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Increased Stress and Effectiveness of Placebos and "Active" Drugs

Abstract. Evidence is presented to indicate that placebos are far more effective in producing carefully defined relief of pathological pain than they are in the case of experimental pain. This is construed as further support for the view that placebos are more effective when stress is great than they are when stress is not so great. A similar situation holds for morphine. Certain drugs are effective in relieving visceral sensations only if an essential psychological state is present. This is, in effect, a new principle of drug action.

This report presents an experimental finding: placebos relieve pathological pain more effectively than they do experimental pain. Two general concepts grow out of this observation as working hypotheses: (i) the effectiveness of placebos increases with increased stress and (ii) the effectiveness of certain "active" drugs increases with increased stress.

In essence, this study is based upon the proposition that pain of pathological origin produces more anxiety, or stress, than does experimentally contrived pain. Like any axiom, this one may be unprovable in a tight mathematical sense, yet its truth is clearly evident. Even so, the material in this report is presented as evidence for, not proof of, the proposition, just as was the case in an earlier study (*1*), where material of another kind was presented. In that earlier paper it was found: (i) in terms of percentage of a given population relieved, placebos are significantly more effective when postoperative pain is severe than they are when the pain is less severe, and (ii) the work of Cleghorn, Graham, Campbell, Rublee, Elliott, and Saffran (*2*) demonstrates that firing of the adrenal glands (measured in objective terms) is far greater in response to a placebo in patients hospitalized for severe anxiety than in patients hospitalized for anxiety of less severe degree.

The new data are presented in Tables 1 and 2. The most important fact arising from these data is that the mean percentage effectiveness of placebos in relieving pathological pain is over ten times that found with experimental pain. It is realized that some of the studies compared are based on large samples and some on small, and that the *t*-test evaluation ignores this fact and gives all studies equal weight. For present purposes this is satisfactory since numerous studies are involved and the difference between the two conditions is great.

It is not my contention that placebo effectiveness is always low in experimental situations. This is demonstrably not the case. The matter is complex, and it may be in these other cases that stress of one kind or another operates when placebo effectiveness is high. It is important to deal, as here, with a limited area at a time; in the present instance attention is given solely to comparison of placebo effectiveness in relieving pain of (i) pathological and (ii) experimental origin.

Placebos, being "inert" agents, can affect only psychological processes. The assumption is that when the psychological component of a situation is important the placebo will have a correspondingly greater opportunity to produce an effect, and this seems to be the case. The primary purpose of this paper is, however, to present observations rather than speculations.

Effects similar to those of a placebo can be found with an "active" drug: morphine, even in large doses, does not dependably relieve pain of experimental origin in man, as indicated by some 15 different groups of investigators (*3*, pp. 123, 124). Morphine in comparable (or smaller) doses is highly effective in relieving pain of pathological origin. Pathology (stress, see below) provides the matrix on which the given drug (morphine), ineffective as it was in relieving experimentally contrived pain, becomes effective when the necessary component—apparently stress—is present (*3*, p. 164). Pathology alone (stimulation of pain endings in battle wounds) is often not enough to give rise to pain. The psychological significance to the subject determines the pain experienced (*3*).

The new principle is: certain drugs are effective in relieving visceral sensations only if an essential psychological state is present. It is not possible at present to define exactly the nature of this state. It appears to be related to the significance of the symptom, to anxiety, and to stress. (And apparently, the stronger the psychological state, the more effective the drugs.) Similarly, certain common symptoms, pain for example, appear to emerge only if an essential psychological state (anxiety, stress) is present (*3*). Physiological derangement (stimulation of pain end-

Table 1. Effectiveness of placebos in relieving pain of experimental origin. The numbers in parentheses in column 1 refer to studies cited in "References and Notes."

Study	Subjects (No.)	Average placebo effect (% relieved)	Comment
		Radiant heat	
(*4*)	16	0.8	Suprathreshold pain, untrained subjects
		0.4	Suprathreshold pain, semitrained subjects
		4.0	Suprathreshold pain, trained subjects
(*5*)	4	0	± 1.1% change from original value
(*6*)	3	0	Obstet. cases; radiant heat pain only
		Radiant heat to forehead	
(*7*)	1	19	1, no effect; four trials
	1		1, 20% rise; no effects 2nd and 3rd trials
	2		2, 28% rise
(*8*)	1	2	
(*9*)	29	0	No consistent trend
		Pressure on forehead	
(*10*)	4	0	Aching pain
		Pressure on forehead, cuff method	
(*11*)	63	0	Inconsistent, variable + and −
		Hydrostatic pressure in biliary system	
(*12*)	8	0	
		Electric shock	
(*13*)	30*	1.3†	Pain intensity comparison; no drug versus
		5.0‡	placebo
(*14*)	3	0	
		Tourniquet	
(*15*)	4	15.5	
(*16*)	4	0	
Totals (13 studies):			
	173	3.2 ± 1.8	Average percentage relieved

* Postaddicts; † $N = 16$; ‡ $N = 14$.

