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BENACTYZINE IN PSYCHONEUROSIS WITH A NOTE ON THE E.E.G. CHANGES IN NORMAL SUBJECTS

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In this paper we are reporting the clinical effect of benactyzine on a small series of out-patients, and the electroencephalographic changes following the administration of the drug to normal subjects.

Benactyzine ("suavitil") is the hydrochloride of benzilic acid diethylaminoethyl ester. It is rapidly absorbed and excreted, and in addition to its anticholinergic, local analgesic, and quinidine-like actions it has recently been claimed to have a central effect which alters reactions to stress (Jacobsen, 1955; *Danish med. Bull.*, 1955).

Animal Experiments

Jacobsen and Sonne (1955) claim that the drug has a "normalizing" effect on the behaviour of rats rendered "tense and immobile" by a technique involving recurrent electrical stimulation. In other experiments, cats were trained to obtain food by opening the lid of the food box, and "conflict-induced behaviour" was then observed in them when a sudden stimulus was used to interfere with their food-seeking activity. This behaviour was said to be "normalized" by the use of the drug (Jacobsen and Skaarup, 1955).

Effect on Human Subjects

Human subjects given 5-6 mg. of benactyzine by mouth or by injection were reported by Jacobsen (1955) to have experienced giddiness which was occasionally very severe, a feeling of muscular relaxation, and thought-blocking. Experiments showed that patients under treatment with the drug exhibited diminished autonomic response to emotional stimuli, and Jacobsen claims that the drug has a specific action raising the "psychic threshold for irritation." Referring to unpublished work done by Hess in 1955, he states that the electroencephalogram showed partial or complete blocking of the alpha rhythm, which started and disappeared at the same time as the subjective changes experienced.

The use of the drug in the treatment of psychoneuroses and psychoses has been described by Munkvad (1955) and Jensen (1955). Munkvad found no effect on 22 psychotics receiving doses of up to 15 mg. four-hourly. Of 15 psychoneurotics, 10 improved with the drug but not with a placebo. The dosage used was up to 1.5 mg. three times a day, and no side-effects of importance were noted. Jensen claimed improvement in 75% of 110 psychoneurotics treated with a similar dosage. Patients with anxiety reactions, depressive reactions, and obsessive compulsive reactions responded favourably. The side-effects were few and insignificant: slight dizziness, slight thought-blocking, and undefined "queerness."

Clinical Trial

The following pilot study was carried out at St. George's Hospital, where the drug was given to a series of psychoneurotics attending the out-patient department.

Selection.—The only criterion of selection was that, no matter what his other symptoms, the patient complained spontaneously of feeling tense, strung up, or overwrought. Tension was thus prominent though not necessarily predominant in the symptomatology of these patients.

Method of Administration.—Only the pharmacist knew whether the patient was given the drug or a placebo of identical appearance, and the courses alternated at intervals varying from 10 days to one month. At each interview the patient was asked to say whether there was any change and, if so, whether he was better or worse. A definite statement was obtained regarding tension, predominant mood, energy, and irritability.

Response to the drug was assessed on the following basis. Where relief of tension was reported but other symptoms persisted the patient was classified as "improved." Where the overall improvement was such that he no longer needed to attend for treatment the patient was classified as "considerably improved." In both these groups the improvement must be attributed to the drug and not to the placebo. Where the placebo seemed to be equally or more effective the patient was classified with those who reported "no change," while "worse" is self-explanatory.

Of the 19 patients included under "no change," nine had reported no change from the drug or the placebo, six had found benefit from the placebo but not from the drug, while four had reported equal improvement with both drug and placebo. Of the six patients who said they were worse, four were made worse by the drug but not by the placebo, while two said they were worse on both.

