A NEW DRUG TO RELIEVE ANXIETY

BY

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Benactyzine hydrochloride ("suavitol") is the hydrochloride of the diethylaminoethyl ester of benzilic acid. The formula is:

It was first described in Switzerland in 1936, and has more recently been studied by Jacobsen and various workers in Scandinavia. They were looking for a way to treat patients with psychological disorder which would assist or replace psychotherapy and would not cause addiction. They started with the working hypothesis that an anticholinergic substance might play the part they sought, because of its possible effect on the basal ganglia and on certain functions such as the perception of movement and maintenance of muscle tone. Details of the chemistry and general pharmacology, as well as information about the toxicity of benactyzine, may be found in Jacobsen's paper (1955).

The responses of rats and cats to the drug with the use of a technique like that of Masserman and his co-workers (1944 to 1946) have been described in four papers. Rats were used by Holten and Sonne (1955) and Jacobsen and Sonne (1955), and cats by Jacobsen and Skaarup (1955a, 1955b). In addition, investigations into autonomic responses during emotion, and the autonomic reactions of psychoneurotic patients under the influence of benactyzine are described in two papers by Jacobsen *et al.* (1955). The drug has been used on human subjects and patients, mainly in Scandinavia. Some of the results may be found in the above two papers, and also in a paper by Munkvad now in preparation.

Claims

It is claimed that the drug relieves anxiety, particularly in psychoneurotic patients, and that no toxic effects are observed in therapeutic doses (1–5 mg. up to four times a day in Scandinavia). Its low toxicity is stressed by Jacobsen (1955) and in personal communications from him. Some patients have received 90 mg. daily subcutaneously in six equally divided doses for a period of six days without any observed toxic effects. Experimenters have taken up to 90 mg. in single doses by mouth, with the characteristic effects about to be described, but without any evidence of toxic damage. It is rapidly eliminated; thus, 4–5 mg. loses its effect after three to five hours. So far the detoxication and elimination of the drug have not been adequately studied.

Effects

The characteristic result of taking benactyzine by normal subjects in moderate doses—that is, between 1 and 4 mg.—is the production of a sense of divorce between outer reality and emotional reactions. This has been described as producing a barrier between the person and his problems. At the same time most people who take the drug as subjects rather than patients say that there is no alteration in the quality of thinking or in the appropriateness of the response they make to the outside world. The difference appears to lie in the speed and completeness with which the emotional reactions can be produced and maintained. Those outside problems which require attention appear to exert a less

worrying influence on the subject; or, to put it another way, they create less tension and the tension response builds up more slowly.

A similar type of reaction may be observed in patients, though usually they are less able to give objective accounts of their feelings than are those who take the drug experimentally. The available evidence, however, suggests that essentially it hinders the speed and degree of emotional reactions in people both with and without symptoms of psychological disorder.

Larger quantities (4–8 mg.) produce a more marked feeling of detachment; the muscles are felt to be relaxed, and the limbs feel like awkward, bloated appendages, with blunted sensibility. Thoughts and feelings are retarded, and the power of concentration is felt to be diminished. Thinking is slowed up, and there is a marked tendency to think of nothing and to react very slowly to stimulation from the outside world. There is also a loss of continuity of thinking, which commonly expresses itself in the phrase: "I have quite forgotten what I was going to say." Nevertheless, the quality of thinking does not appear to be impaired, and in the group studied in this paper no abnormal activities were observed, such as feelings of elation, silly or fatuous behaviour, or a tendency to behave recklessly. (There may be one rather important exception to this which is mentioned later—namely, the driving of cars.)

Objective tests show that the capacity to perform normal tasks may be little affected by the drug in therapeutic doses (1–4 mg. up to four times a day in this series). Thus, simple mental tests are performed as well after as before, though the tested person may overestimate the time he has taken to carry out the test. There is little evidence to suggest that it has any effect directly upon sleep, particularly in the normal subject. Nevertheless, for reasons which are given later, it may have a considerable indirect influence.