Table 2. Effectiveness of placebos in relieving pain of pathological origin. The average percentage relieved in Table 2 differs from the average percentage relieved in Table 1: $t = 9.28$ and $p = 0.0001$.

Study	Subjects (No.)	Satisfactorily relieved by placebo (%)
Severe postoperative wound		
(*17*)	118	21
(*18*)	29	31
(*19*)	34	26
(*20*) (The av. percentage relieved by placebo was 33%.)	52	40
	36	26
	44	34
	40	32
(*21*) (The av. percentage relieved by placebo was 39%.)	14	50
	20	37
	15	53
	21	40
	15	40
	15	15
Pain from angina pectoris		
(*22*)	66	38
(*23*)	19	26
(*24*)	27	38
Pain from metastatic disease		
(*25*)	67	42
Headache		
(*26*)	199	52
Totals (10 studies):	831	Av. 34.6 ± 2.9

ings) is not enough. Thus there is exposed in this new framework unsuspected ties between mind and body, revealed by the study of drug action.

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A Function for Ascorbic Acid in the Metabolism of an Insect

Abstract. Homogenates of *Blattella conjuncta* oxidize L-tyrosine. The reaction is diminished by dialysis, but may be reactivated with L-ascorbic acid. Glutathione, pyridoxal phosphate, and folic acid also activate the system.

It has been demonstrated (*1–3*) that ascorbic acid will activate the L-tyrosine oxidase system of mammalian liver. However, the function of the compound in insect metabolism is unknown. Previous investigations (*4*) have demonstrated that the cockroach contains large amounts of ascorbic acid. In fact, the concentration in the whole insect (10 to 19 mg/100 gm) greatly exceeds that in whole guinea pigs [2.4 mg/100 gm (*5*)]. This concentration presumably indicates that ascorbic acid plays an important role in insect metabolism. The present study was undertaken to study tyrosine oxidation by insect tissues which, by analogy with the process in mammalian tissues, would be expected to require ascorbic acid.

Blattella conjuncta was captured locally in the Upper Hutt Valley, near Wellington, New Zealand. The adult insects were killed by decapitation, and the whole insects were homogenized with two volumes of ice-cold 0.14*M* potassium chloride solution in a Potter-Elvehjem apparatus. Insoluble materials were removed by centrifugation at 2°C. The supernatant was adjusted to *p*H 7.5 and dialyzed in a cellophane bag against 0.14*M* potassium chloride solution for 24 hours at 4°C. The resulting solution was used as the source of the tyrosine oxidase system.

Table 1. Effects of ascorbic acid and other cofactors on the tyrosine oxidase activity of a dialyzed insect homogenate. The activity is given in microliters of oxygen per hour.

Components added to homogenate	Activity
None	11
α-Ketoglutarate (α-K)	14
α-K + ascorbic acid	31
α-K + glutathione	15
α-K + pyridoxal phosphate	14
α-K + folic acid	21
α-K + ascorbic acid + glutathione	42
α-K + ascorbic acid + glutathione + pyridoxal phosphate	49
α-K + ascorbic acid + folic acid	37
α-K + ascorbic acid + glutathione + pyridoxal phosphate + folic acid	50

Activity was determined by Warburg techniques at 37°C in air with sodium hydroxide papers in the center wells of the vessels. Each vessel contained 1.0 ml of the dialyzed solution, 1.0 ml of 0.2*M* phosphate buffer at *p*H 7.2, and 6 μmole of L-tyrosine. The side arm contained 0.1 ml of 0.1*M* α-ketoglutarate and 0.1 ml of a solution of cofactors. The total volume in each vessel was 3.0 ml. The following cofactors were used in some experiments: ascorbic acid (1 mg), glutathione (1 mg), pyridoxal phosphate (10 μg), and folic acid (200 μg). The reaction was initiated by tipping the side arm. Manometric readings were taken for 1 hour.

The results of a typical experiment are given in Table 1. It is clear from these figures that the tyrosine oxidase system is activated by ascorbic acid. It is also activated by folic acid. The greatest effect results from additions of ascorbic acid, glutathione, and pyridoxal phosphate.

It is clear that the oxidation of L-tyrosine by homogenates of this insect probably follows a pathway similar to that in mammals. It is known that the latter deaminate tyrosine by a transamination reaction with α-ketoglutarate which requires pyridoxal phosphate (*6*). The resulting *p*-hydroxyphenylpyruvic acid is oxidized to homogentisic acid and carbon dioxide. This process involves 2,5-dihydroxyphenylpyruvic acid as an intermediate and requires ascorbic acid and glutathione. The effect of folic acid on the system is difficult to explain, but a similar effect has been reported for the mammalian system and it has been suggested that the stimulation is not due to a direct effect of the compound on the enzymes (*2*).

The present study clearly establishes a function for ascorbic acid in insect metabolism.

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