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Psychological stress and cardiovascular diseases

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WHEATLEY D. Psychological stress and cardiovascular disease. *Scand J Work Environ Health* 10 (1984) 415—417. Mental stress may directly influence coronary heart disease (CHD) and also a number of its etiologic risk factors. Research work carried out by the Psychopharmacology Research Group in the United Kingdom indicates that antianxiety drugs may have an application in the management of the stress factors influencing CHD. In one study there was a significant reduction in the glyceryl trinitrate requirements of patients treated with a tranquillizer, but this result was not confirmed in two other studies. However, out of a total of 77 patients treated with a placebo, there were five cases of myocardial infarction during the trial periods as compared to no such cases among 81 patients treated with the anti-anxiety drugs.

Key terms: anxiolytics, hypertension.

> The ultimate measure of a man is not where he stands in moments of comfort and convenience, but where he stands at times of challenge and controversy.
>
> Martin Luther King, Jr (4)

The changing nature of the stresses that challenge man's existence in modern civilization (3) have sorely taxed his coping mechanisms (6). Stress is indeed a normal component of life (8), but at some times and in some individuals it can produce devastatingly adverse effects.

Stress, overt or covert, may play a part in many organic and psychiatric disorders, including ailments of affect, cardiovascular conditions, sexual disorders, premenstrual syndrome, menopause, geriatrics, and sleep disturbances. Furthermore a number of organic illnesses may be adversely affected by stresses occurring in the patient's life, and notable among them are asthma, gastrointestinal disorders, arthritis, and dermatologic conditions, to mention a few. In addition to the effects of stress on organic illnesses, there are the many types of stress which affect the individual's ability to function in his or her everyday life.

The Psychopharmacology Research Group in the United Kingdom is involved in work on stress. We are at present investigating the following nine areas in which stress factors may play an important role, and we are quantifying these factors so that the impact of their interrelations is immediately apparent and can be used in subsequent case management: patient history and background data, social stress, life events, psychiatric rating, sexual stress, sleep and stress, stress and the heart, stress and old age, and menstrual stress. In the present communication I would like to concern myself with our work in the area of "stress and the heart."

It is not always appreciated that several etiologic factors of coronary heart disease (CHD) have psychogenic components associated with life habits and situations. Psychic and physical stresses may directly influence CHD (7, 10), and the psychic factors are potentially capable of modification, particularly by the use of antianxiety drugs. In like manner, the etiologic factors themselves are potentially capable of modification by similar means.

For example, alcohol in excess (2) and smoking (1) are potent risk factors with strong psychogenic components. If patients are denied tranquillization from cigarettes and alcohol, ought these not be replaced chemically, provided that the drug used is harmless?

Sexual activity may also exert an adverse effect on patients with CHD, and sudden deaths do occur during and shortly after sexual intercourse, usually under clandestine circumstances (15). [Far safer perhaps the placid ambience of the marital bed than the illicit pleasures of the bordello!] But a chemical tranquillizer may help prevent such unfortunate complications of one of the natural pleasures of life.

Of the nonpreventable factors of CHD, heredity is undoubtedly the most important (9). The psychological effects of a family history or racial predisposition to CHD may be of considerable importance. Fear of succumbing to the same ailment that killed one's forebearers may constitute a potent causal factor.

One can see that stress and anxiety may exert many ubiquitous influences on patients with CHD, and so it has seemed to be a logical approach to assess the role of anxiety-relieving drugs in preventing and minimizing these influences.

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Our group has undertaken several double-blind placebo-controlled studies of tranquillizing drugs and CHD (13). The first of these concerned a group of patients who had experienced their first myocardial infarction and so might have been particularly susceptible to anxiety lest they suffer a second and potentially fatal incident. In this study it was found that, in comparison to the use of a placebo, the addition of clorazepate to the patients' treatment regimes resulted in reduction in the anginal attack rate and glyceryl trinitrate requirements (11). Since then, we have undertaken two similar studies.

In one of these trials, clorazepate was again compared to a placebo. The patients suffered from angina pectoris but had not yet had an actual infarction. The design of the trial was similar to that of the first study, but it was only possible to include 35 patients, and this small number did not show any significant differences on any measure (13, 14).

For ethical reasons the use of other cardiac drugs was allowed in these studies as necessary, and the requirements for such drugs were used as an additional measure of assessment. For example, in the postinfarction study (11), more patients receiving the placebo required additional medication as compared to those on clorazepate. In the preinfarction study there were no significant between-group differences (13, 14).

Clearly, it is better to standardize cardiovascular medication, and so, in another study, all patients were treated throughout with the calcium antagonist, verapamil, and either diazepam or a placebo was added on a double-blind basis. The treatment period was shorter (six weeks) with a preliminary two-week control period during which verapamil alone was administered. Altogether, 86 patients entered the trial (diazepam 41, placebo 45), and for all four patient measures (anginal attacks, feelings of well-being, glyceryl trinitrate requirements, and exercise tolerance) there was significant improvement, but with no significant between-group differences.

Hypertension may be another important etiologic factor in CHD, and fluctuations in blood pressure levels may be influenced also by psychogenic factors (12). In a two-month trial to compare medazepam to a placebo added to standard methyldopa therapy, there was no evidence that medazepam resulted in either better relief of anxiety symptoms or better control of either systolic or diastolic blood pressure, nor was there any "sparing" effect on the methyldopa dosage required to control blood pressure.

In view of the antianxiety effects of propranolol, a further study was undertaken (12), along the same lines, to compare propranolol alone to methyldopa alone, but similar results were recorded. Thus, relief of anxiety accompanied the reduction in blood pressure, but propranolol was no more effective than methyldopa in this respect.

Methyldopa was chosen as the standard antihypertensive drug in the previous two trials because, at the time, it was the antihypertensive most widely used in the United Kingdom. However, since that drug has tranquillizing properties per se, a drug with no such properties, namely, bendrofluazide, was chosen for the next trial.

In a four-group comparison, bendrofluazide was compared to lorazepam, a placebo, and the combination of lorazepam + bendrofluazide (14). With the exception of lorazepam alone, the treatments resulted in a significant reduction in systolic and diastolic blood pressure, but with no significant between-group differences. However, the combination of lorazepam with bendrofluazide was the only treatment which produced mean reductions in both the systolic and diastolic blood pressure to below normal values.

The preceding research has led to a seeming paradox, without providing an answer concerning the possible benefits of tranquillization on CHD and hypertension. However, one of the most important aspects of this work is to determine whether prophylaxis with antianxiety drugs may reduce the incidence of subsequent myocardial infarction. In the first trial (11) there were three cases of further myocardial infarction in the placebo group but none in the clorazepate group; in the second trial (13, 14) there was one case of infarction in the placebo group and none in the clorazepate group; and in the third trial (13, 14) there was one infarction in the placebo group and none in the diazepam group. Therefore, in all three trials together, there were five cases of myocardial infarction among a total of 77 patients treated with a placebo, as compared to no such cases among 81 patients treated with the antianxiety drug. This difference was statistically significant.

This last observation provides a new reason to continue further research, but over longer periods of time. Thus it may be possible to determine how long the placebo effect persists and whether long-term treatment with antianxiety drugs may prove beneficial after all.

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