

PLACEBOS IN THE TREATMENT OF RHEUMATOID ARTHRITIS AND OTHER RHEUMATIC CONDITIONS*

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Medications and procedures reputedly helpful in treating chronic illnesses such as arthritis are multiplying to a degree confusing not only to the lay public but also to physicians.

Many or most of drugs have come into use empirically. Remissions, often spontaneous and characteristic of rheumatic disease, may coincide with the taking of some advised substance or the performance of some procedure. Autosuggestion and increased security engendered by contact with the healer can result in an improved mental attitude of faith and hope. This can account for improved physiological function which in its turn is conducive to lessening of symptoms or even to remission of the disease.

Material

Patients seen in the Arthritis Clinic at Cook County Hospital commonly have skeletal disease with chronicity expressed in months or years. They have been exposed to an almost unbelievable number of nostrums, cultists, chemicals, and physical agents, all of which have failed, as evidenced by admission to our clinic.

Methods

A complete medical history and physical examination formed part of the first visit. During this study lactose 0.3 g. was prescribed to be taken after each meal during the ensuing week of laboratory tests and studies by consulting hospital services. No promise of improvement accompanied the tablets, and such a

prescription does not affect the sedimentation rate, serum uric acid, or the eosinophils. At succeeding visits lessened symptoms or improved findings resulted in continuance of the placebo tablets, but lack of benefit would lead to a placebo injection. Failure to improve while receiving the injected placebo would be followed by employment of a presumed antirheumatic or currently used drug. Dietary, physical medicine, and hygienic and surgical advice were added at ensuing visits, after discontinuing the placebo studies.

During the weekly clinic interviews, care was taken to avoid rhetorical or leading questions. The procedure of the placebo study was planned to duplicate a customary office visit. The patient was asked "How are you as compared to your last visit? Are you better, worse, or the same? Were the tablets as helpful as aspirin? Do you think it worth while to take more tablets?" Equivocal or apologetic replies, such as "I think I am a little better" or "On that sunny day, I felt fine, but since it turned colder —", were classed as placebo failures. Seven physicians attending at the Clinic independently interviewed and examined the patient on his return visits. Check-ups were aimed to be objective.

Results

Of 151 patients with rheumatoid arthritis given a placebo, only 88 were studied in sufficient detail to justify inclusion in this report (Table I, opposite). 51 of them received the tablets for 4 weeks or less. Thirteen (25 per cent.) of these patients were found to be improved. The 38 patients (75 per cent.) in whom no improvement was seen included those with higher degrees of placebo resistance and those dis-

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illusioned by the lack of "miracle effects" as well as a few in whom the improvement lasted for less than 4 weeks. Out of 37 patients 31 were helped continuously or progressively for 2 months to 20 months. Patients reported as improved for 2 or more months are still maintaining their improvement, have ceased to improve after the given period, or have failed to return. From other patients we occasionally learn of patients failing to return because of continued remissions.

TABLE I

PLACEBO TABLETS BENEFITED ONE-HALF OF ALL PATIENTS, 12 PER CENT. FOR LONGER THAN 6 MONTHS

Duration of Therapy (months)	Number of Patients	Improvement			
		None		Moderate + Marked	
		No.	%	Number	%
1 or less	51	38	75	9 + 4	25
2	10	2	20	3 + 5	80
3	7	3	43	3 + 1	57
4 to 6	9	1	11	6 + 2	89
6 to 18	11	0	—	5 + 6	100
Total	88	44	50	26 + 18	50

Although the series is too small to have a worthwhile statistical value, it is apparent that a large percentage of patients with rheumatoid arthritis immediately resisted the placebo. This percentage of placebo resisters is higher than in degenerative arthritis (75 per cent. as against 52 per cent.). The relatively greater resistance of the patient with rheumatoid arthritis may be attributed to the higher degree of discomfort which he has to endure as compared with the average patient with degenerative arthritis, but such an assumption is not substantiated by grading the group with rheumatoid arthritis on the basis of severity of joint involvement and response to placebo (Table II).

TABLE II

PLACEBO TABLETS BENEFITED MOST OF THE PATIENTS WITH THE SEVERER GRADES OF ARTHRITIS

Severity of Arthritis	Number of Patients	Improvement			
		None		Moderate + Marked	
		No.	%	Number	%
Mild	37	21	57	5 + 11	43
Moderate	33	16	48	13 + 4	52
Severe	18	7	39	8 + 3	61
Total	88	44	50	26 + 18	50

In this small group of patients, those with the severer forms of rheumatoid disease were more

favourably influenced by placebo tablets than those with milder forms.

In our series, female patients outnumbered the males by 2 to 1, but the number of white males was one and a half times as great as the number of white females. Coloured females outnumbered coloured males by 10 to 1. Disregarding sex, the coloured and white races were equally represented.

