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Research Article

EXPERIMENTAL REACTIVATION OF SUBSIDING RHEUMATIC FEVER

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When anti-inflammatory therapy is reduced or discontinued in patients with acute rheumatic fever, a flare-up of disease activity frequently occurs, manifested by clinical abnormalities or by changes only in laboratory tests. The nature of this rebound phenomenon was recently analyzed in a retrospective survey of 265 patients with acute rheumatic fever (1, 2). The results indicated that most clinical rebounds were not due to any of the three possible causes to which they have been attributed in the past: *1*) polycyclic rheumatic activity, *2*) an insufficient duration of therapy or *3*) relative hypoadrenalism. Instead, the data strongly suggested that these rebounds represented the appearance of the inflammation that had been suppressed during the antirheumatic therapy. This hypothesis was based on the findings that the incidence of clinical rebounds increased with greater severity of cardiac involvement, that rebounds were more frequent in patients treated with steroids alone than in those treated with salicylates, that rebounds were more likely to occur after long courses of steroid therapy than after short courses, that they were rare after long courses of salicylates, and finally, that the incidence of post-steroid rebounds could be reduced by adding salicylates when the steroid reduction began, and by continuing salicylates for several weeks after steroids were stopped.

This new hypothesis has important implications regarding the natural history of rheumatic fever and has practical significance for its treatment. One of the implications has been used in the present study to provide a method of testing the validity of the theory. If the hypothesis is correct, it should be possible to "create" a rebound by giving anti-inflammatory therapy at a time when the convalescent rheumatic patient has no clinical abnormalities but is still in a subclinical inflammatory state. The use of profoundly suppressive therapy at this time might permit the remaining suppressed inflammation to reach an amount large enough so that clinical abnormalities occur when the treatment is discontinued. The occurrence of such an event had been noted previously (2) in one asymptomatic patient who was inadvertently given a short course of steroid therapy several weeks after his previous treatment had been discontinued and who had a clinical rebound when the steroid treatment was stopped.

The present work was undertaken as a prospective study of these phenomena in an effort to confirm or reject the proposed theory. The results, as noted below, confirm the new hypothesis.

CLINICAL MATERIAL AND METHODS

The patients ranged in age from 4 to 18 years and had all been admitted to Irvington House during the period beginning April 1959 for either acute or convalescent care of an attack of rheumatic fever which, in each instance, fulfilled the modified Jones diagnostic criteria (3). Because the initial course of anti-inflammatory therapy was usually begun elsewhere, the patients had been treated in different ways and for different lengths of time. Some had received only salicylates and some only steroids. Some had received "overlap" therapy in which salicylates were added to steroids and continued after the steroids were stopped, while others had received "combined" treatment in which steroids and salicylates were used together in a variety of ways other than the "overlap" technique.

After admission to Irvington House, anti-inflammatory treatment was begun, altered or concluded according to the individual clinical situation. In general, treatment was concluded within 12 weeks after onset of the acute rheumatic attack. In addition, the patients received oral prophylaxis daily, with sulfadiazine, 1.0 g, or with potassium penicillin G, 200,000 U, to prevent streptococcal infections. The absence of such infections during the present study was assured by periodic throat cultures and measurement of streptococcal antibodies.

After their initial treatment was stopped, some patients may have had a reappearance of rheumatic activity with laboratory or clinical abnormalities, and the

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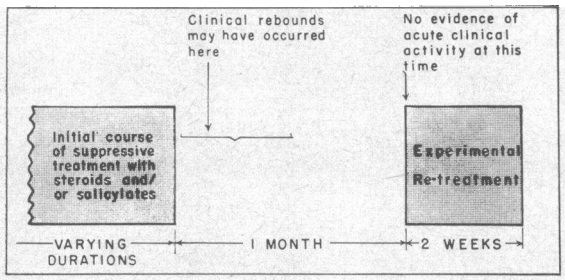

FIG. 1. PLAN OF EXPERIMENTAL THERAPY USED IN PRESENT STUDY.

latter sometimes received additional treatment before these derangements subsided. Patients became eligible for the present study after they had been without any anti-inflammatory therapy for 1 month. Although they may have had rebounds during that interval, they invariably had no *clinical* symptoms or signs of rheumatic activity when the experimental study began. The 1-month interval was chosen because of previous demonstrations (1) that post-therapeutic rebounds usually occurred within 2 weeks and were rare beyond 4 weeks after cessation of therapy. Therefore, when the experimental study was begun, all patients were beyond the "clinical rebound period" of their initial course of therapy. They were convalescent, asymptomatic and free of *clinical* evidence of acute rheumatic activity.

