonary oedema, and cardiac cirrhosis of liver.

Case 6.—A 6-year-old boy was admitted to a U.K. centre, severely ill in the seventh week of his first (?) attack. He showed evidence of carditis with apical systolic and mid-diastolic murmurs and the signs of congestive failure. One subcutaneous nodule was noted on the right elbow. The temperature was normal and the erythrocyte sedimentation rate elevated. Because of intractable vomiting, the digitalis and aspirin were temporarily stopped late in the first week, with immediate improvement. At the beginning of the second week small doses of aspirin—20 gr. (1.3 g.) per day—were given for three days and then omitted because of lack of improvement from therapy. The patient gradually improved without treatment, but congestive failure persisted. During the fifth and sixth weeks, amidopyrine —7½ gr. (0.5 g.) per day—was given without effect on the patient's gradual improvement, which continued until the ninth week. Digitalis was then stopped and the patient discharged to a convalescent home.

The patient continued in moderate congestive failure, leading a bed-and-chair existence. Five months later he developed an upper respiratory infection, treated with sulphadimidine and penicillin. Tachycardia (145 per minute) and a pericardial friction rub developed. A six-weeks course of A.C.T.H. was given, with disappearance of acute symptoms, congestive failure continuing. The patient had a rapid increase in weight, marked moonface, and moderate hypertension, all of which gradually disappeared.

Ten months after admission to the study the patient developed another upper respiratory infection, treated with sulphonamide drugs and penicillin. He then went rapidly downhill and was transferred back to the centre, where he died in severe congestive failure after one week's treatment with A.C.T.H., digitalis, and diuretics.

Necropsy showed hypertrophy and rheumatic pneumonia, congestive failure with mitral stenosis, cardiac dilatation, acute and chronic lesions of mitral, aortic, and tricuspid valves, fibrinous pericarditis, and numerous Aschoff bodies.

In summary, there were no appreciable differences in the course of seriously ill cases, since the behaviour of congestive failure, pericarditis, or both, appeared to be similar in the treatment groups, and there were only six deaths (one on A.C.T.H., two on cortisone, and three on aspirin).

Re-treatments

Apart from the six patients who died, there were some in each treatment group who, during the one-year period, were re-treated for persisting or recurring manifestations. Thus.

re-treatment was given to 10 of the 161 A.C.T.H. patients surviving to one year. None of these re-treatments were given during the three-weeks observation period. One case was treated for chorea, and one had two courses of re-treatment. In all except the case with chorea, the symptoms demanding re-treatment were moderately severe.

Re-treatment was given to 8 of the 165 cortisone cases surviving the one year, one of which was re-treated during the observation period. All were moderately severe cases except one, having only erythema marginatum and fever. None was re-treated for chorea. One case required two re-treatments.

Re-treatment was given to 19 of 165 aspirin cases surviving to one year. Four were re-treated during the observation period, two receiving aspirin and the other two receiving cortisone. Thirteen of the 19 cases were moderately severe; of the remaining 6, 5 were re-treated for recurrent chorea and 1 for a mild illness consisting of elevated temperature and sedimentation rate.

When the cases given re-treatment are analysed according to duration of disease at start of therapy, it is seen that the differences among the three treatment groups are due entirely to the chronically ill cases. Thus in the 0–14-day group there were six A.C.T.H., four cortisone, and six aspirin cases to which re-treatment was administered. In the 15–42-day group the cases were two, one, and four, respectively; in the group of those ill 43 days or more they were two, three, and nine—a preponderance of aspirin cases in this chronically ill group.

Excluding the cases re-treated for chorea, the number of cases remains the same in the 0–14-day group, becomes one on each treatment in the 15–42-day group, and two A.C.T.H., three cortisone, and seven aspirin in the 43+-day group.

In summary, re-treatment was given to a greater proportion of cases in the aspirin than in the A.C.T.H. and cortisone groups; but this difference occurred only among the chronic cases, and was slightly affected by the larger number of cases initially admitted with chorea to the aspirin group.