As will be seen from Table I, none of those with neurotic depression was improved. Of the obsessive compulsive cases which reported an improvement, none noticed any

TABLE I.—Results

	Total	Worse	No Change	Improved	Considerably Improved
Neurotic depressions	10	2	8	—	—
Obsessive compulsive neurosis	8	—	4	4	—
Hysteria	4	3	1	—	—
Anxiety neurosis ..	18	1	5	4	8
Miscellaneous:					
Colitis	1	—	—	1	—
Pruritus	2	—	1	1	—
	43	6	19	10	8

change in the compulsive rituals or ruminations, but simply reported less tension in performing them. Of the four hysterics, three were made worse and one reported no change.

Of 18 cases of anxiety neurosis 12 showed improvement, and eight of them considerable improvement. Those patients who benefited from the drug spoke of "not worrying ahead so much," "developing a couldn't care less attitude," "feeling calmer," and similar changes indicative of diminished tension. Most of the patients with anxiety

neurosis who derived benefit had had symptoms for less than a year, but four of them had illnesses of from one to three years' duration, while one had had symptoms for eight years.

Of the anxiety neurotics who were not helped, one had had symptoms for a year, and the rest for over three years.

Most of the patients benefiting from the drug appeared first to notice an improvement towards the end of the first week of treatment.

Side-Effects.—These seemed to be produced in most patients on a dosage of 3 mg. three times a day if the dosage were started at that level. About half the patients on a dosage of 2 mg. thrice daily experienced side-effects, though these were often mild. Where the dosage had to be lowered it was in some cases subsequently raised without producing side-effects, provided this was done gradually. Among the side-effects experienced were (1) a feeling of heaviness in the limbs—the legs were principally affected and patients variously described “rubber legs,” “weighted legs,” and “inflated legs”; (2) giddiness; (3) ataxia and clumsiness; (4) difficulty in reading small print; (5) poor concentration; (6) diarrhoea; (7) increased anxiety; and (8) drowsiness.

Illustrative Cases

The following are brief summaries of two cases. The first is typical of the cases we have grouped as neurotic depressions, and in the second occurred the most chronic illness which responded to the drug.

Case 1.—An unmarried woman of 35 complained of feeling depressed and tense, with accesses of panic and palpitation for eight weeks. The onset was insidious and was, she thought, related to changing conditions at her office. She had been unable to work for three weeks, during which time her depression had worsened. It was not a sustained depression, and the pattern of variation was ill defined and obviously much influenced by environmental stimuli. Her appetite was poor, but she had not lost weight and she was sleeping well with a mild hypnotic. Benactyzine was no help to her.

Case 2.—A married man of 34 complained that for eight years his sleep and that of anyone in his vicinity had been disturbed by his groaning in the early hours of the morning. This symptom had recently become worse and he had been referred for psychiatric advice. He was a highly intelligent man, and, apart from an occasional attack of migraine and the presenting symptom and anxiety about his work, there seemed to be nothing amiss. He had already received a number of sedative drugs with little help, and a narco-analysis, though throwing some light on the psychopathology, had been of no lasting benefit to him. When he was given benactyzine his groaning ceased for the most part, and when it did occur it was “muted,” and easily terminated. What he found even more striking was his new relaxed attitude, especially to pressure of work. He commented that he worried less about his own efficiency, worked at a more leisurely pace, yet seemed to do more.

Electroencephalographic Changes

The investigation of electroencephalographic changes was carried out in the department of neurology at University College Hospital. The drug was given by subcutaneous injection to 10 healthy volunteers, and an electroencephalographic examination was made both before and after. The second part of the recording was started when the volunteer noted the first subjective effect, or 15 minutes after the injection if there were none. The recordings were taken on an eight-channel E.E.G. machine with the subject recumbent, using bipolar antero-posterior lines of electrodes on both sides of the head.

After a run of several minutes with eye-opening and eye-closure the subject was asked to calculate (successive subtraction of 7 from 1,000) for one minute, in order to determine the effect of mental attention on any changes in the

alpha rhythm. After calculation the recording was continued for three minutes of voluntary overbreathing, and later with photic stimulation.

The main subjective effects and E.E.G. change are shown in Table II.