The plan of the experiment is shown in Figure 1. The experimental treatment was begun exactly 1 month after the previous anti-inflammatory treatment was stopped, and was continued for 2 weeks with one of the following regimens: *1*) prednisone, 60 mg per day for 1 week and 40 mg per day for the second week; *2*) aspirin, ¾ grain per lb per day for 1 week and ½ grain per lb per day for the second week; *3*) no therapy (control group).

For allocation into the experimental therapeutic groups, the patients were divided into three clinical categories. One group was considered to have "no valvular involvement" because they lacked significant cardiac murmurs, according to criteria which have been described elsewhere (1, 4, 5). The second group of patients had "valvular involvement" with no significant cardiac enlargement, i.e., no chamber more than 1+ enlarged. The third group had "valvular involvement" with significant cardiac enlargement. After classification into one of the three cardiac categories, each patient was allocated consecutively to one of the three experimental therapeutic groups. Because the number of patients was relatively small and because the consecutive order of allocation to the three therapeutic groups was followed rigorously within the clinical categories, the use of statistical random-number tables was not considered necessary. The plan for assignment of experimental therapy did not classify patients according to their previous treatment because the variations in its agent(s) and duration were too great. The most effective randomization seemed to be provided by considering the cardiac status and by maintaining the common property of being therapy-free for 1 month before onset of experimental treatment.

During the study the patients were observed for changes in clinical status and vital signs. Laboratory measurements were made of hematocrit, white blood cell count, sedimentation rate (Westergren and Wintrobe, uncorrected), serum C-reactive protein, and occult blood in

TABLE I

Status of patients before experimental treatment

Cardiac status	Previous treatment	No. of patients	Types of post-therapeutic rebounds		
			None	Laboratory	Clinical
No valvular involvement	Steroids or "combined"	18	3	11	4
	Salicylate	12	10	1	1
	"Overlap"	2	1	1	0
	Subtotal	32	14	13	5
Valvular involvement without significant cardiomegaly	Steroids or "combined"	14	5	5	4
	Salicylate	14	6	5	3
	"Overlap"	7	2	4	1
	Subtotal	35	13	14	8
Valvular involvement with significant cardiomegaly	Steroids or "combined"	11	1	4	6
	Salicylate	5	1	2	2
	"Overlap"	5	1	4	0
	Subtotal	21	3	10	8
Entire group	Steroids or "combined"	43	9	20	14
	Salicylate	31	17	8	6
	"Overlap"	14	4	9	1
	Total	88	30	37	21

TABLE II

Relationship of clinical status and types of rebounds after 2 weeks of experimental suppressive therapy in patients with subsiding rheumatic fever *

Clinical status	Experimental therapy	No. of patients	Types of rebounds after experimental therapy: No rebound	Laboratory rebound	Clinical rebound
No valvular involvement	Prednisone	11	3	5	3
	Aspirin	10	10	0	0
	Control	11	10	1	0
	Subtotal	32	23	6	3
Valvular involvement without significant cardiomegaly	Prednisone	11	4	5	2
	Aspirin	12	11	1	0
	Control	12	10	2	0
	Subtotal	35	25	8	2
Valvular involvement with significant cardiomegaly	Prednisone	7	0	3	4
	Aspirin	7	4	2	1
	Control	7	7	0	0
	Subtotal	21	11	5	5
Entire group	Prednisone	29	7	13	9
	Aspirin	29	25	3	1
	Control	30	27	3	0
	Total	88	59	19	10

* Treatment given 1 month after cessation of previous therapy.

the stools (by guaiac test). These observations were made before, during, and after the experimental period of therapy. Three-position chest X-rays with barium were taken before and after the experimental therapy.