Tablets.—Table I shows that 50 per cent. of the 88 patients benefited by placebo tablets. The improvement was largely but not wholly subjective. The patients were improved objectively, but not to the same degree as their subjective symptoms, and often a marked discrepancy was observed between the effect upon the symptoms and upon the objective changes in the disease. As regards objectivity in skeletal disease, it is worth while to note that "tenderness" has in it a strong subjective element, and even "stiffness" is strongly subjective. Swelling, on the other hand, is a purely objective observation. Improvement in the erythrocyte sedimentation rate lagged considerably behind other evidences of remission. The patient often volunteered improvement in sleeping, eating, bowel action, and general well-being coincident with relief of his arthritis. About one-fourth of the patients complained that the lactose tablets were "just like aspirin" in that they caused nausea or tinnitus. Other investigators have reported side-reactions from placebos similar to those following drugs used for anticipated pharmacological action.

Injections.—Contemplating the future study of the treatment of these patients by possibly effective materials given parenterally, we measured their placebo response level by hypodermic injections of normal saline solution. Patients not responding, or ceasing to respond, to placebo in tablet form were given hypodermic injections of an isotonic solution of sodium chloride (Table III).

TABLE III

PLACEBO INJECTIONS BENEFITED MOST OF THE PATIENTS RESISTANT TO PLACEBO TABLETS

Duration of Therapy (months)	Number of Patients	Improvement			
		None		Moderate + Marked	
		No.	%	Number	%
1 or less	19	11	58	7 + 1	42
2	6	2	33	4 + 0	66
3	3	1	33	2 + 0	66
4 to 6	4	0	—	1 + 3	100
6 to 30	7	0	—	0 + 7	100
Total	39	14	36	14 + 11	64

In most cases an injection of 1 ml. was found as effective as a larger dose. The saline solution was routinely injected in the region of the deltoid muscle, but many patients said that the injection gave them more relief if injected in the proximity of the affected part. The patients' reports were about evenly divided as to the time when improvement was noted; in about half the improvement was immediate and in the rest it was felt 4 to 6 hours after the injection. About one-third of the patients complained that the relief from the injections lasted only about 72 hours, and were gratified by receiving the injections twice weekly.

An example of how not to use placebos is worth reporting. A patient showing progressive improvement on placebo injections was sent to a nursing home, and the nurse in charge indignantly refused to administer the helpful saline injections, telling the patient, "Why, it is just salt water!"

One is justified in making only tentative assumptions from this small group of 39 patients. From figures so far available the injections were the best placebo, and relieved 64 per cent. of patients found resistant to placebo tablets. Placebo injections gave the greatest relief to white men and coloured women. The relief was at least as marked in the severe as in the milder forms of arthritis (Table IV).

TABLE IV

BENEFIT OF PLACEBO INJECTIONS UNRELATED TO SEVERITY OF THE ARTHRITIS

Severity of Arthritis	Number of Patients	Improvement			
		None		Moderate + Marked	
		No.	%	Number	%
Mild	15	6	40	3 + 6	60
Moderate	13	3	23	8 + 2	77
Severe	11	5	45	3 + 3	55
Total	39	14	36	14 + 11	64

The radiological changes were not observed to improve under any form of therapy.

Other Rheumatoid Conditions.—Four patients with psoriatic arthritis, six with gouty arthritis, ten with low back ache due to involvement of the soft tissues, and eighteen with shoulder syndromes (described as tendinitis, bursitis, and pericapsulitis) responded to placebos in the same manner as did those with rheumatoid arthritis (Tables V and VI).

TABLE V
TABLETS AS PLACEBOS IN OTHER "RHEUMATIC" CONDITIONS

Condition	Number of Cases	Duration of Therapy (wks)	Failure	Improvement
Tendinitis	18	4 or less 4-24	5 1 — 6	5 7 — 12
Psychogenic Arthritis	11	4 or less 8-52	4 1 — 5	4 2 — 6
Shoulder-hand Syndrome	4	3-8	4	

TABLE VI
INJECTIONS AS PLACEBOS IN OTHER "RHEUMATIC" CONDITIONS

Condition	Number of Cases	Duration of Therapy (wks)	Failure	Improvement
Tendinitis	5	4 or less 8-59	2 0 — 2	0 3 — 3
Psychogenic Arthritis	7	4 or less 8-130	2 1 — 3	1 3 — 4
Shoulder-hand Syndrome	1	52		1

Eleven patients with psychalgia, a psychogenic rheumatism, who were expected to respond most brilliantly to placebos, merely yielded figures comparable to those found in rheumatoid arthritis.

Four patients with shoulder-hand syndrome, a condition with a moot relation to arthritis, were not relieved by placebo tablets.

Discussion

Any procedure practised upon a conscious individual with an avowed or suspected intention of affecting the patient therapeutically has a placebo effect. This effect may be enhanced in many ways. In general, it is apt to be proportional to the intensity of its influence on the patient's sensory apparatus, and to the awareness of the patient. The placebo effect is absent in an unconscious individual and in infants.

The therapist is as often unaware of this placebo mechanism as is the patient.

The effect of suggestion, usually regarded as psychical (unrelated to organic processes), is un-

doubtedly ultimately organic. Suggestion sets off a chain of sensory effects, and the stimulus is conducted to and through the nervous system by way of autonomic fibres concerned with vasomotor control and the release of steroids. These phenomena have recently been grouped by Hans Selye of Montreal under the heading of "reaction to stress".