Side-effects of Treatment

In both countries, practically all the A.C.T.H. and cortisone cases showed one, or a combination, of the following side-effects of therapy: moonface, hirsutism, acne, or striae. There were only 10.5% of the A.C.T.H. and 4.8% of the cortisone cases with none of these side-effects by the end of the ninth week (Table 29). These effects were recorded less frequently in the U.K. than in the U.S. cases, being absent in 15.0% of the U.K. and 6.1% of the U.S. A.C.T.H. cases, and in 10.0% of the U.K. and none of the U.S. cortisone cases.

TABLE 29.—*Side-effects of Therapy in A.C.T.H. and Cortisone Cases: U.K. and U.S., all Cases*

Side-effect	Percentage of Cases Showing Side-effect					
	A.C.T.H.			Cortisone		
	U.K.	U.S.	Total	U.K.	U.S.	Total
Moonface ..	77·5	90·2	84·0	80·0	96·6	88·6
Hirsutism ..	15·0	19·5	17·3	13·8	16·1	15·0
Acne	26·2	63·4	45·1	8·8	17·2	13·2
Striae	12·5	12·2	12·3	18·8	12·6	15·6
None	15·0	6·1	10·5	10·0	0·0	4·8
Total No. of cases ..	80	82	162	80	87	167

There were no appreciable differences between the A.C.T.H. and cortisone cases in frequency of moonface, hirsutism, or striae, but acne appeared much more often among the A.C.T.H. cases. With the exception of striae, each side-effect was recorded more frequently among the U.S. than among the U.K. cases. Although these side-effects appeared almost equally in the hormone groups, those severe enough, in the opinion of the investigator, to require stopping treatment occurred only among the A.C.T.H. cases (Table 1).

In addition to the side-effects of hormone treatment already noted, many others were reported, but, not being specifically requested, they were not uniformly recorded. These included cases of hypertension, mental symptoms, convulsions, renal haemorrhage, water and salt retention, glycosuria, infections, hepatomegaly, febrile reactions, pigmentation, increased fat deposition, and unusual increase in appetite.*

Relatively few aspirin cases developed side-effects, and these all appeared in the first week of therapy in both countries while the dosage was relatively high. In the U.K., among 80 cases there were four with tinnitus or deafness, seven with nausea, and one with hyperventilation. Comparable figures in the 88 U.S. cases were 9, 19, and 5. The few side-effects and the maintenance of the dosage schedule of aspirin without interruption, except in a rare case, suggests that these cases did not receive the maximum tolerated dosage.

In summary, very few patients in the hormone groups did not exhibit one or more side-effects. Further, there was little difference between U.S. and U.K. cases on differing schedules of A.C.T.H. or between those on A.C.T.H. and those on cortisone in either country (Table 29). In other words, the dosages of both hormones were large enough to produce a recognizable side-effect in nearly all cases.

Discussion and Conclusions

The object of the present co-operative study, set up in 1950, was to measure the relative effects of A.C.T.H., cortisone, and aspirin when given uniformly in all centres according to defined schedules. These schedules (dosages, periods of administration, and auxiliary therapy) were based mainly upon existent knowledge regarding apparent efficacy and toxicity. They had also to be practicable, not only in the length of time that patients could be kept in hospital during the trial itself, but to allow their subsequent application in medical practice if they proved to have value. It is obvious that innumerable other studies could be designed employing larger (or smaller) dosages, longer (or shorter) periods of treatment, or individualized dosage schedules which would need to be based on predetermined criteria for changes in dosage. It cannot be maintained that such other schedules are either more or less effective than those used here without adequate controlled study.

Evaluation of treatment of such a complex and not wholly understood disease as rheumatic fever poses a large number of problems. Acute rheumatic fever may be considered a specific type of generalized inflammatory reaction, but no means are available for measuring this quantitatively. Since it is impossible to correlate the observed manifestations with the severity of the pathological process, it must be accepted that the available data may represent only approximate indices of the severity of the disease. Furthermore, since many of the clinical evaluations are subjective, their interpretation must take into account observer error and acuity. For example, although there is general agreement on the importance of apical mid-diastolic murmurs as an index of carditis, inconsistencies in reporting them and difficulties in distinguishing them from a third heart sound or gallop rhythm gave this index uncertain value in this study. In general, such difficulties were reduced by the large number of patients in each treatment group and by the equal allocation of the three drugs within each study centre.