The criteria used for post-therapeutic clinical and laboratory rebounds have been defined elsewhere (1, 2) and will be reviewed here only briefly: A laboratory rebound consisted of an elevation either in sedimentation rate (over 20 mm per hour) or in C-reactive protein (trace or higher), without any clinical abnormalities. A clinical rebound was a laboratory rebound with associated clinical abnormalities. These could be manifested by fever, sleeping tachycardia, joint symptoms, or new features of carditis.

RESULTS

Status of patients before experimental therapy (Table I). Table I shows the situation of the present group before the beginning of experimental treatment. In the entire group, the initial treatment was followed by clinical rebounds in 6 of 31 patients who received salicylate, in 14 of 43 who received steroids or "combined" treatment, and in 1 of 14 treated with the "overlap" regimen. The incidence of clinical rebounds increased with increasing severity of cardiac damage. Laboratory rebounds were common, and bore somewhat similar relationships to the clinical state and the therapeutic agent. The results noted in this group are almost identical with those observed in other patients during earlier surveys (1, 2) of rebound phenomena and demonstrate that while no initial course of suppressive treatment was entirely able to avoid post-therapeutic clinical rebounds, the latter were more frequent after steroids and less frequent when salicylates were given alone or in such a way as to "overlap" the steroids.

Incidence of rebounds after experimental therapy (Table II). There were 88 patients in the study. Of the 29 who were experimentally treated with prednisone, 9 had clinical rebounds and 13 had laboratory rebounds after prednisone was discontinued. Of the 29 patients treated with aspirin, 1 had a post-therapeutic clinical rebound and 3 had laboratory rebounds. In the 30 control patients, there were no clinical rebounds and 3 laboratory rebounds.

Within the cardiac categories, the incidence of post-prednisone rebounds was the same in patients with no valvular involvement as in those who had valvular involvement without significant cardiomegaly (3 of 11 in the first group and 2 of 11 in the second). No clinical rebounds occurred in the

salicylate or control groups for either of these two clinical categories. In the group with significant cardiomegaly, the short course of salicylate was followed by a clinical rebound in 1 of 7 patients, while prednisone therapy provoked a clinical rebound in 4 of 7 patients. No clinical rebound occurred in the untreated group.

Within the experimentally treated prednisone group, therefore, the incidence of clinical rebounds was greater in patients with cardiomegaly than in those with no or slight heart damage. Aspirin therapy had effects significantly different from those in the control group *only* in patients with significant cardiac enlargement.

It is apparent that the short course of experimental therapy was able to induce clinical rebounds in patients who might otherwise have continued their course without complication if left untreated. The features of these clinical rebounds and the number of patients in whom they occurred were as follows: fever, 5; tachycardia, 1; fever and tachycardia, 1; fever, tachycardia and erythema marginatum, 1; arthralgia, 1; congestive heart failure, 1. All these manifestations subsided spontaneously without retreatment except for the congestive failure. The latter occurred in a patient with cardiomegaly who received prednisone; its clinical features disappeared with digitalis and diuretics.

Correlation between the previous post-therapeutic rebounds and those which followed the experimental course of therapy (*Table III*). Table III shows the relationship between the events in the 1-month interval which preceded experimental therapy and the events which followed it. In patients who had no rebound after their *previous* course of treatment, experimental therapy was not able to provoke a clinical rebound, although laboratory rebounds occurred in 6 of the 13 patients who received prednisone, in 1 of 8 who received salicylate and in 1 of the 9 controls. In patients whose *previous* therapy was followed by a laboratory rebound, the experimental course of salicylates produced essentially the same results as those seen in the control group: no clinical rebounds occurred and only 2 of the 26 patients had laboratory rebounds after the experimental period. By contrast, 6 of the 11 patients in this category who were treated with steroids had clinical rebounds and the other 5 had laboratory rebounds.

In the group of patients whose previous course of therapy was followed by a clinical rebound, there were no clinical rebounds in the controls. Subsequent clinical rebounds occurred in 1 of the 9 who were experimentally treated with salicylates, and in 3 of the 5 patients who received steroids.

