PSYCHOLOGICAL FACTORS AND PAIN IN THE ASSESSMENT OF RHEUMATOID THERAPY*

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During the past year, with the advent of potent therapy by means of cortisone and ACTH, a large series of substances have been tried in rheumatoid arthritis, and several authors have shown that methods are now being evolved whereby the value of any particular therapy can be decisively assessed. Discrepancies between the results of therapeutic trials in different series have shown the necessity of careful control in such trials to eliminate psychological factors.

In many diseases psychological factors frequently produce changes in the nature or severity of symptoms as well as in the emotional attitude of the patient. These changes in symptoms may not be accompanied by any changes in the actual disease process, though psychological factors frequently directly influence the disease process, as in peptic ulceration. These interpolating factors can complicate the assessment of therapy, particularly in disease where objective data may not be readily available. Such considerations apply to rheumatoid arthritis because here the clinical picture is so often dominated by pain, the chief *modus operandi* of psychological factors in this disease. This situation helps to account for the vast number of so-called remedies which have been so readily accepted in the past by doctor and patient alike.

The relationship between psychological factors and pain in general is a close one, and has been the subject of intensive study and experimental analysis by Wolff and Goodell (1943), who showed that the cutaneous pain threshold could be altered considerably, even in critical subjects, by psychological influences.

In a series of experiments Wolf (1950) demonstrated the influence of psychological reactions on the autonomic responses to drugs acting on the gastric mucosa of a patient with a gastric fistula. It would be of interest to investigate in rheumatoid arthritis the effect of psychological factors and pain on autonomic responses, such as the circulatory changes described by Janus (1950).

Placebo Effects in a Series of Uncontrolled Cases

The effect of psychological factors in the course of rheumatoid therapy was well seen in a series of patients treated with DOCA and ascorbic acid. Eighteen unselected patients with rheumatoid arthritis were given injections of 2·5 mg.

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deoxycortone by intramuscular injection and 500 mg. ascorbic acid by the intravenous route. The patients were told that they were being given a new type of treatment which had given very good results elsewhere. They were asked to watch for, and carefully observe, any effect on joint symptoms, appetite, and well-being. This, together with the current publicity of the remarkable effects of cortisone therapy, which many of them had read about, engendered in most, though not all, of the patients an attitude of hopeful anticipation, which was reflected in the results that followed. Observations were made on the amount of spontaneous pain, joint movement, and ability to carry out certain actions such as walking, sitting, and standing. The power of grip was measured with a calibrated spring grip-meter, and joint tenderness was graded by the response to firm pressure on the joints. By these criteria, twelve showed improvement after the initial injection, and in six there was no appreciable change. Objective observations such as joint swelling, sedimentation rate, and pyrexia were not significantly altered. In the light of a controlled investigation which was then carried out, and which was entirely negative in its results, it was concluded that in the preliminary uncontrolled trial, the changes observed were essentially placebo effects; i.e. effects produced not directly by the agents administered, but by accompanying psychological responses.

Cases Illustrating Marked Placebo Effects.—In the twelve patients who showed subjective improvement, the response was remarkable in several cases.

(1) *Male, aged 51*, with active disease of four years' duration, lost all his pain, joint tenderness, and stiffness. Whereas before the injection he could only walk slowly and painfully, after it he spontaneously leapt over beds and ran down the ward. Power of grip was increased, and he became very euphoric and anxious to demonstrate his improvement. He had been told to watch the effect on his appetite, and this was rapidly and markedly increased. If a film had been made of this patient the result would have been more spectacular than that seen in the film on the effect of cortisone therapy, shown by Dr. Hench to the Heberden Society in 1950.

Euphoria was observed in four cases, but one patient became more depressed in spite of improvement in joint symptoms. The improvement usually started within an hour and frequently within 15 minutes of the injection, the average duration of response being 18 hours. In suitably conditioned patients later injections of saline reproduced the same response, even to the length of the latent period. In general there was usually a diminished response to further injections, in fact a progressive falling off. Sometimes a good response was followed by rebound aggravation of symptoms probably due to overuse of affected joints. Occasionally later injections resulted in aggravation of symptoms. When the injections lost their effect, the patient sometimes denied that any benefit had ever occurred, although such improvements had been admitted previously. The possibility arose that the psychological response to the injections had activated an endocrine mechanism, which had caused an ACTH like effect. However, the absence of objective evidence of improvement was against this. In addition, in six patients in whom there was a good response, no significant eosinophil decrease was

observed as a result of the injections. There were no overt psychological abnormalities present in any of the patients, and no relation to age, response to previous courses of injections such as gold, or to duration or severity of joint damage, could be established. The marked personal factor involved in placebo response was seen in the following case:

(2) *Female, aged 48*, with a ten-year history of active and progressive disease, had a moderate response in the preceding trial of injections. However, 3½ hours after her first interview with a spiritual healer, she had a remarkable response. This latent period is interesting as the improvement started after she had ceased to expect benefit, illustrating the subconscious nature of the mechanism. Her joint tenderness disappeared; so that, whereas before she was so crippled that she could only walk slowly and with sticks, after the interview she walked quite normally and without pain, and the following day she walked several miles unaided, without apparent ill effect. She continued to visit the spiritual healer and although improvement was maintained for two months, there was a gradually diminishing response and at the end of this time her symptoms had completely relapsed.