The drug may have certain immediate side-effects. In the group studied here, mild degrees of palpitation, described as forceful action of the heart, as well as occasional complaints of dryness in the mouth, were observed. (The drug has an atropine-like action in common with other anticholinergic substances.) The most common complaint, however, was that of a loss of concentration and a feeling of woolliness or vagueness, which some of the patients regarded as a new symptom of illness. The dizziness which has been described by Jacobsen and others has less often been observed in the cases in the present series, but this may be due to the relatively low dosage. The highest dosage employed was 16 mg. daily for several months. In this patient no side-effects or toxic sequelae were found.

The present paper is an attempt to summarize certain impressions gained from the use of benactyzine, both alone and in combination with other substances. No attempt has been made to assess the results with controls at this stage. The drug has been given to all patients by mouth only.

It has been tried empirically, as a means of relieving tension and anxiety, irrespective of the cause, in order to try to discover whether it may be expected to exercise a beneficial effect in all cases of tension, or whether the action is more subtle and discriminating.

So far 110 patients have been treated (56 men and 54 women), 74 in an out-patient department and 36 in a mental

TABLE I

Diagnosis	Male	Female	Total
Schizophrenia	4	4	8
Endogenous depression ..	3	11	14
Manic-depressive illness ..	—	2	2
Hypomania	—	1	1
Anxiety neurosis	15	7	22
Hysteria	1	4	5
Obsessional states	2	5	7
Psychogenic asthma	2	3	5
" eczema	5	1	6
" colitis	2	—	3
Drug addiction (alcohol) ..	11	5	16
Group showing tension, anxiety, and depression	11	10	21
Totals	56	54	110

hospital or other institution. The drug has been given to those undergoing electroplexy modified by premedication, thiopentone, and scoline, without ill effect, though not within less than seven hours of this treatment; it has also been given with substances of the antihistaminic group.

Table I shows sex and diagnoses of the 110 patients in this series. Some representative cases are described below.

Case 1. Neurosis

A farmer aged 37 complained of difficulty in sleeping for the past ten years, and a fear of having a raised blood pressure. He also described attacks of depression with early-morning waking, and anxiety related to his very considerable business activities. The family history showed pronounced instability and insecurity: both grandfathers and the father were alcoholics. At interview the patient showed evidence of ambition, energy, and ability, with a jolly or blunt manner which partly concealed obvious agitation and anxiety. His attitude revealed anxious expectation and fear of new situations. He disliked change and would take a road he knew rather than some sensible short-cut. A part of the depression appeared to be due to the anxiety itself. He showed some hypochondriacal preoccupations.

He was treated with reassurance and a regime of sedatives and dexamphetamine; the latter was given in the same tablet with amylobarbitone ("drinamyl"). This treatment had a bad effect, in that he felt worse and feared to take any of the tablets. Part of this response was almost certainly due to his dread of new medicines.

At the next visit a fortnight later benactyzine was begun in doses of 1 mg. three times a day, and he experienced immediate relief. He said he felt quite calm, his sleep was normal, and his appetite had improved as his digestive disturbances disappeared. He added that occasionally he flew off the handle when "squaring up" his foreman, and still became upset under various circumstances; on analysis these proved to be those which threatened his well-being by introducing some new feature into his environment even though these might be indirect, such as his car being out of order. He asked whether the drug would make him somewhat forgetful, and stated that he was inclined to pay a little less attention to everything than previously.