TABLE II

Case No.	Age and Sex	Main Subjective Effect After 5 mg. Drug	E.E.G.
1	26 M	Sweating, numbness of face, headache. Slight drowsiness. Flicker patterns more intricate	No significant change
2	40 F	Slight headache	"Increase" in muscle artifact. Reduction in quantity of alpha rhythm, which was restored during calculation. Appearance of irregular low-voltage slow activity
3	20 M	Slight headache. Weak, heavy limbs. Drowsiness. Flicker patterns highly coloured	
4	22 M	Dryness of mouth, huskiness of voice, slight nausea. Heavy limbs; heavy shoes. Light-headed. Drowsiness	Marked decrease in quantity of alpha rhythm. Increase in slower activity.
5	22 M	Weak, heavy limbs. Objects felt uncommonly heavy. "Difficulty in putting thoughts into words"	Stabilization of alpha rhythm. No significant change
6	25 M	Numbness of face, weakness of limbs. Light-headedness. Photic pattern more highly coloured and intricate. Floor appeared sloping	Decreased quantity of alpha rhythm. Increase in artifact
7	25 M	Weak limbs. Lightheaded. Drowsiness. Floor further away. Fear almost to the point of panic	Decreased quantity of alpha rhythm. Increase of muscle artifact
8	25 M	Headache. Heavy limbs. Lightheaded	No significant change
9	20 M	Headache. Weak limbs. Lightheaded	" " "
10	21 M	Heavy limbs. Objects felt unusually heavy	Marked reduction of quantity and voltage of alpha rhythm

Subjective effects were reported by all but one. These usually came on 10 to 15 minutes after the injection. The commonest was a sensation in the limbs, which were described as feeling “heavy” or weak or “as if they weren’t there.” Three subjects remarked that objects picked up after the experiment felt surprisingly heavy—one, in fact, rejected his shoes as not being his own. Three remarked that the flicker patterns were more highly coloured or intricate, two noted that distances seemed changed, and two commented on a difficulty in expressing themselves.

Significant E.E.G. changes occurred in only five. There was a substantial reduction in the quantity of alpha rhythm, usually associated with some low-voltage slow activity or increase in muscle artifact. These changes persisted throughout the recording, and are probably non-specific and associated with alterations in the patient’s state of consciousness and tension, and his attention to the rather unusual subjective effects of the drug. They are similar to those seen following mescaline, which are attributable to drowsiness, or the attention evoked by the visual hallucinations (Greville and Heppenstall, 1950).

Discussion

The estimation of the value of a new drug in the treatment of psychoneurotics must always be difficult. The use of a placebo and the assessment of results in the way described may, it is realized, be open to certain objections. As Jacobsen (1955, personal communication) has pointed out, the fact that a patient continues to improve on the placebo after having had a course of the drug does not necessarily imply that the initial response to the drug was spurious. The interruptions by the placebo periods make it extremely difficult to assess the average length of treatment required.

It is still too early to assess the lasting results of the medication, but the improvement in patients with anxiety neurosis noted by Jensen and Munkvad was confirmed.

However, in contrast to the findings of these observers, patients with neurotic depressions were not benefited. There was an impression that in certain cases the drug was superior to barbiturates, and a further trial is in progress to determine whether this can be substantiated.

The subjective effects noted following injection of the drug during the E.E.G. investigation are of some interest. Jacobsen (1955) interprets the feeling of heaviness of the legs as being due to muscle relaxation. We believe that it is more likely to be due to a change in perception, since some of the subjects reported other perceptive changes; objects felt heavier, patterns for flicker were more coloured or intricate, and distances seemed altered.

Therefore it seems likely that the electroencephalographic change observed in five of our subjects is comparable to that following mescaline in which the subject's attention to altered perceptions is thought to be an important factor.

Summary and Conclusions

Benactyzine ("suavitil") is a new drug at present under trial for the treatment of certain psychiatric disorders. A brief review is given of its properties; on the basis of animal and human experiment it has been claimed to alter reactions to stress.