Other difficulties encountered in the evaluation of certain data were the lack of normal standards and the absence of normal values to serve as base lines at start of therapy. Moreover, variables which have been analysed separately may be interdependent. An example of these difficulties is interpretation of the changes in P–R intervals with changing pulse rates and heart size.

*With an initial average body weight of a little less than 70 lb. (32 kg.) in each treatment group, patients on A.C.T.H. and cortisone gained by the end of the ninth week an average of 11.3 and 11.8 lb. (5.13 and 5.35 kg.), whereas those on aspirin gained an average of 4.3 lb. (1.95 kg.).

In addition to grouping by duration of disease, various types of classification of patients were made. The most useful was based on the presence or absence of cardiac involvement on admission to the study. Owing, however, to the random allocation of patients to treatment and the consequent balance of characteristics, such additional groupings had roughly equal numbers in the three treatment groups. Each manifestation was analysed in several ways, and that method chosen for presentation which gave the clearest picture.

It should be noted that nowhere in this report have analyses of combinations of measurements and clinical signs been presented. Since in clinical practice the patient is assessed as a whole, attempts were made to integrate the separate manifestations in individual patients. These attempts were unsuccessful in providing new information, but, observing each case over the entire 6–9-weeks observation period, the proportion without any manifestation of rheumatic fever was found to be greater in the aspirin than in either of the hormone groups. This difference was observed whether or not a murmur at this time (6–9 weeks) was considered to be a manifestation. Thus, including a murmur as a manifestation, there were, with no manifestations at all, 11 cases on A.C.T.H., 11 on cortisone, and 25 on aspirin. This difference, however, is almost entirely due to the smaller proportion with an elevated erythrocyte sedimentation rate and/or raised pulse rate among the cases in the aspirin group. Adding the cases with only these signs to the group showing no manifestations, the numbers of the latter become 34 on A.C.T.H., 32 on cortisone, and 34 on aspirin. If the presence of a murmur at this time (6–9 weeks) is not regarded as a manifestation, the numbers with no manifestations during the whole 6–9-weeks period were 31 on A.C.T.H., 26 on cortisone, and 53 on aspirin. Adding to these the cases with only an elevated erythrocyte sedimentation rate and/or raised pulse rate, the figures become 71 on A.C.T.H., 62 on cortisone, and 72 on aspirin.

In attempting to assess the relative efficacy of A.C.T.H., cortisone, and aspirin in altering the acute disease or suppressing its manifestations, the following conclusions appear permissible.

1. During the acute illness and the first year of follow-up very few deaths occurred—one in the A.C.T.H., two in the cortisone, and three in the aspirin group. Re-treatments were given to some cases in all three groups, but apart from a slight excess in the late-treated cases on aspirin, there was no marked difference in the groups.

2. The temperature and pulse rate during sleep returned to normal during treatment in the great majority of cases in all treatment groups, but there was a greater tendency in the groups treated with the hormones for the rates to become elevated in the 6–9-weeks observation period.

3. The erythrocyte sedimentation rate decreased more rapidly during treatment in the hormone-treated groups, but was elevated more frequently in the 6–9-weeks observation period. There were no differences between the treatment groups at the 13th week.

4. The behaviour of joint involvement, chorea, and erythema marginatum was essentially the same in the three treatment groups. Nodules, however, disappeared more rapidly in the patients treated with A.C.T.H. and cortisone, although new nodules appeared in some patients during treatment in all three groups.

5. The analysis of the effects of the drugs on carditis, while undoubtedly most important, is especially difficult, and the conclusions the least clear. The following, however, seem justified :

(*a*) There appeared to be no relationship between the treatment given and the behaviour of congestive failure and pericarditis.

(*b*) There was more frequently an increase in heart size as measured by a change of 0.6 cm. or more in each of the hormone groups as compared with the aspirin group. This may be related to a possible increase in blood volume or, in some cases, to abdominal distension. It was not related consistently to weight gain, since heart size increased frequently in the 0–3-weeks period of treatment and much less frequently in the observation period (6–9 weeks) although the average weight gain during these two periods was very similar. At the one-year follow-up examination there was no appreciable difference between the three groups.