Over a period of a month the dose was increased to 3 mg. three times a day, and he then said he found his work required deeper thought if he was to avoid a tendency to feel idle. On the other hand, he had no complaint of the quality of his thinking, and said that on the whole he was managing to do more and to react more efficiently. After three months the forgetfulness and idleness had both disappeared; it was difficult to determine whether they had really gone, or whether tolerance had been established and a lower standard of performance accepted. However, the impression he had that he was working better was thought likely to be correct, for those about him thought him more efficient. He said he tended to dream very much more. The benefit he obtained from the drug may be gauged by his successful work during the fruit season, which in the previous ten years had caused a minor or major breakdown. During this last fruit season he maintained the full dose of 9 mg. a day, and took the very occasional $\frac{1}{2}$ gr. (32 mg.) of phenobarbitone; on this regime he remained practically symptom-free.

Case 2. Neurosis

A chief accountant aged 42 complained of progressive worry since 1947, with unhappiness at his work, and many years of indigestion; this was associated with considerable depression. A typical statement was, "I am not so perturbed about it myself, so long as I am physically able to withstand the strain." The patient's father, an ex-Navy stoker, was described as a tough customer who could cope with anything; his mother, an ex-schoolteacher, was a worrier. The patient was the only child. He did well in local government service and had a good though undis-

tinguished career in the Navy (1940-6). He went into his present job in 1947, and since then had had no promotion, a point which he made to illustrate his unhappiness. His manner at interview was peculiar; he sat gripping the lapels of his coat and talking in a philosophical way, as though he was managing the interview. He was evasive, circumlocutory, and pompous. Deeper inquiry showed a mildly paranoid attitude to his superiors, accompanied by downright criticisms of his colleagues and allegations that they were jealous of his capacity. He was particularly upset with his immediate boss, whom he blamed for the lack of promotion. In addition he felt he had been put upon so far as the amount of work he had to do was concerned. He slept badly and complained of frequent attacks of migraine. He stated that his home was very happy and his wife could not do too much for him; he gave the impression that he therefore argued, "What a fine fellow I must be."

He was regarded as a tense, worried man, obviously working under pressure, who had a tendency to mild paranoid ideas with slight compensatory grandiosity; anxiety and tension were prominent, and it seemed possible they might be the cause of his indigestion. He was put on benactyzine, 1 mg. three times a day, and reported at his next visit that he felt immediate benefit, with lightening of mood and a greater feeling of ease. This marked change continued, so that on the next occasion he entered with a smile and said, "I feel much better. My wife says I am easier to get on with and not so irritable. I have no headache now. My only trouble is that I am too happy-go-lucky when I drive. I relax too much." His wife reported: "He is a different man. I can now in fact cope with him; he's easy to live with."

He continued treatment, and five months later remained very well, the most obvious improvement being the tranquillity. He no longer found his problems insoluble, and a previous complaint of sweating had disappeared. He continued to wonder whether his driving standards were as good as they had been, for he felt he was happy-go-lucky and without regard to others on the road. He mentioned that a tyre had burst on one of his journeys and his attitude to the incident was quite detached; previously he would have worried. This did not impair his performance, however, in stopping the car and changing the wheel. He could not better his description that he was having less regard to other people. After six months he reported that he had an absolutely tranquil mind and that he no longer noticed any of the forgetfulness he had felt when first taking the tablets. He also reported that the relationships in his office seemed to have improved and that he was able to speak his mind and still feel calm and confident.

Case 3. Manic-depressive Psychosis

A woman aged 63 had suffered from severe manic-depressive psychosis for many years. Depressive phases in which she showed retardation, depression, ideas of unworthiness, and thoughts of suicide were predominant. During hypomaniacal phases she had been interfering and full of all kinds of plans. In a recent phase which came on after the death of her husband she made elaborate plans to marry one of her medical advisers, though he already had a wife and three children. The depressive phase which followed this attack was very severe, and was marked by much agitation and retardation.

The patient was eventually admitted to a mental hospital and treated with benactyzine up to 4 mg. three times a day. The subjective effects were difficult to gauge, for the patient continued to complain in much the same manner as before, but objective assessment showed that there was a considerable change over a period of time. Electroplexy was no longer suitable as treatment owing to her physical state, and so it was possible to assess treatment with benactyzine for several months. She became less agitated and more easy to manage; it was felt that her complaints lacked the drive and intensity they showed before medication began. It is of course very difficult to estimate the effects of any treat-

ment in this condition, because of the alterations which take place in the natural course of the disease. Nevertheless the impression was gained that benactyzine in fairly large doses may help to control the symptoms of such patients, particularly if electroplexy cannot be used.

