dystonia. It is perhaps too early to draw any conclusions from this, but the facts just quoted may suggest that extrapyramidal rigidity and disturbances of posture are due to abnormal impulses descending from above the brain-stem level.

The pathological states I have been considering may be regarded as local disturbances in that they can exist in fragmentary form. There are, however, some more general disturbances of posture which are of interest. There is considerable evidence that the posture adopted by a patient in a major epileptic attack is the result of a discharge of impulses from nuclei in the brain stem probably closely related to those concerned in the maintenance of decerebrate rigidity. There is a type of epilepsy, known as akinetic epilepsy, which leads to what are called "drop-attacks." In these the patient suddenly falls to the ground without warning, there is no convulsion, loss of consciousness if it occurs is only momentary, and he is immediately able to get up again. Such attacks must presumably be due to a sudden inhibition of the anti-gravity postural mechanisms. In cataplexy, which is associated with narcolepsy, strong emotion causes a rather more gradual loss of power in all the muscles, so that the patient sinks to the ground and is completely immobilized for a short time. This again has been explained in terms of an inhibition of motor mechanisms generally. Finally, in patients with lesions of the frontal lobes and in some psychotic states, we find a condition of postural plasticity in which an attitude imposed by passive movement is maintained indefinitely, or the patient may remain spontaneously immobilized in the same attitude for a long time.

Conclusions

The facts to which I have been drawing attention may have many implications, in relation both to health and to disease. Perhaps we do not sufficiently appreciate the physiological miracle by which, without effort and without conscious thought, we balance our not inconsiderable bulks upon two surfaces of a few square inches each, let alone the greater miracles of the co-ordination of hand, foot, and eye achieved by athletes, or the apotheosis of postural control attained by the high diver, who can rotate round his long axis as well as turning one and a half somersaults while falling thirty feet.

Whether we are considering normal or abnormal postures, we must begin thinking at the spinal segmental level in terms of the stretch reflex and the lengthening and shortening reactions. Here the physiological unit, so to speak, is not a receptor or motor point, but a circuit, though disease may disturb the circuit at many different points. Understanding of even the simplest postural circuit involves knowledge of the muscle-spindle and how it is influenced by normal and abnormal states of muscle—and of the latter we know little or nothing—the afferent impulses, the interneurones and synapses in the spinal cord, the motoneurones, the myoneural junction, and the physio-chemistry of muscular contraction. We must bear in mind also not only that through these mechanisms bad postures tend to perpetuate themselves, but also that normal reactions may be interfered with by nociceptive reflexes set up by painful states. At higher levels we need to consider the particular importance of the head, stressed by Sherrington, and the influence of the labyrinth and the neck upon bodily posture as a whole. Lastly, there are psychological problems, almost an untilled field. In the realm of positive achievement, what is the relationship between conscious effort and unconscious habit, and how does the one pass into the other? On the negative side, how is posture affected by psychological tension, and what is the part played by conscious relaxation in re-education?

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EFFECTS OF IPRONIAZID IN DEPRESSIVE SYNDROMES

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In 1958 one of us published some preliminary findings on the use of iproniazid ("marsilid") in the treatment of depressive illness (Dally, 1958). Several other papers have appeared, before and since, all stressing the value of this drug in depressive states, and recovery rates of between 25% and 75% have been repeatedly claimed (Robie, 1958a; Delay and Buisson, 1958; Kline, 1958; Settel, 1958). In this department we have continued to study the response of depressed patients to iproniazid, since it is clear that not all groups of such patients respond equally well to the drug. Also, iproniazid can sometimes be dangerously toxic and this makes it of even greater importance to find out the type of patient and the symptoms most benefited, especially if it can also be shown that these do not respond to other treatments at present at our disposal. We have now used iproniazid in over 500 patients in the past two years, and, as a result, we have started to recognize a group of patients showing somewhat atypical depressive states, sometimes resembling anxiety hysteria with secondary depression, who seem to be specifically and

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almost completely relieved of their disabling symptoms by iproniazid after the failure of all other forms of treatment.