These data show that the experimental retreatment with prednisone provoked either a laboratory rebound or a clinical rebound in all patients who had had evidence of rheumatic activity after their previous course of therapy. It pro-

TABLE III

Correlation between rebounds which followed the initial course of therapy and those which followed the experimental 2-week course of therapy 1 month later

Nature of rebound after initial course of therapy	Experimental therapy	No. of patients	Types of rebounds after experimental therapy		
			None	Laboratory	Clinical
None	Prednisone	13	7	6	0
	Aspirin	8	7	1	0
	None	9	8	1	0
	Total	30	22	8	0
Laboratory	Prednisone	11	0	5	6
	Aspirin	12	11	1	0
	None	14	13	1	0
	Total	37	24	7	6
Clinical	Prednisone	5	0	2	3
	Aspirin	9	7	1	1
	None	7	6	1	0
	Total	21	13	4	4
Total		88	59	19	10

TABLE IV

Relationship of previous therapy to experimental therapy and the rebounds after experimental therapy

Previous therapy	Experimental therapy	No. of patients	Types of postexperimental rebounds		
			None	Laboratory	Clinical
Steroids or "combined"	Prednisone	16	3	5	8
	Aspirin	14	12	1	1
	None	13	12	1	0
	Subtotal	43	27	7	9
Aspirin	Prednisone	9	3	6	0
	Aspirin	10	9	1	0
	None	12	10	2	0
	Subtotal	31	22	9	0
"Overlap"	Prednisone	4	1	2	1
	Aspirin	5	4	1	0
	None	5	5	0	0
	Subtotal	14	10	3	1
	Total	88	59	19	10

voked a clinical rebound in more than half of the patients whose first course of treatment was followed by only a laboratory rebound. These effects did not appear after the experimental treatment with salicylate. In this group, laboratory rebounds occurred in only 3 patients and clinical rebound in only 1. With the exception of the latter patient, the results of the experimental treatment with salicylate did not differ significantly from those of the control group. By contrast, none of the experimental therapeutic regimens was able to alter the course of the disease when rheumatic activity had subsided completely without rebound after the previous course of therapy.

Relationship of previous therapy to experimental therapy and postexperimental rebounds (Table IV). This table shows the occurrence of rebounds after experimental therapy in relation to the therapy which had been given before the experimental period. The three experimental regimens were divided about equally among the patients in each of the three "previous therapy" groups. Of the 43 patients who had been previously treated with steroid or "combined" therapy, 9 had clinical rebounds after the experimental treatment. The only salicylate-induced clinical rebound in this study occurred in 1 of these patients. Of the 31 patients treated with salicylate only, none developed clinical rebounds in response to experimental treatment. One of the 14 "overlap" patients had a clinical rebound after the subsequent course of prednisone.

Table I shows that clinical or laboratory rebounds may have occurred after the initial course of therapy in all three types of therapeutic regimens, less frequently in the salicylate group. Table IV shows that patients treated initially with salicylate failed to develop clinical rebounds after experimental therapy and that the greatest susceptibility to the experimental rebounds was in patients treated initially with steroids or "non-overlapping" combined therapy.

Effect of experimental treatment upon the erythrocyte sedimentation rate (Figure 2). With minor numerical differences, the Westergren and uncorrected Wintrobe sedimentation rates showed identical variations. For convenience of illustration the Wintrobe rates have been used in Figure 2.

Using a value of 20 mm per hour as the upper limit of normal, the sedimentation rates in the "no valvular involvement" group were abnormally elevated before experimental therapy in 3 of 11 controls, in 4 of 10 patients who received aspirin, and in 3 of 11 treated with prednisone. In the patients with noncardiomegalic "valvular involvement," the pretreatment sedimentation rate was elevated as follows: controls, 5 of 12; aspirin, 6 of 12; prednisone, 4 of 11. In the group with significant cardiomegaly, an abnormal pretreatment sedimentation rate was found as follows:

controls, 5 of 7; aspirin, 4 of 7; prednisone, 4 of 7.