Case 4. Alcohol Addiction

A man aged 60 suffered from alcoholism and showed changes typical of chronic addiction. He had been drinking for twenty years, very heavily in the past ten, and was physically ill and toxic at the time of referral. He was admitted to hospital, where he was detoxicated, and he later attended the alcohol clinic for supervision, where it was possible to encourage him to abstain from alcohol. Treatment with benactyzine was started in doses of 1 mg. three times a day, increased three weeks later to 2 mg. three times a day. He stated that his spirits rose immediately; he was no longer oppressed by his circumstances and the continual need to keep up his guard against alcohol. He meant by this that not only did he feel better in himself but he no longer had the same degree of craving. He mentioned as side-effects pounding of the heart and slight dizziness; the latter disappeared shortly, but his sense of a more forceful action of the heart persisted.

He remained sober for eight months (and continued to do so) on a dose stabilized at 2 mg. three times a day. At first he contradicted himself in an amusing manner by saying he felt anxious because he was no longer anxious enough. He had a feeling that he ought to be more worried than he was and that there was therefore "a catch in it somewhere," as he put it. In this patient the nearest approach to elation was observed, though this did not lead to any undesirable conduct. It rather seemed as though more abundant energy had been set free, for he became very active in trying to help his fellow alcoholics, and founded a local group of Alcoholics Anonymous.

Case 5. Psychogenic Asthma

This patient, aged 66, a widow for over twenty years, with an only daughter, gave a history of good health until five years previously, when she began to get bronchitis. Four years ago, at a time of increasing stress and nervousness, she had a persistent attack of typically bronchial asthma of the so-called true type, with mucous casts of the bronchial tree containing eosinophils. The nervousness and the attacks became steadily worse, despite various treatments. The most useful drug proved to be intravenous aminophylline; adrenaline had little effect.

Analysis showed nervous factors to be predominant, despite the coincident finding of an innocent tumour the size of an orange in the upper lobe of the right lung, which in the opinion of an eminent authority was not connected with the asthma nor the cause of any symptoms. Her history revealed the patient as a woman of capacity, for she carried on her husband's manufacturing business effectively for eight years after his death to complete her daughter's education.

On examination the patient was excitable, effusive, and somewhat defensive. She showed evidence of numerous life-long nervous traits, such as fear of crowds and enclosed spaces. She also showed well-marked over-meticulousness and a need to have everything just so. She made it clear that she did not like others to do things for her, and was at pains to show herself in a good light, though not in a hysterical manner. She asked, for example, "Can I do without my pills? I am such a nuisance to everyone. . . . I get worried over silly little things, like people turning their cars in our driveway."

She was treated with rest in bed and simple psychotherapy; the diet was made as interesting and full as possible, as she had lost 2 stone (12.7 kg.) in weight during the past two months of severe asthma. She was given $\frac{1}{2}$ gr. (32 mg.) of phenobarbitone and 1 mg. of benactyzine three times a day. There were no side-effects, though she had had considerable anxiety about the possibility that some

untoward feeling would appear. Recovery was immediate and uninterrupted; the asthma ceased within 48 hours, and since that time, except for one attack, has been minimal. The anxiety rapidly diminished and she has remained almost symptom-free on the same dosage of phenobarbitone and benactyzine for five months. This effect was not due to psychotherapy and phenobarbitone only, for reassurance and sedation previously were without beneficial results.