The placebo factor belongs to every therapeutic effort, illogical, poorly conceived, or even dangerous, even when backed by the best physiological and pharmacological information. The placebo, long recognized as an important factor in the results of physician-patient contacts, has recently received much attention. (Abbot, Mack, and Wolf, 1952; Beecher, 1955; Lasagna, Mosteller, von Felsinger, and Beecher, 1954; Leslie, 1954; Ross, 1951; Therapy Conference, 1946; Traut and Passarelli, 1956; Wolf and Pinsky, 1950, 1954).

The thickness of books on therapy, whether pharmacopeial, manipulative, or surgical, and the success of therapists from earliest times, medicine men, cultists, healers, Christian Science practitioners, priests, physicians, patent medicines, or the currently flourishing drug houses, attest to the benefits, ranging from occasional to frequent to usual, which result from giving to a conscious person advice, ointments, pills, X-ray treatments, or laying-on-of-hands. In our time the knife-wielder is held in particularly high regard. The surgeon practises and has practiced the most powerful, dangerous, but most highly-regarded and most generously-rewarded type of placebo treatment; witness the uterine suspensions and oophorectomies, now displaced by hysterectomies, removal of "sluggish" gall bladders, and operations for adhesions resulting from previous surgical adventures.

The size and number of hospitals, clinics, medical centres, and even of some cities, are due in an important measure to the placebo effect on ailing mankind.

An unrecognized placebo effect plays a great role in the treatment of two groups of illnesses, namely those recovering spontaneously such as the common cold, and the chronic diseases characterized by remissions. Treatment of these conditions challenges the therapist's discrimination.

Controls are particularly necessary in the evaluation of the treatment of joint diseases, because of the fluctuating character of these illnesses, and the many factors influencing them and their principal symptom, pain. Pain is a function of the cerebrum, and is a symptom profoundly affected by suggestion.

"Rheumatoid arthritis remains an incurable disease", but it is capable of minor to major remissions. It must be recognized that ACTH, cortisone,

or phenylbutazone have not altered the natural course of the disease over a long period in a large series of patients "in a significant manner".

Reports showing the beneficial effects of drugs or procedures in rheumatoid arthritis, or indeed in any other disease characterized by remissions, must take cognizance of the great numbers of patients who are benefited by placebos, substances supposedly devoid of any pharmacological effect.

The successful management of rheumatoid arthritis is currently assessed by the initiation of a remission or the relief of symptoms. The effect of a given procedure in initiating or continuing a remission of the disease or its symptoms is difficult to evaluate. The favourable effects of therapy are usually judged on a *post hoc propter hoc* basis, by their proximity to the waxing or waning of the disease manifestations.

The question of ethics always arises in every study of placebo effect. We considered the use of supposedly inert substances justified after listening to thousands of patients reporting on the negative effects of the whole roster of empirically used chemicals and procedures, many of them known to be harmful. After noting the bags, boxes, and bottles of ineffective salicylates, vitamins, sedatives, hormones, and other assorted chemicals carried away by the average patient for years, we have felt duty-bound to assess the value of medicine-giving in its most general sense.

Summary

The number of rheumatic patients found to benefit from placebos is about the same as the number favourably influenced by any or all of the methods of therapy reported in other studies.

The benefits from placebos in patients with rheumatoid arthritis resemble those obtained by placebos in degenerative arthritis. About 82 per cent. of patients improve—enough to justify the continuation of placebo administration. The number of patients benefited did not seem to be essentially altered by resorting to salicylates or even to cortisone.

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Les remèdes factices dans le traitement de l'arthrite rhumatoïdale et d'autres conditions rhumatismales

RÉSUMÉ

On a constaté que le nombre de malades rhumatisants soulagés par des remèdes factices est à peu près le même que celui favorablement influencé par l'une ou toutes les méthodes thérapeutiques signalées dans d'autres études.

Les améliorations dues aux remèdes factices chez les malades atteints d'arthrite rhumatoïdale ressemblent à celles obtenues par les remèdes factices dans l'arthrite de dégénérescence. Environ 82% des malades sont suffisamment améliorés pour justifier la continuité de l'administration de remèdes factices. Le nombre de malades améliorés n'a pas semblé être sensiblement changé en revenant aux salicylates et même à la cortisone.

Remedios facticios en el tratamiento de la artritis reumatoide y de otras condiciones reumáticas

SUMARIO

Se comprobó que el número de enfermos reumáticos aliviados por remedios facticios es aproximadamente igual al de los aliviados por uno o todos métodos terapéuticos señalados en otros estudios.

Los beneficiados de los remedios facticios en los enfermos con artritis reumatoide se parecieron a los obtenidos con los remedios facticios en la artritis degenerativa. Cerca de un 82 por cent. de los enfermos acusan una mejoría razón suficiente para continuar la administración de remedios facticios. El número de enfermos mejorados no pareció cambiar esencialmente cuando se volvió a emplear los salicilatos y mismo la cortisona.