The pretherapeutic values of the sedimentation rate and the response to experimental treatment are shown in Figure 2. In all three clinical categories of the control group, the erythrocyte sedimentation rate (ESR) remained the same or showed only slight changes. During the experimental salicylate treatment, the ESR rose in 9 patients and fell when treatment was discontinued; in the other patients it remained the same or declined slightly. [This paradoxical rise in sedimentation rate with aspirin has been noted in the past (6). It appeared mainly in patients who showed some gastric intolerance of the drug. Its mechanism is obscure; it may be related to gastritis or to occult bleeding.] By contrast, the ESR fell during treatment in all prednisone patients, regardless of its initial value. In almost every instance, the ESR after treatment was higher than its pre-prednisone value. These data suggest that steroid therapy suppresses inflammation profoundly (as measured by sedimentation rate) and is followed by recrudescence of the inflammation to levels greater than those which existed previously.

The heavy black lines in Figure 2 show the course of the patients who developed clinical rebounds after the experimental therapy was stopped. In 6 of these 10 patients the sedimentation rate was above 20 before experimental treatment and in 8 it was above 20 at the time of the clinical rebound. The 2 patients without a high sedimentation rate at that time had abnormal values for serum C-reactive protein. The variations in reaction of these parameters presumably reflect the

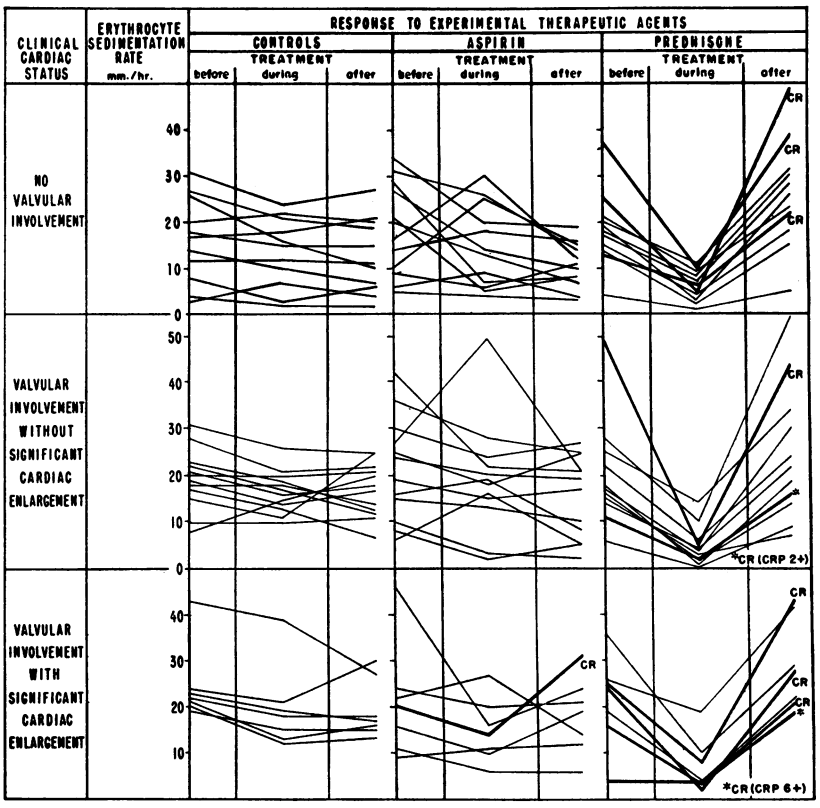

FIG. 2. RESPONSE OF SEDIMENTATION RATE TO EXPERIMENTAL THERAPY AND APPEARANCE OF POST-THERAPEUTIC CLINICAL REBOUNDS IN PATIENTS CONVALESCENT FROM RHEUMATIC FEVER. Sedimentation rate is the uncorrected Wintrobe value. CR = clinical rebound. Heavy black lines used for patients with clinical rebounds. CRP = serum C-reactive protein value, shown for patients whose sedimentation rate was below 20 at time of clinical rebound.

different capacities with which they measure the existence of inflammation in different patients.

Effect of experimental treatment upon the serum C-reactive protein (Table V). The values found here parallel those observed with the sedimentation rate. Of the 29 patients receiving prednisone, 2 had an abnormal value before the experimental therapy, none had an abnormal value during therapy and 6 had abnormal tests afterward. Five patients on salicylate treatment had a pretherapy elevation in C-reactive protein which became normal thereafter. In 7 patients, abnormal values for C-reactive protein appeared during therapy but were negative previously and afterward. The effect of salicylate in elevating this acute phase reactant is consistent with its effects, noted simultaneously, upon sedimentation rate and with those noted in earlier experiments with serum transaminase (7). In the control group, 3 patients had abnormal values before treatment, 1 during treatment and none thereafter.