Case 6. Psychogenic Eczema

A ledger clerk aged 32 had suffered from recurrent skin rashes at intervals for some years. A seborrhoeic eruption of the face, with some secondary infection, finally made him consult a dermatologist, who made a note that this occurred after his responsibilities at work had increased owing to promotion. Later he developed an acute eczema of the face, neck, and hands which waxed and waned for the next 14 months.

At psychiatric examination he was seen to be a well-nourished anxiously smiling man with a well-marked family history of nervous instability. The patient himself had been much fussed over in his youth by his mother, in whose eyes a small ailment became a major disease. Nevertheless he had succeeded in making his way well in the Army and had risen to be a tank commander by the time of the Rhine crossing. He said he was very surprised that anyone should have considered his trouble nervous in origin, and added jocularly that "the next step after seeing one of those psychologist chaps would be a nerve rest home," a euphemism for the mental hospital. After his confidence had been gained, however, he admitted that he often fell into minor arrears of daily work because of his over-conscientiousness, and added that with increasing responsibility the circumstances had become more and more difficult. At the same time it was clear that he was essentially an ambitious man with a considerable amount of determination. His over-carefulness at times became frankly obsessional behaviour, and then he would check and recheck his figures. At interview his obvious tension showed itself by quivering of the facial muscles and inability to stay still.

Some time was taken in explaining the manner in which nervous stress might result in psychosomatic disorder, and he was reassured that this did not mean he was mentally ill in the customary meaning of that term. He was advised to try benactyzine (1 mg.) at breakfast and another after lunch. Seven days later he felt much better in himself and the skin rash was disappearing, as a result, he thought, of the great reduction in irritation and scratching. He had noted no side-effects, but stressed what he called a glorious sense of well-being. With regard to work, he said that, far from finding any lack of concentration (about the possibility of which he had been warned), he had managed to get through more and with less trouble than had been possible for months. He ended his report by saying that everything at the office seemed to go smoothly and he was able to take in his stride such snags as cropped up; and he noted that his desire to smoke had diminished, with a reduction in consumption of three or four cigarettes a day.

Seven weeks later, owing to an oversight, he ceased taking the tablets, and was without them for a further seven weeks. He then reported that he had had a nasty flare-up of his skin condition, which had taken place after he had been soaked through while out fishing. He also noticed a lack of confidence, with obsessional checking of his figures up to three, four, and even five times. He also said he had to get up at night to see whether the lights were switched off, and he worried over questions about his skin condition. Benactyzine was started again, 1 mg. three times a day for seven days, and then 2 mg. three times a day subsequently. After seven days he said his report was almost a replica of the first. He had felt moments of perfect well-being and his cigarette consumption had declined to 15 from 20 a day, without conscious effort on his part. However, he had this time noticed one of the side-effects, a queer taste in the mouth as if he had smoked too

many cigarettes, though this effect lasted for only three days. Coincidentally the skin condition had again improved. At an interview a few days later he was asked to sum up the effects: he stated that he had less itching, better sleep, less desire to smoke, and a lessening of aggravation owing to problems and snags in the office and everyday life.

Case 7. Severe Obsessions and Phobias—with Depression

A man aged 21 was admitted as a voluntary patient to a mental hospital after the onset of severe acute phobic obsessions and depression, mainly concerned with fears of death in his sleep. He felt very ill, and despite his fear of hospital was ready to do anything for relief. It was possible, therefore, to keep him under constant supervision, and maintain daily contact between him and the medical staff. He was regarded as suitable for modified electroplexy, and had eight treatments without effect; he then refused further treatment. Next, sedation was tried for two weeks, which was largely ineffective. Then for twenty days he had 100 mg. of chlorpromazine hydrochloride three times a day, with some small benefit. This was stopped and benactyzine was begun in doses of 1 mg. three times a day for one week, followed by 2 mg. three times a day for one week, and thereafter 3 mg. three times a day. The effect was immediate and complex.