(*c*) The appearance for the first time of apical systolic murmurs was infrequent in all three treatment groups and unrelated to therapy. No consistent difference in the behaviour of murmurs present at the start of treatment was noted except that the soft apical systolic murmurs disappeared more rapidly in hormone-treated groups. At the end of one year, however, no significant difference remained. The differences in the treatment groups with respect to apical mid-diastolic murmurs in the U.K. and basal diastolic murmurs at one U.K. centre have been discussed.

(*d*) The P–R intervals decreased more frequently and more rapidly in the hormone groups than in the aspirin group. This difference between the groups lessened during the observation period and was absent at nine weeks and one year. Since the values at these later times might be closer to normal than those recorded during acute illness, it may be questioned whether the early decrease is an effect of the hormones on the disease or merely a direct effect on atrioventricular conduction time.

(*e*) At one year the proportion with residual cardiac damage was similar in the three treatment groups. A final determination of cardiac status must await results of a prolonged follow-up.

It is apparent that this study presents no evidence that rheumatic fever in children can be uniformly terminated by any of the three agents. There is evidence that hormone treatment results in more prompt control of certain acute manifestations, but this more rapid disappearance is balanced by a greater tendency for them to reappear for a limited period of time at the end of treatment. Treatment with the hormones also leads to the more rapid disappearance of nodules and of soft apical systolic murmurs. At the end of one year, however, it is clear that there was no significant difference between the treatment groups in the status of the heart.

Summary

Six centres in the United Kingdom, five in the United States, and one in Canada have collaborated in a trial of the relative merits of A.C.T.H., cortisone, and aspirin in the treatment of acute rheumatic fever and the prevention of rheumatic heart disease. The present report relates to children under the age of 16 and compares the effects of the three drugs on the acute course of the disease and on the persistence and development of rheumatic heart disease through one subsequent year.

The records of 497 patients are presented (240 U.K. and 257 U.S., including the Canadian centre in the latter). Each case met specified diagnostic criteria on admission to the trial and was allocated at random to treatment with one of the three drugs. Each treatment was given for six weeks according to a defined schedule, and detailed observations were continued for a further three weeks. Follow-up examinations were made at specified times after these nine weeks, and the present report extends to the examination made one year later —that is, 61 weeks from the start of treatment.

The study was designed to ensure a balance of cases in the three treatment groups for each centre, for the duration of illness at start of treatment, and for the time of year when cases were admitted. Random allocation of cases within this balanced design was relied upon to secure a reasonably equal distribution of cases according to age, sex, and severity and frequency of manifestations of disease. This design permits many comparisons of the total groups on each treatment.

In 51% of the patients, treatment was begun within 14 days of the onset of the attack ; in nearly two-thirds there was no history of a previous attack or evidence of pre-existing rheumatic heart disease. The treatments were therefore tested on patients of whom a large proportion were still in the early stages of the disease and had no established heart disease.

The three randomly constructed groups on A.C.T.H. (162 cases), cortisone (167 cases), and aspirin (168 cases) were notably alike in most respects at the start of the trial. The results of the treatments were measured in relation to separate manifestations of the disease—namely, temperature, pulse rate during sleep, erythrocyte sedimentation rate, joint involvement, chorea, erythema marginatum, nodules, and such aspects of the status of the heart as heart size, atrioventricular conduction time, murmurs, and, in particular, those indicative of serious illness, congestive failure, and pericarditis.

There was no evidence that any of the three agents resulted in uniform termination of the disease, and on all treatments some patients developed fresh manifestations during treatment. Treatment with either of the hormones resulted in more prompt control of certain acute manifestations, but this more rapid disappearance was balanced by a greater tendency for the acute manifestations to reappear for a limited period upon cessation of treatment. Treatment with the hormones also led to more rapid disappearance of nodules and soft apical systolic murmurs. At the end of one year there was no significant difference between the three treatment groups in the status of the heart. During the period of treatment, observation, and one year of follow-up there were only six deaths among the 497 cases, under the age of 16, admitted to this study.