Changes in hematocrit during and after experimental treatment (Table VI). The hematocrit values during and after treatment were compared in all patients with those which were present before the experimental treatment began. The changes are listed in Table VI. In the control group there was no essential difference during or after treatment. The mean hematocrit of the salicylate group fell during treatment while that of the prenisone group rose. Both mean changes, compared with those of the control group were statistically significant. Within 1 to 2 weeks after stopping the experimental treatment, the hematocrit returned to its previous levels with no significant difference between the treatment groups and the controls.

TABLE V

Behavior of C-reactive protein in relation to experimental therapy

Experimental therapy	No. of patients	No. of patients with abnormal C-reactive protein		
		Before therapy	During therapy	After therapy
Prednisone	29	2	0	6
Aspirin	29	5*	7†	1
Control	30	3	1	0

* The 5 patients with pretherapy elevations in C-reactive protein had no abnormalities thereafter.

† The 7 patients whose abnormal C-reactive protein appeared during therapy did not have it previously.

TABLE VI

Changes in hematocrit during and after experimental treatment, compared with pretreatment value

Treatment	No. of patients	Mean changes in hematocrit	
		During treatment	After treatment
Prednisone	29	+3.3* ± 3.2	−0.2† ± 3.3
Aspirin	29	−1.4* ± 3.1	+0.1† ± 2.1
Controls	30	0 ± 2.1	−0.1 ± 1.5

* The difference between these means and that of the controls is more than twice the standard error of the sampling.

† The difference between these means and that of the controls is *not* more than twice the standard error of the sampling.

Changes in white blood cell count during experimental treatment; other changes. As was expected (8), all patients receiving the experimental course of prednisone had an elevation in white blood cell count during the 2-week treatment period; the white counts returned to their previous levels shortly after treatment was stopped. Salicylate had no effect upon the white count.

The stool guaiac test became positive in 2 patients who received salicylate therapy and became negative after treatment was stopped. There were no abnormalities in the stool guaiac tests of patients who received prednisone or in the control group. There were no significant changes in the cardiac size of any patients, during or after therapy, as measured by three-position chest X-rays.

DISCUSSION

These data provide the first evidence that rebounds of clinical activity in rheumatic fever can be deliberately produced by the use of an apparently benign therapeutic procedure. A 2-week course of anti-inflammatory therapy, given to asymptomatic rheumatic patients in a convalescent state after an acute attack, was followed by a recrudescence of clinical activity in 9 of 29 patients who received prednisone and in 1 of 29 who received aspirin. The untreated control group remained asymptomatic. Clinical rebounds after the experimental therapy occurred only in patients who had shown some clinical or laboratory evidence of rheumatic activity following their original course of suppressive treatment and only in pa-

tients whose original treatment included steroids.

The results have several sets of implications:

A. They help confirm, and can be explained only by, the hypothesis that a rheumatic post-therapeutic rebound represents the reappearance of the inflammation which was previously suppressed. The alternative explanations for the events noted in the present study and the evidence against them are as follows: *1*) Recurrent episodes of rheumatic fever did not cause the flare-ups because there had been no associated streptococcal infections. *2*) Polycyclic rheumatic activity was unlikely, since it did not appear in the control group and because the flare-ups noted here were so heavily localized in the prednisone group. *3*) A nonspecific reaction, perhaps hypoadrenalistic, to steroid cessation is an unlikely explanation for these reasons: *a*) a clinical rebound occurred in a salicylate-treated patient; *b*) the rebounds were more frequent in patients with more severe heart disease; *c*) in two patients the rebounds had clinical features characteristic of acute rheumatic fever —erythema marginatum and congestive heart failure—and were not merely *nonspecific* inflammatory responses; and *d*) the experimental post-steroid symptoms did not occur randomly but appeared only in patients who had had some form of rebound previously after their initial course of therapy. Patients who had had no evidence of rheumatic activity after their initial therapy were clinically unresponsive to the experimental steroid treatment.