He reported that side-effects were worse than with chlorpromazine, in that he felt more blank and sleepy and occasionally dizzy; on account of this he preferred chlorpromazine. Nevertheless, further inquiry showed that despite these subjective findings the severe phobic symptoms were receding more effectively into the background with benactyzine than with chlorpromazine, and this after less than twelve days' treatment. Furthermore, on objective assessment he seemed happier, and if asked about how he felt would confess to feeling happier. At the same time he had less interest in things around him than he had with chlorpromazine, and said, "The new tablets make me less interested in things—sort of cut off—sort of less clear." He was in no doubt, however, that his anxiety and phobic symptoms were much improved.

Results

The quantitative results of treatment are outlined in Tables II and III. Table II shows the responses of the whole group by sexes under the three headings "unchanged," "worse," "improved." Table III illustrates the degree of improvement by sexes under the headings "fair," "good," "marked," and shows the percentage in each group of the total number of patients. The definitions are: fair, a re-

TABLE II

	Unchanged		Worse		Improved		Total
	M	F	M	F	M	F	
Schizophrenia ..	3	3	—	—	1	1	8
Depression ..	2	1	—	—	1	10	14
Manic-depressive illness ..	—	1	—	—	—	1	2
Hypomania ..	—	1	—	—	—	—	1
Anxiety neurosis ..	6	1	—	—	9	6	22
Hysteria ..	—	3	—	1	1	1	5
Obsessional states ..	—	1	1	1	1	3	7
Psychogenic asthma ..	—	—	—	—	2	3	5
" eczema ..	—	1	—	—	5	—	6
" colitis ..	—	1	—	—	2	—	3
Alcoholism ..	3	2	—	—	8	3	16
Mixed group ..	3	3	1	4	7	3	21
Total ..	17	18	2	6	37	30	110

TABLE III

Degree of Improvement	Male	Female	Total	% of All Cases
Fair ..	22	18	40	44
Good ..	9	8	17	18.7
Marked ..	6	4	10	11
Total ..	37	30	67	73.7

duction in severity of symptoms; good, disappearance of some symptoms, lessening of others; marked, persistent disappearance (several months) of main symptoms.

It will be seen that of the cases treated the males responded better than the females and that of the cases which reacted badly six were female and only two male.

Discussion

Analysis shows that the treated patients may be roughly divided into two classes by their reactions or lack of them to benactyzine, irrespective of the nervous illness from which they suffer. Those who consciously or unconsciously want help appear to derive some benefit, provided they have definite symptoms or signs of anxiety or agitation in the make-up of their disorders. On the other hand, those who have a hostile attitude, whether obviously or in the form of projections, or by means of hysterical mechanisms, do badly and interpret the results of the tablets as inimical. It may be that several interviews are required to win the patient over into a positive or co-operative attitude; frequently it is impossible to do so.

An example of the unproductive attitude is that shown by a girl of 20 with a severely hysterical immature personality and gross signs of anxiety and social difficulty, who could not find words grave enough to describe the horror of her feelings after a single dose of benactyzine. The blankness which she felt filled her with dread. She seemed to interpret this blankness as a factor which diminished her capacity to observe outer reality, from which she was constantly expecting unpleasant surprises. Her case seems like that of many who are constantly on the watch for trouble, and who react badly to any substance or situation which impairs the capacity for attention. A similar reaction occurs in phobic patients; one of them became profoundly hostile after two or three doses and inferred that there should be a law against such medical practices as would impair a patient's capacity to keep a lookout for her enemies.

Another patient who also reacted badly and who belonged to the group of obsessional illnesses complained that the drug made her feel strange; she said nothing made her feel worse than to have to put up with some new factor in her environment. This patient was a woman of some intelligence, and she was able to add that any such new factor compelled her to produce new reactions, which was difficult owing to her rigid way of thought, dominated as it was by obsessional mechanisms. Two other patients, one a man and one a woman, who belong to the mixed group, both complained that the drug made them feel unreal. Both had previously mentioned rather vague sensations of depersonalization and had complained of a fear of going mad. The woman patient felt that her fear was coming true as she experienced the first effects of benactyzine.