Placebo Effects in Ankylosing Spondylitis.—Placebo effects were much less marked in six patients with ankylosing spondylitis who were treated in the same way as the series of rheumatoids. One patient said that his pain was relieved by the injections to the same extent as after an injection of morphia. However, he was not impressed with them as his functional capacity was limited by stiffness and ankylosis and was not affected.

Series of Controlled Cases

When a series of rheumatoid patients were treated with saline injections, followed by injections of DOCA and ascorbic acid under controlled conditions, no appreciable effect on joint tenderness, pain, movement, or performance tests was noted. Neither in these patients nor in normal subjects was any euphoria or effect on appetite produced. The absence of any response, even after the first injections, in these subjective criteria was attributed to the neutral attitude preserved by all concerned in the injection courses, combined with the fact that there was no suggestion that the patients should take particular note of their symptoms. This absence of placebo effect may be correlated with the observation made by Schumacher and others (1940) that the pain threshold in man shows uniformity under standard conditions.

Mechanism of Placebo Response

The mechanism whereby placebos cause subjective improvement in rheumatoid arthritis is a matter for speculation. The link is the reduction of pain, and hence of tenderness, brought about by the patients' subconscious and conscious expectation of improvement. Performance tests, such as walking and making repetitive movements, are limited primarily by pain in many cases, muscle spasm, joint swelling,

ankylosis, contractures, and tendon lesions being limiting factors in others. Thus one patient with ankylosing spondylitis and severe peripheral joint involvement, who had an intelligent insight into his condition, was able to say that before his disease became too advanced, one tablet of codeine compound enabled him to throw away his crutches until the analgesic effect wore off. Many patients in a rheumatism clinic, of course, remark that aspirins enable them to keep going.

The euphoria produced by placebo agents is of considerable interest; it is due to the elimination of pain and its depressing emotional repercussions, together with the patient's conviction that the disease is regressing. It is this latter factor that prolongs the action of placebo effect and makes it more potent than the action of analgesics.

The intensity of the euphoria in a few cases raises the suspicion that its occurrence after cortisone or ACTH therapy may be not altogether a specific effect of these compounds, but largely a reaction to the improvement produced.

Case of Painless Rheumatoid Arthritis

A remarkable preservation of function in the face of severe rheumatoid arthritis was seen recently in a 40-year-old woman; this could only be accounted for by the absence of pain, which in her case characterized the disease. Her wrists, fingers, right elbow, ankles, and feet were actively affected with damage to the bone and soft-tissue swelling, and the erythrocyte sedimentation rate (corrected Wintrobe) was 31 mm. in one hour. The disease had been progressive for 11 years and throughout this time she had worked as a telephonist at a busy exchange and engaged in extra work in her spare time. This work involved continual manipulative movements of the most affected joints, but she had never lost a day's work, being inconvenienced only by joint stiffness and slight joint discomfort, not amounting to pain. Her cutaneous pain threshold, measured after the method described by Hollander (1939), was found to be grossly elevated. A pressure of 250 mm. Hg on a cheese grater placed against the skin evoked only minimal discomfort, as compared with control values of 35, 50, and 20 mm. in normal subjects. The negative history and examination in relation to a wide range of pain-producing situations and stimuli in this patient, showed that although she appeared otherwise normal psychologically and neurologically, she had an apparent constitutional hypo-algesia. In this respect she resembled a patient described by Kunkle and Chapman (1943) and this fortunate trait seemed largely to neutralize the crippling effect of the disease.

Discussion

As criteria of rheumatoid activity, estimates of pain and tenderness provide evidence of a subject nature, and this also applies to joint-range, measurements, performance tests, and grip-meter readings, when pain participates in their limitation.

Accordingly these tests can be altered under circumstances which do not influence the disease process. To avoid any fallacies in the assessment of rheumatoid therapy, the New York Rheumatism Association recommended the strictly objective criteria formulated by Steinbrocker and others (1949) to the exclusion of subjective criteria. This system devised before the advent of cortisone and ACTH has, however, certain disadvantages where rapid assessment of a range of substances is necessary. Firstly, objective signs may be scanty where systemic

signs of the disease are absent or minimal, e.g. cases where there is no elevation of the sedimentation rate. Joint swelling may be slight and is not always easily measured, though here a graded series of rings devised by Dr. Dudley Hart, are of considerable help in proximal interphalangeal joint measurements. One of the N.Y.R.A.'s criteria of an effective remedy is its ability to reduce or eliminate restriction of joint mobility, other than that associated with irreversible change. This association is not easily assessed, and joint range, as has been stated above, is not strictly objective since it can be influenced in many cases by placebo measures. Even serial joint biopsies, the most direct of objective criteria, are not infallible owing to difficulties in taking comparable specimens, a point stressed by Hench (1950).