B. The explanation which best fits these and previous (1, 2) data is that an attack of rheumatic fever is associated with a stimulus or substance which produces inflammation and which is then consumed or dispersed in the inflammatory process. The usual course is for the inflammation to create clinical manifestations at first, to become subclinical later, and finally to cease. In most attacks of rheumatic fever, there seems to be a finite amount of this hypothetical substance; it creates a finite amount of inflammatory reaction and is dispersed by it in a finite length of time. The amount of this substance, and hence of the inflammation, will vary with individual rheumatic attacks and with individual patients, and will determine the severity of the attack, the residual cardiac damage, and the duration of measurable abnormalities (9) in laboratory tests.

Therapy with steroids or salicylates or both will generally suppress the inflammation and will reduce the severity of its clinical and laboratory manifestations. Although the expression of inflammation may be suppressed, the underlying disease remains active and the production of the hypothetical substance continues. The salicylates or subtherapeutic doses of steroids will suppress inflammation only partially, so that it is manifested by laboratory abnormalities without associated clinical features. During the period of partial suppression, some of the hypothetical substance can be dispersed as the subclinical inflammation proceeds. When the suppression of inflammation is total, as with large doses of steroids, little or no dispersion occurs and the substance accumulates. When the total or partial suppression ceases, the clinical or laboratory magnitude of the inflammation which then appears will depend upon how much of the substance remains to be dispersed.

This hypothesis explains the types of rebounds seen in earlier surveys (1, 2) of initial treatment of rheumatic fever. It also explains the present findings that profound suppression of rheumatic inflammation, at a time when it has reached subclinical levels but has not yet ceased, may be followed by clinical manifestations later when the inflammatory reaction resumes. These concepts appear to apply equally well to the rebound events noted in treatment of acute thyroiditis (10) and invite analogy regarding autoimmune phenomena in rheumatic fever.

C. These concepts do not apply to a small percentage of severely ill patients with rheumatic fever who show "chronic" or unusually prolonged clinical rheumatic activity (11) with spontaneous remissions and recrudescences unrelated to preceding therapy. There were no such patients in the present study.

D. Finally, the data indicate that anti-inflammatory drugs, particularly steroids, should *not* be given to patients with rheumatic fever who do *not* show acute clinical abnormalities, since the therapy itself may provoke a recrudescence of clinical activity and iatrogenic "chronicity" of the disease. This is particularly pertinent in situations where resumption of therapy is contemplated because its initial cessation was followed by abnormalities only in acute phase reactants. Previous work has

shown that these "laboratory rebounds" subside spontaneously (1, 2) and the present data show that their treatment may provoke clinical rebounds.

SUMMARY

A 2-week course of treatment with prednisone or aspirin was given experimentally to clinically asymptomatic patients who were convalescing from acute rheumatic fever. The experimental treatment was begun exactly 1 month after the initial course of suppressive treatment was ended. When the experimental therapy was stopped, a recrudescence of clinical rheumatic activity occurred in 9 of 29 patients treated with prednisone, in 1 of 29 treated with aspirin and in none of 30 controls. The experimental clinical rebounds, which were more frequent in patients with severe cardiac damage, occurred only in patients who had shown clinical or laboratory evidence of rheumatic activity after their previous course of treatment and only in those whose previous treatment included steroids.

The experimental treatment with prednisone caused a fall in the sedimentation rate of all patients (regardless of its initial value) and its discontinuation was followed by a rise, often to greater than pretreatment levels. It elevated the white blood cell count in all patients and caused a statistically significant rise in mean hematocrit values. The experimental treatment with aspirin caused paradoxical rises in sedimentation rate and C-reactive protein in about one-fourth of the patients; it produced positive stool guaiac tests in 2 of 29 patients and a statistically significant fall in mean hematocrit of the group.

The data are consistent with, and help confirm, the hypothesis that the post-therapeutic rebound phenomenon in rheumatic fever occurs because suppressive therapy, in preventing or inhibiting the inflammatory process, also prevents or inhibits the dispersion of the stimulus that causes inflammation. The subsequent removal of the suppressive agent is followed by the resumption of inflammation in magnitude proportional to the remaining causative stimulus.

The results indicate that anti-inflammatory treatment should not be begun or resumed for patients with rheumatic fever whose acute abnormalities are only in laboratory tests.

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