Similar reactions, though less marked, can be observed with barbiturate and sedative drugs. For example, phenobarbitone may be provocative of such reactions, particularly if insufficient care has been taken over the psychological preparation of the patient beforehand. One female patient obtained considerable benefit of a kind typical of benactyzine medication during periods in which the psychotherapeutic situation was favourable and her own circumstances fairly tranquil; when, however, adverse factors became more pronounced she presented the benactyzine reactions as inimical and unpleasant and made them the foundation of new symptoms. Apparently these reactions are not reported after chlorpromazine and drugs of that class, which suggests that there may be some degree of similarity between benactyzine and the sedatives on the one hand, and the various drugs with chlorpromazine-like action on the other.

The patients who have benefited from benactyzine treatment have described their feelings in terms which are strikingly similar. The tendency to forgetfulness has already been mentioned; this is very commonly reported at the beginning of treatment. The more purely beneficial feelings

are described in the following phrases: "I am tranquil," or "I feel calm" (17 patients); "It is a feeling of well-being" (14 patients); "I feel soothed" (7 patients).

Other patients have used words which on analysis bear the same meaning as the examples quoted above. One patient, a highly intelligent man who suffered from a long-standing neurasthenic depression, at times severe, was able to compare drinamyl, benactyzine, and benactyzine to which 2.5 mg. of dexedrine had been added for each milligram of benactyzine. He found that the dexedrine with the benactyzine tended to keep him awake, though he felt more active. On the other hand, benactyzine alone was much more effective in reducing anxiety. He expressed the opinion that benactyzine alone was likely to be most effective when some positive interest was already in mind, for it enabled the patient to dismiss more easily competing and less attractive ideas. He found the drinamyl helped the depression, but he required a night sedative, which he did not on benactyzine alone.

It is difficult at this stage to sum up the effects of benactyzine in those cases in which anxiety predominated (37 cases). The impression was gained, however, that diagnosis alone is not a sufficient criterion to foresee whether its use would be justified or not, or to enable any forecast to be made of its probable effect. The feeling obtained at the psychiatric interview, and the judgment of the case which depends upon that feeling, seem to be more important: if the psychiatrist has a sense of contact with his patient and an ability to handle the aggression and hostility at the interview, then the signs are probably favourable for the use of the drug. Frank hostility, however, no matter from what cause it may come, is a contraindication.

Psychosexual disorders should be approached carefully, particularly in women. One of Jacobsen's cases (personal communication) and one of those in the present series showed overt homosexual behaviour after benactyzine. The case under review here was that of a woman who had had two leucotomy operations and whose history and psychopathology indicated unconscious homosexual feeling. She was treated with benactyzine in hospital (dosage 12 mg. daily), and shortly after formed an overt homosexual relationship without feelings of shame. The response of patients with a psychosomatic disorder has been encouraging. Of 14 cases only two have failed to improve; both these were complicated by the presence of long-standing depression. The other cases, in all of which improvement was either adequate or marked, showed basically productive types of personality without evidence of direct aggression or hostility. This was also true of the two cases of mucous colitis, which improved. These patients were men with much apprehension about the immediate side-effects, to the extent that both stopped treatment for some days. They were persuaded to resume, however, with the consequence that each benefited by a substantial lessening of tension and diminution of the bowel symptoms.

Ambulant patients with endogenous depression in whom agitation is severe are now reporting better control of symptoms with doses of 9 to 15 mg. a day: this is also true of patients with marked agitation and depression in a phobic setting. Patients with reactive depression—that is, tension and depression mainly associated with their environment—are not relieved. Psychotic hospital patients do not benefit appreciably from benactyzine in doses up to 12 mg. daily, but recently the responses of two schizophrenic and three melancholic patients to 18 mg. daily have been encouraging enough to suggest that a trial should be made with both chronic and disturbed patients.