The National Heart Institute of the United States Public Health Service supported the study with grants to the co-ordinating centre and to the co-operating centres in the United States and by a travel grant to the Medical Research Council of Great Britain. The Medical Research Council provided support for the six centres and for a co-ordinating registrar in the United Kingdom. The centre in Toronto received a grant from the Canadian Arthritis and Rheumatism Society. In the United States, the costs of the medical care of its patients were met by each co-operating centre, and in Great Britain by the National Health Service. The American Heart Association provided office space for the American Co-ordinating Centre and a grant for statistical services.

This co-operative clinical trial was first proposed by Dr. John R. Mote, then assistant general manager of the Armour Laboratories. For the planning of the study, funds were provided by Armour Laboratories and Merck and Company, and space and services by the Helen Hay Whitney Foundation.

Grateful acknowledgment is made to the resident and technical staffs at the co-operating centres, without whose devoted efforts the collection of these data would have been impossible.

In the planning and conduct of this trial much is owed to the wise advice and guidance of the late Dr. T. Duckett Jones and the late Sir James Spence.

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APPENDIX

Form 1

ADMISSION REPORT

1. Hosp. No.....
2. Study No. ..... (*from assignment envelope*)
3. Study centre.....
4. Date adm. to centre.....
5. Date study therapy began.....
6. Name of patient.....
7. Date of birth..... 8. Age..... 9. Sex..... 10. Race.....

(*Please put a X in each relevant "box".*)

	Has condition been present in this attack	Date first observed in this attack	Is condition present at start of therapy	Used as criterion for admission to study
MAJOR CRITERIA				
11. Active Carditis	Yes ☐ No ☐	.....	Yes ☐ No ☐	Yes ☐ No ☐
a. Development of or change in murmurs	Yes ☐ No ☐	.....	Yes ☐ No ☐	
b. Increase in heart size	Yes ☐ No ☐	.....	Yes ☐ No ☐	
c. Pericarditis	Yes ☐ No ☐	.....	Yes ☐ No ☐	
d. Congestive failure	Yes ☐ No ☐	.....	Yes ☐ No ☐	
(1) Dyspnoea	Yes ☐ No ☐	.....	Yes ☐ No ☐	
(2) Orthopnoea	Yes ☐ No ☐	.....	Yes ☐ No ☐	
(3) Liver enlargement	Yes ☐ No ☐	.....	Yes ☐ No ☐	
(4) Râles	Yes ☐ No ☐	.....	Yes ☐ No ☐	
(5) Jugular venous pressure	Yes ☐ No ☐	.....	Yes ☐ No ☐	
(6) Oedema	Yes ☐ No ☐	.....	Yes ☐ No ☐	
12. Polyarthritis (*two or more joints*)	Yes ☐ No ☐	.....	Yes ☐ No ☐	Yes ☐ No ☐
13. Chorea (*definite*)	Yes ☐ No ☐	.....	Yes ☐ No ☐	Yes ☐ No ☐
14. Nodules	Yes ☐ No ☐	.....	Yes ☐ No ☐	Yes ☐ No ☐
15. Erythema marginatum	Yes ☐ No ☐	.....	Yes ☐ No ☐	Yes ☐ No ☐
MINOR CRITERIA			Max. measurement in present attack	
16. Fever	Yes ☐ No ☐	.....	Yes ☐ No ☐	Yes ☐ No ☐
17. Elevated ESR (15 *mm./hr. or over, corrected Wintrobe*)	Yes ☐ No ☐	.....	Yes ☐ No ☐	Yes ☐ No ☐
18. Previous strep. infection	Yes ☐ No ☐	.....		Yes ☐ No ☐
a. Culture		.....		
b. ASO titre		.....	.....	
c. Sore throat with fever	Yes ☐ No ☐	.....		
19. Increased P-R interval (*see criteria*)	Yes ☐ No ☐	.....	Yes ☐ No ☐	Yes ☐ No ☐
20. Previous history of rheumatic fever or rheumatic heart disease:				Yes ☐ No ☐

a. Total No. of attacks *including* present attack..... Reliability of history { Good ☐ Questionable ☐ Poor ☐

b. Date 1st attack ..... Manifestations .....
Date 2nd attack ..... Manifestations .....
Date 3rd attack ..... Manifestations .....

c. Residual heart damage from these or any unrecorded attacks:
(1) History of .....
(2) Present findings .....