A pilot study on 43 out-patients with various psychiatric disorders suggests that patients with a symptomatology in which anxiety and tension predominate respond favourably (of 18 cases, 8 were much improved and 4 improved); those with depressive, hysterical, and obsessive symptoms do not. About half the patients receiving 2 mg. three times a day experienced side-effects, the commonest being heaviness of the limbs. On a dosage of 1 mg. three times a day side-effects did not occur, and the higher dosage could be tolerated provided its increase was gradual.

Ten healthy volunteers were given the drug subcutaneously. Subjective effects and E.E.G. changes were noted. Changes in perception were predominant, and in half the subjects there was a marked diminution in the amount of alpha rhythm. This change is thought to be non-specific and comparable to that seen following the administration of mescaline.

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ADDENDUM.—Since this paper was submitted two other reports have appeared. Beresford Davies (1956) claims improvement in 67 of 110 patients, with particularly encouraging results in patients with anxiety symptoms and psychosomatic disorder. Coady and Jewesbury (1956) found no effect on muscle tone in a group of 80 neurological patients. Flexor spasms, however, appeared to be relieved in some cases. They also note a striking suppression of the normal rhythm of the E.E.G. in two cases.

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OCULAR SARCOIDOSIS

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The cause of sarcoidosis is unknown. It is probably an indolent infection, but, since no causal organism has been isolated, early recognition of the disease depends upon an awareness of the various clinical manifestations. Diagnosis may often be confirmed by histological examination of affected tissue. The systemic nature of sarcoidosis is indicated by the widespread distribution of the lesions, which may be found in the lungs, skin, lymph nodes, spleen, liver, kidneys, nervous system, bone, and eyes. In all these sites the histological picture is the same, the lesions consisting of aggregates of large pale epithelioid cells and occasional giant cells grouped into nests compressing or displacing normal tissue. There is little or no necrosis or caseation, which distinguishes the appearance from that of tuberculosis.

In the course of time these active granulomatous lesions resolve and are replaced by acellular hyaline material. This in turn is followed by dense fibrosis. At an intermediate stage in this evolution, granulomatous foci, hyaline tissue, and fibrosis may be seen together. Although these pathological changes are common to all involved tissues, their effects vary with the sites of the deposits, the most serious symptoms occurring when the eyes and the lungs are involved. Iridocyclitis is the commonest ocular manifestation of sarcoidosis, and, while in most cases this is self-limiting, the fibrosis associated with healing may lead to disorganization of the globe and loss of sight. Often the eyes are involved, and the importance of early diagnosis cannot be overstressed, since the prognosis is greatly improved by early treatment.

Present Series

Eye Changes

In a series of 100 patients with histologically confirmed sarcoidosis, eye changes were observed in 28 (see Table).

Ophthalmic Manifestations Seen in 28 Cases

Subacute iridocyclitis	8
Chronic iridocyclitis	12
Keratoconjunctivitis sicca with enlarged lacrimal glands	2
Keratoconjunctivitis sicca alone	1
Enlarged lacrimal glands alone	1
Infiltration of eyelids	1
Eales's disease (periphlebitis retinae)	1
Macular oedema	1
Phlyctenular conjunctivitis	1

Subacute Iridocyclitis.—This was unilateral in two and bilateral in six cases. The clinical picture was similar in all these cases. The patients complained of sudden onset of pain in the affected eye or eyes, usually accompanied by lacrimation and mistiness of vision. The eyes showed ciliary congestion, and, in addition to this, turbidity of the aqueous humour, due to excess protein and circulating cells, could be observed by using the biomicroscope. In each instance the iridocyclitis was associated with active sarcoidosis elsewhere. In four patients there was associated erythema nodosum and bilateral hilar lymphadenopathy, one had sarcoid meningitis, and two developed transient enlarged cervical and supraclavicular glands at the same time as the