An analysis of the nature of anxiety is outside the scope of this paper, but it is natural that the beneficial effects of this drug should provoke thought about it. It seems that anxiety which springs from tension between the patient and his environment, particularly if it is related to a fear of failure at an executive level, is relieved effectively. It has already been mentioned that patients with a basically constructive attitude to life, but whose efforts are marred by

anxiety, can obtain relief even though their anxiety may centre on some particular difficulty in the outside world. It is also evident that the drug relieves those who have a superfluous fund of anxiety, always ready to attach itself to all kinds of problems rather than convert itself into symptoms, as may be seen in hysteria. A number of patients in whom shyness and fear of gatherings have been pronounced have said that the drug helps them. These are people who worry about their impact on their fellows, and spend an anxious evening discussing whether or not they did or said right at the cocktail party of that day. It is in these cases that the indirect effect of benactyzine on sleep may be observed. Such people fall asleep more easily after medication because the drug prevents nocturnal ruminations based upon an anxious review of the day's events.

Conclusions

Benactyzine appears to be an important addition to the therapy of psychological disorders. It is easy to give by mouth, is quickly eliminated, and there is no evidence that it is cumulative. In usual therapeutic doses (1–4 mg. thrice daily) there have been no toxic results from its use, though there are certain immediately unfavourable results in patients who do not tolerate it. It is suitable for use with other sedatives, particularly phenobarbitone, and there may be value in using it in combination with such other drugs. A note of caution should be sounded concerning its use in patients with phobic obsessional disorders or feelings of depersonalization or unreality. It is advisable that the drug should be used with discrimination, for otherwise good results may not be obtained, and this would prejudice the use of a potentially valuable means of therapy. The findings so far indicate that further trials are advisable.

Summary

Benactyzine hydrochloride is a benzilic acid compound advised for the relief of anxiety.

Of the 110 patients treated with this drug, 25 were psychotics and 85 neurotics. The cases are described and the results assessed; 67 patients derived benefit; there were no toxic effects.

The contraindications to the drug seem to depend on dynamic factors, which may be subtle. The results suggest that benactyzine is not suitable for indiscriminate use in all cases of anxiety.

I wish to thank Dr. Erik Jacobsen and his co-workers for all their help; also Dr. K. J. R. Ford, senior psychiatric registrar, and Drs. J. G. Weir, J. Littlejohn, and A. Orwin, psychiatric registrars at Addenbrooke's and Fulbourn Hospitals. I am also indebted to Glaxo Laboratories Ltd. for kindly providing large supplies of the drug.

REFERENCES

- Holten, C. H., and Sonne, E. (1955). *Acta pharmacol. (Kbh.)*, **11**, 148.
 Jacobsen, E. (1955). *Dan. med. Bull.*, **2**, 159.
 ———, Kehlet, H., Larsen, V., Munkvad, I., and Skinhøj, K. (1955). *Acta psychiat. neurol. scand.*, **30**, 607, 627.
 ———, and Skaarup, Y. (1955a). *Acta pharmacol. (Kbh.)*, **11**, 117.
 ——— (1955b). *Ibid.*, **11**, 125.
 ———, and Sonne, E. (1955). *Ibid.*, **11**, 135.
 Masserman, J. H. (1945). *Trans. N.Y. Acad. Sci.*, **7**, 61.
 ———, and Siever, P. W. (1944). *Psychosom. Med.*, **6**, 7.
 ———, and Yum, K. S. (1946). *Ibid.*, **8**, 36.
 Munkvad, I. (1956). *In press.*

The Federal Republic of Germany has contributed a sum of 200,000 DM. (\$50,000) to the World Fund for Malaria Eradication. This is the third contribution to the fund, the first two having come from Brunei and China. The fund was constituted last May by the World Health Assembly to receive voluntary contributions from governments and private sources. It is to be used to finance research, and to provide equipment, supplies, and services for malaria control and eradication.