21. Previous Therapy:	Date begun	Total amt. given	Date stopped
ACTH (*any attack*)	.....	.....	.....
Cortisone (*any attack*)	.....	.....	.....
Salicylates (*this attack*)	.....	.....	.....

SUMMARY

22. General description of progress, course, and severity of attack up to time of entry of trial:

.....
.....
.....
.....
.....

23. Present cardiac diagnosis:—Anat. .....
Physiol. .....

24. Date of onset (*present attack*) .....
25. Study group (*put X in box below*):

Duration from Onset	Age: Under 16 yrs.	Age: 16 yrs. and over
0–14 days		
15–42 „		
43 days and over		

26. Therapy group—ACTH ☐ Cort. ☐ Salic. ☐
Excluded from study ☐ "Out" ☐
(*If case was excluded from study, explain fully on back of form.*)

27. Investigator (*sign.*) .....
28. Date reported to centre .....

Form 2

PROGRESS REPORT

1. Hosp. No..... 2. Study No..... 3. Study centre.....
4. Date adm. to centre..... 5. Date study therapy began.....
6. Name of patient..... 7. Age..... 8. Sex..... 9. Race.....

10. a. Date (month and day)	*D*							
b. Days from onset	*D*							
c. Day of therapy	*D*							
11. Temp. (max. for day)	*D*							
12. Sleeping pulse	*D*							
13. Weight	*D*							
14. Blood pressure	*DW*							
15. Gallop rhythm *0 or +*	*DW*							
16. Arrhythmias *0 or +*	*DW*							
17. Murmurs	*DW*							
a. Apical organic systolic (*0—3*)								
b. Apical mid-diastolic (*0—3*)								
c. Basal diastolic (*0—3*)								
d. Apical presystolic (*0—3*)								
18. Precordial pain *0 or +*	*DW*							
19. Pericardial a. Rub *0 or +*	*DW*							
b. Effusion *0 or +*	*W*							
20. Failure *0—3*	*DW*							
a. Orthopnoea *0 or +*								
b. Dyspnoea *0 or +*								
c. Liver enlargement (*cm.*)								
d. Oedema *0 or +*								
e. Rales *0 or +*								
f. Jugular venous pressure (*cm.*)								
g.								
21. a. TD/ID (*mm./mm.*)	*W*							
b. Contour *0 or +*	*W*							
22. PR/Vent rate	*W*							
23.								
24.								
25. Joints *0—3*	*DW*							
26. Nodules *0 or number*	*DW*							
27. Erythema marg. *0 or +*	*DW*							
28. Chorea *0—3*	*DW*							
29.								
30.								
31. ASO titre	*M*							
32. ESR (*uncorrected*)	*W*							
33. Haematocrit	*W*							
34. Eosinophils	*Date*							
35. pH	*W*							
36. CO_2 (*meq.*)	*W*							
37. K (*meq.*)	*W*							
38. Urine sugar *0—3*	*W*							
39.								
40.								
41. A.C.S. *24 hr. dosage*	*D*							
No. doses/day	*D*							
42. KCl (*gm. p. d.*)	*D*							
43. Digitalis (*specify*)	*Date*							
44.								
45.								
46. Chemotherapy *Amt.*	*Date*							
47. Toxic symptoms *0 or +*	*D*							
48. Complications	*Date*							
49. General condition { improved / unchanged / worse }	*W*							

D daily; DW daily for days 1–7 and 42–56, otherwise weekly; W weekly; M monthly.

PROGRESS NOTES

Date	Notes	Observer

WEEKLY SUMMARY OF GENERAL CONDITION OF PATIENT

SIDE-EFFECTS OF THERAPY

Date special therapy began .....

Date special therapy ended .....