It is the purpose of this paper to define and discuss this particular group of depressions, and to contrast the effects of iproniazid on them with those seen in the more classical types of endogenous depression and in some recurrent depressive illnesses. Some of our patients with recurrent depression have been attending a special clinic in this department for up to eight years, and the natural history of their illnesses has become well known. In some of them we have found that iproniazid seems so far to have prevented or modified the recurrence of their depressive episodes at the expected times when every other treatment tried over the years has failed to do so.

Method and Selection of Case Material

Initially we planned to use double-blind methods of trial. This proved unsatisfactory in practice. Iproniazid has easily recognized side-effects and often produces a rather typical facial flush, so that in a double-blind trial the psychiatrist would know in many instances when the patient was receiving the active drug. Furthermore, depressive illnesses are not an entity, and it is difficult to select a homogeneous group for study. If the group studied is not homogeneous, dramatic improvement in a few cases within the larger group may not reach statistical significance and may be ignored. Yet such improvements may be of the greatest importance and may even help to elicit a new clinical syndrome. In this investigation, therefore, we have finally assessed our results in retrospect. We have picked out a group of patients most rapidly and obviously helped by iproniazid, especially after the failure of other treatments. These patients have been examined on the basis of their symptomatology and previous personality. The result was the emergence of the particular group of depressions discussed below.

In testing out the drug, most patients began treatment with 50 mg. (one tablet) three times a day. They were warned to reduce the drug by 50 mg. a day if side-effects, particularly persistent dizziness, became troublesome, and to stop it altogether if they felt ill. Doses of 50 mg. three times a day were generally continued for only two weeks, and if improvement was shown this was reduced to 50 mg. twice a day. The aim was to reduce the dosage to the lowest effective level as soon as possible, the more intelligent patients later being able to judge this for themselves. Out-patients were generally seen at weekly, fortnightly, and then monthly intervals if all went well. The maximum dosage given initially to any patient was 150 mg. daily for two months, while a later minimum maintenance dosage found to be effective could be as low as 25 mg. a day in some patients.

Results

The Table shows the analysis of symptoms in 101 patients, 58 of whom showed a good response to iproniazid. Within this group we found that the most rapid and unexpected responses to iproniazid have been in a special group of "atypical or hysterical" depressions. Many of these patients had been ill for years, and often the original depressive symptoms had become masked to a great extent by phobic anxiety symptoms. Some patients gave an initial impression of general inadequacy rather than true depression. They have appeared anxious and overreactive and have sometimes been diagnosed as primarily "hysterical" and only secondarily depressed. The overreactivity in the somatic field was seen in their tremulousness and circulatory lability. Fatigue was also a prominent complaint, and yet they could not get off to sleep at night. Typically depressive early morning wakening did not always occur. They were not markedly self-reproachful, as in so many of the more classical endogenous depressions, nor were they always worse in the mornings, getting better as the day wore on; rather they tended to become worse in the evening. Weight loss was not constant. The use of E.C.T., too, had sometimes brought about temporary improvement, but usually these patients had become more and more anxious and fearful of it. A temporary unreality state or troublesome amnesia also seemed to develop more easily in this group after E.C.T. Other drugs, whether stimulant or sedative, had caused only a partial improvement and in general these patients seemed more easily upset by most drugs than patients with other depressions.

Analysis of Symptoms in 101 Consecutively Treated Cases of Depression

	Responded to Iproniazid	Did Not Respond
No of patients	58	43
Average age	41 ± 12·2 years	47 ± 11·8 years
,, length of illness	3·0 ± 2·9 ,,	2·4 ± 2·1 ,,
History of previous attacks	25·9%	30·2%
Positive family history of mental illness	36·2%	30·2%
Self-reproach	17·2%	44·2%*
Worse a.m.	20·7%	48·8%*
,, p.m.	20·7%	2·3%*
Difficulty in getting to sleep	72·4%	60·4%
Early waking	17·2%	48·8%*
Hypochondriasis	37·9%	37·2%
Retardation	22·4%	23·2%
Bewilderment	31%	23·2%
Phobias	44·8%	23·2%*
Hysterical conversions	7·2%	0*
Tremor	29·3%	7·0%*
Cardiovascular symptoms	77·6%	41·8%
Gastro-intestinal symptoms	44·8%	27·9%
Other somatic	79·3%	72%
Given E.C.T. at some time	63·2%	86%
% E.C.T. cases made worse by E.C.T.	22·2%	8·1%*

* Significant at $P < 0.05$ (χ^2 test).

