related to the presence of non-myelinated free nerve endings in such tissue.

Pain thresholds in hairy tissues were raised considerably 48 h after the first session; touch thresholds were unchanged. Pain thresholds in hairless tissues were the same or somewhat lowered, thereby indicating that a general adjustment to pain does not underlie the rise. Since, in the first session, only six painful stimuli, and sometimes more than one hundred touch stimuli, were delivered to a given electrode site, pain thresholds in hairy tissue are raised solely from effects of the passage of current.

Pain thresholds on hairy tissue obtained with stimuli of varying repetition rates and pulse numbers were converted to average current per millisecond of stimulation[2]. An approximately rectangular hyperbolic relation was obtained between average current per time unit and stimulus duration, for durations as long as two seconds. Thus pain thresholds on hairy tissues are properly specified in units of average current flow and total time, not power. This finding, together with the importance of long rest intervals to sting threshold stability, points to a chemical intermediary.

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Placebo Reactor

It is often believed that there exist, in the community, certain individuals who are 'placebo reactors', and that these individuals must be excluded from a controlled clinical trial if the 'true' effects of the drug in question are to be correctly assessed. Glaser[1] expressed the extreme view when he wrote "a dummy" [that is, a pharmacologically inert substance] "identifies those patients who can be disregarded, either because they need no treatment or else because they can be cured by psychological influences, and this is as reasonable a procedure as the exclusion from experiments with anti-asthmatic drugs of patients who do not have attacks of bronchial asthma".

The story of the 'placebo reactor' can largely be traced back to Jellinek[2], who reported an investigation of headache in which he found that a proportion of the sufferers obtained relief from a placebo; he further observed a U-shaped distribution of individuals, with regard to this placebo reaction, so that some 'definitely' responded while others 'definitely' did not, only very few being partially relieved. It has since been shown[3–6] that this U-shaped distribution is by no means characteristic of all drug responses, and that the incidence of placebo reactions can vary greatly with the circumstances of a trial. Nevertheless, the mythical person who 'once a placebo reactor' is 'always a placebo reactor' dies so hard that an extra nail for his coffin will perhaps do no harm.

There is, of course, no doubt that some individuals are more amenable to suggestion than others, and in a given situation this increases the likelihood of their deriving some satisfaction from a placebo[7]. Also, the cause of the symptoms is of obvious importance, as Jellinek[2] himself recognized when he wrote "the difference in response to placebo must reflect a difference in the nature of headaches". It was, indeed, a shrewd physician who said "the treatment of scarlet fever depends on what is the matter with the patient"[8].

Apart from the variability of the individual and his symptoms, the design of a drug trial may influence the number of 'placebo reactors' who are discovered, particularly in a complex situation in which several methods of grading the response to the drug are available. This is well shown in my own work on post-operative pain, with which—unlike headache—'complete relief' and 'complete non-relief' rarely occur. The design and purpose of these investigations are explained elsewhere[9]; their present interest lies in the fact that they have provided several different criteria against which 'relief of pain' may be deemed to have occurred after treatment with morphine and a placebo (normal saline).

Table 1. Incidence of 'Placebo Reactors' after Upper Abdominal Surgery

	Improvement of pain alone (%)	Improvement of pain, movement and coughing (%)	Vital capacity (%)	Peak expiratory flow rate (%)
Change of 1 grade or more = 'relief'	45	50	22	12
Change of 2 or more grades = 'relief'	0	0		

Using an arbitrary pain score, only three out of 21 of my patients failed to achieve an improvement of at least 1 grade after morphine; but if this were to be accepted as 'relief', 8 of 18 patients were relieved by saline. If an improvement of two grades was required for 'relief', no patients were relieved by saline and only 2 by morphine. Movement and coughing are especially painful after upper abdominal operations; when ability to move and cough was taken into account, an improvement of one grade or more was achieved by 19 patients after morphine (91 per cent) and by 9 after saline (50 per cent), while an improvement of two or more grades was obtained by 10 of the 21 morphine cases and by none of those who had saline. Finally, an indication of the painfulness of deep breathing and coughing was obtained objectively by measuring vital capacity and peak expiratory flow rate: the vital capacity improved in 10 of the 12 patients after morphine, and in 2 of 9 after saline; peak expiratory flow rate improved in 4 of 12 cases given morphine and in 1 of 8 given saline. Allowing for a moment that percentages can legitimately be derived from such small numbers of individuals, the incidence of patients who obtained 'relief of pain' from an injection of saline, according to these several criteria of 'relief', was as shown in Table 1.

All these figures relate only to pain after upper abdominal surgery; other types of case yielded different responses to saline. Thus, the percentage of 'placebo reactors' among my patients could be made to vary from 0 to 50 according to the stringency of my criteria of 'pain relief'. As a greater improvement is required before 'pain relief' is deemed to have occurred the number of 'placebo reactors' falls; but, at the same time, the 'effectiveness' of morphine diminishes. The investigator is at liberty to choose whether he has 'placebo reactors' or 'morphine non-reactors' among his patients.

All this makes it difficult to understand how so-called 'placebo reactors' can reliably be identified and excluded from a clinical trial, and how the 'true' effects of a drug can be dissociated from its psychological effects. In contrast to Glaser's views[1], one might observe that bronchial asthma itself not infrequently responds to psychological influences, and that "there must be something the matter with a man who comes to a doctor when there is nothing the matter with him"[10]. It is perhaps not even too much to suggest that given the appropriate circumstances each one of us has the makings of a 'placebo reactor'.

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