The advantages of subjective methods of assessment are their ease and simplicity and their universal application, although observer error and daily variations have to be allowed for.

Summary

To avoid interference by psychological factors the following precautions are advisable in therapeutic trials in rheumatic diseases:

(1) The establishment, as far as possible, of a neutral attitude in all concerned with the trials. This cuts out bizarre placebo effects and makes for steady base-line observations, which enable an effective remedy to show its action more strikingly even in a small series.

(2) The use of inert control substances, the identity of which is unknown to patient, observer, nursing staff, and all in contact with the patient.

(3) A preliminary period of observation and assessment during which an in-patient may settle down in hospital and the course and tempo of the disease may be noted under standard conditions.

(4) The simultaneous assessment of all available objective data.

With these precautions, psychological interference is reduced to a minimum, allowing subjective changes to parallel rheumatoid-disease activity, and to be used in its assessment.

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References

Hench, P. (1950). Lecture to the Heberden Society at the West London Hospital on October 5, 1950.
Hollander, E. (1939). *J. Lab. clin. Med.*, **24**, 537.
Janus, O. (1950). *Brit. med. J.*, **2**, 1244.
Kunkle, E. C., and Chapman, W. P. (1943). *Res. Publ. Ass. nerv. ment. Dis.*, **23**, 100.
Schumacher, G. A., Goodell, H., Hardy, J. D., and Wolff, H. G. (1940). *Science*, **92**, 110.
Steinbrocker, O., Traeger, C. H., and Batterman, R. C. (1949). *J. Amer. med. Ass.*, **140**, 659.
Wolf, S. (1950). *J. clin. Invest.*, **29**, 100.
Wolff, H. G., and Goodell, H. (1943). *Res. Publ. Ass. nerv. ment. Dis.*, **23**, 434.

Other Relevant Articles

Harris, R. (1950). *Brit. med. J.*, **2**, 947.
Lewin, E., and Wassén, E. (1949). *Lancet*, **2**, 993.
Quin, C. E., Mason, R. M., and Knowelden, J. (1950). *Brit. med. J.*, **2**, 810.

Les Facteurs Psychologiques et la Douleur dans l'Évaluation du Traitement du Rhumatisme

Résumé

Pour éviter l'ingérence des facteurs psychologiques au cours des essais thérapeutiques dans les affections rhumatismales on recommande les précautions suivantes:

(1) Créer, autant que possible, une attitude neutrale chez tous les intéressés. Ceci éliminera les effets surprenants chez les témoins et offrira aux observateurs un critère invariable, de manière qu'un remède efficace puisse montrer sa valeur d'une façon frappante même dans un petit nombre des cas.

(2) Utiliser des substances-témoins inertes dont l'identité soit inconnue au malade, à l'observateur, aux infirmières et à tous ceux qui approchent le malade.

(3) Instituer une période préliminaire d'observation et d'évaluation; pendant que le malade s'adapte à la vie à l'hôpital on notera la marche et le tempo de l'affection dans des conditions standard.

(4) Evaluer simultanément toutes les données subjectives disponibles.

Ces précautions réduisent au minimum l'ingérence psychologique ce qui permet dans l'évaluation de tenir compte des signes subjectifs se manifestant en fonction de l'activité rhumatismale.

Factores Psicológicos y Dolor en la Valoración de la Terapia Antirreumática

Resumen

Para evitar la interferencia de factores psicológicos las siguientes precauciones son recomendables durante pruebas terapéuticas en casos de enfermedades reumáticas:

(1) Establever en lo posible una actitud neutral en todos los interesados en las pruebas. Eso permite eliminar los efectos sorprendentes que se suele ver con las substancias de control y ofrece una línea de mira fija las observaciones. De esta manera, un remedio eficaz puede manifestar su acción en forma destacada hasta en un pequeño número de casos.

(2) Usar, para el control, substancias inertes cuya identidad debe ser desconocida para los pacientes, observadores, personal clínico y todos aquellos en contacto con los enfermos.

(3) Crear un período preliminar de observación y de valuación durante el cual el paciente pueda adaptarse a la vida hospitalaria, y el curso y marcha de la enfermedad puedan ser observados bajo condiciones estandardizadas.

(4) La valoración de todos los datos objetivos disponibles debe realizarse simultáneamente.

Con estas precauciones, la interferencia psicológica se reduce al mínimo, los signos subjetivos se manifestan en función de la actividad reumática y pueden servir así para la valoración.