We also noticed, in studying this group, that doctors who had previously seen and treated these patients had often regarded them as having some special problem, conscious or unconscious, which they could not bring themselves to face. A careful, and often independent, history showed, however, that they had been able to cope with their problems before the illness had started, and that the previous personality had been a relatively good one. Subsequent follow-up showed that many of the seemingly "insuperable" problems were very easily resolved by the patients once they had recovered with the drug.

It was found that patients with lifelong inadequate personalities, who presented with a rather similar clinical picture, did not respond to iproniazid in anything like the same dramatic way. This emphasizes the necessity of differentiating the pre-illness personality. Improvement took place quickly, usually around the fifth to the eighth day after treatment had been begun, but sometimes even sooner. There was a shorter latent period between beginning the treatment and the occurrence of clinical improvement in this group than

was seen in the more typical endogenous depressive states, where up to a month's treatment might be needed before recovery or improvement occurred. The subjective improvements reported consisted of general feelings of greatly increased well-being, cheerfulness, improved mental functioning, and an obvious decrease in anxiety; this might be followed by improvement in long-standing phobic and psychosomatic symptoms. Weight gain might be rapid with a noticeable increase of appetite, and the physical appearance often changed markedly and obviously for the better. The coincidental physical and mental improvement shown could be very striking.

In some cases we are still having to continue iproniazid, since withdrawal or lowering of the dose below the therapeutically effective level has caused relapse, usually within four days. Resumption or increasing the dose of the drug reverses these changes. By gradually reducing the dosage it is thus possible to find out when a patient has no further need of the drug or the minimum effective dose needed for maintenance. In our group this has varied from 100 to 25 mg. a day. Three of these patients have now had iproniazid for over one year, and the duration of iproniazid therapy to date for the 58 patients in the Table varies from 3 to 20 months.

One of the most remarkable responses of many seen in this group occurred in the following case.

The patient, a married woman, had been a cheerful and stable woman until 10 years previously. Since then she had become depressed and anxious, unable to cope with her work, and had at times seemed bewildered and depersonalized. She had been afraid to go out alone, and for the last two years her husband has had to do the shopping for her. Emotional stresses of any kind, and particularly the thought of leaving the house, provoked attacks of Raynaud's phenomenon in the hands and feet, and a severe tachycardia. There was a strong family history of Raynaud's phenomenon. She had also become convinced that she had severe heart disease. She had been in mental hospitals several times and had been diagnosed as an "atypical depression." No treatment had helped her, and E.C.T. had made her feel unreal. Her symptoms had become so chronic and so disabling that modified leucotomy was being considered. After starting treatment with iproniazid, 150 mg. a day, she improved dramatically in four days. Within 10 days she was able to go out alone without fear and to travel on buses and trains, which she had not been able to do for the past two years. Raynaud's phenomenon also no longer showed itself under stress; whether this is due to a specific autonomic effect of iproniazid or to the improved emotional state is not clear. Stopping iproniazid led to the quick return of all her symptoms. These cleared up as soon as the drug was given again. She is now leading a completely normal life on 50 mg. twice a day.

Endogenous Depressions

We have found that patients with more classical endogenous depressive illness can also be helped by iproniazid, but rarely as quickly and as completely. The response is more gradual than in what we have termed the "atypical" group. The suffering involved in waiting for a remission in severe endogenous depression and the risk of suicide can be so great that E.C.T. has often had to be employed before the full iproniazid response, which other authors also find may take a month to develop. However, several patients have been treated with 150 mg. of iproniazid a day for four weeks, with only slight improvement. But it does seem that the use of iproniazid may reduce the amount of E.C.T. needed in this group, and we are continuing to investigate its possible E.C.T.-sparing effect.

It is well known, too, that some cases of depression respond to E.C.T. but soon relapse again. We have found iproniazid useful in some of these patients. A woman of 83, for instance, with long-standing recurrent depressive attacks who has had to have 170 E.C.T.s as an out-patient since 1950, persistently relapsing within six weeks of stopping E.C.T., has now remained completely well for the past five months on 25 mg. of iproniazid a day. This was a most striking and totally unexpected result.