ACTH	
CORTISONE	
ACETYLSALICYLIC ACID	

Symptom	Date of first appearance	Date of disappearance	Describe severity
1. Moonface			
2. Abnormal fat deposition			
3. Hirsutism			
4. Acne			
5. Striae			
6. Amenorrhoea			
7. Mental changes (*specify*)			
a.			
b.			
c.			
d.			
8. Weakness			
9. Pigmentation			
10. Other (*specify*)			
a.			
b.			
c.			
d.			
11. Salicylism (*specify*)			
a.			
b.			
c.			
d.			
e.			

FOLLOW-UP REPORT *Form* 3

1. Hosp. No..... 2. Study No..... 3. Study centre.....
4. Date adm. to centre..... 5. Date study therapy began.....
6. Name of patient ..... 7. Age..... 8. Sex.....
9. Race.....

10. Date (month and day)								
11. Fever a. Temperature								
b. History	*0 or +*							
12. Sleeping pulse (if I.P.)								
13. a. Weight								
b. Height (inches)								
14. Blood pressure								
15. Gallop rhythm	*0 or +*							
16. Arrhythmia	*0 or +*							
17. Murmurs								
a. Apical organic systolic	*0—3*							
b. Apical mid-diastolic	*0—3*							
c. Basal diastolic	*0—3*							
d. Apical presystolic	*0—3*							
e. Basal systolic	*0—3*							
18. Precordial pain								
a. At follow-up exam.	*0 or +*							
b. History	*0 or +*							
19. Pericardial a. Rub	*0 or +*							
b. Effusion	*0 or +*							
20. Failure	*0—3*							
a. Orthopnoea	*0 or +*							
b. Dyspnoea	*0 or +*							
c. Liver enlargement	*(cm.)*							
d. Oedema	*0 or +*							
e. Râles	*0 or +*							
f. Jugular venous pressure	*(cm.)*							
g.								
21. a. TD/ID	*(mm./mm.)*							
b. Contour	*0 or +*							
22. PR/Vent rate								
23.								
24.								
25. Joints	*0—3*							
26. Nodules	*0 or number*							
27. Erythema marg.	*0 or +*							
28. Chorea								
29.								
30.								
31. ASO titre								
32. ESR (*uncorrected*)								
33. Haematocrit								
34.								
35. Upper respiratory infection	*0 or +*							
36. Days in bed	*0 or number*							
37.								
38.								
39. Rheumatic activity	*O C R or N*							
40. Cardiac diagnosis								
a. Anatomical								
b. Physiological								
c. Functional capacity								
41.								
42.								
43. Digitalis therapy	*(gr./day)*							
44. Other therapy	*0 or +*							
45. Chemoprophylaxis	*G P or O*							
46. Urine sulphonamide	*0 or +*							
47. Toxicity	*0 or +*							
48. Examiner								

FOLLOW-UP NOTES

Date of Follow-up	Notes	Observer

A-V BLOCK AND CARDIAC OUTPUT

BY

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The Starling heart–lung preparation provides a means of determining the effect of varying degrees of A–V block and of auricular fibrillation on the output of blood from the brachio-cephalic artery of the dog. We therefore describe observations we have made in which we have produced A–V block by driving the auricles electrically at increasing rates, and also observations in which we have produced auricular fibrillation by infusing acetylcholine at a uniform rate into the blood entering the superior vena cava and applying electrical stimuli in conjunction. A description of the effects of infusing acetylcholine in this way has been given in another paper (Burn, Vaughan Williams, and Walker, 1955).

Methods

The methods employed were the same as those already described. When the heart–lung preparation of the dog was set up, leads to a Cossor electrocardiograph (model 1314) were attached to the right and left forelegs and the left hindleg. Electrodes which did not pierce the tissue were applied to the tip of the right auricle, and stimuli of 1 mA strength and of 0.9 msec. duration were applied at varying rates. In experiments on fibrillation acetylcholine was infused from a burette at known rates. The output was measured by deviating the blood before it entered the venous reservoir through a T-piece into a cylinder for a period of 15 sec.

Results

Output at Varying Rates of Stimulation

Stimuli were applied to the auricle at a rate about 20 per minute faster than the spontaneous rate. The application continued for about one minute, during which the output was measured and a record of the E.C.G. was taken. Higher rates of stimulation were then tried in succession, the range of stimuli being usually from 160 to 560 per min. During