Recurrent Depression

Patients with recurrent depressive illnesses have been attending a special out-patient clinic for up to eight years. This clinic was organized especially for research into and investigation of the effects of various drugs and hormones on this hitherto most resistant condition to all treatments. Consequently the natural history of their illnesses has been observed and known to us for long periods. Up till now we have found that the recurrence of their attacks has been uninfluenced by any other of the available treatments. E.C.T. has not prevented them going into an attack, and it may help to bring them out only if given towards the expected end of any particular attack.

Twelve such patients have now been treated with iproniazid, for periods ranging from 3 to 18 months. When patients became well the maintenance dose used has generally been 50 mg. daily, but they have been warned to increase the dose to 150 mg. daily as soon as the symptoms of an impending attack are felt. In 10 out of these 12 patients iproniazid appears so far to have prevented or greatly modified recurrences of depression, and we now believe this is more than mere coincidence. But relapses can occur. One woman, with attacks of deep depression dating back to 1929, went into a depressive attack in spite of a regular dose of iproniazid. In another patient with recurrent attacks the drug only lightened the depressive phases and did not abolish them. We are continuing to investigate possible differences between those who relapse and those who do not, and it may be that both the type of depression treated and the dosage play some part.

Side-effects and Toxicity

Side-effects are common with iproniazid, particularly dizziness and constipation. Paraesthesiae and muscle-twitching may also develop. Sudden weight gain with pitting oedema has occurred in some patients, and in this event we have usually stopped the drug. Lethargy may be felt even though improvement occurs in other respects, but can usually be satisfactorily counteracted by stimulant drugs such as dexamphetamine. In some men delayed micturition, impotence, or inhibition of ejaculation are other sources of complaint. In the elderly, particularly, hypotensive effects may be marked.

The most serious toxic effect of iproniazid is liver-cell damage, leading to jaundice and in some cases to acute hepatic necrosis (Benaim and Dixon, 1958; Kahn and Perez, 1958; Pare and Sandler, 1959). The incidence both in this country and in America is said to be around 1 in every 2,000 cases treated, and it may prove to be more frequent than this (Briggs, personal communication 1958; Robie, 1958b). Of the patients who developed jaundice, 20% are said to die from it. This liver toxicity is said not to depend on the amount

of drug given or on the length of time it is administered, but is thought to be a sensitivity phenomenon. In the nine cases reported by Kahn and Perez the mean time of onset was 40 days, and the dosage varied from 10 to 150 mg. daily.

In the series of over 500 cases treated here, only one case of jaundice has occurred and the patient recovered from its effects. But two colleagues working with us have also had a case of iproniazid jaundice in other patients treated outside this hospital. While there is no certain way of preventing this risk of jaundice, we feel that keeping the dosage at the lowest effective level, seeing the patients frequently, and warning them and their general practitioners that any suspicious departure from normal health should be a matter for immediately stopping the drug, may have helped to keep our incidence of jaundice low. One should also avoid treating patients with a history of liver damage. Pare and Sandler have recommended weekly estimations of serum glutamic oxaloacetic transaminase. We are still investigating the value of this test in giving warning of liver damage during iproniazid therapy.

Some have taken the view that iproniazid should not be used at all because of this toxicity. We feel, as we have indicated, that iproniazid is so valuable a drug in the particular special groups we have described—it can be effective in a way no other treatment can be at the present time—that its continued careful use in persons severely disabled by their illness has been more than justified over the past two years, and more good than harm has certainly so far come from using it. Untreated depressive illness carries with it a very definite mortality, including suicide, and it is in this context also that the risks of iproniazid must be properly weighed. It is hoped, however, that non-toxic derivatives will soon be available to reduce our very natural anxieties on this score, and the drug should not be given unless considered essential.*

Discussion

Most authorities have not differentiated the clinical types of depression responding to iproniazid. Robie (1958c) refers to the improvement occurring in patients unresponsive to other forms of therapy and to the prevention of recurrent depressions. Delay and Buisson (1958) state that they found iproniazid best in the less severe depressive states. Alexander (1958) remarks that iproniazid is indispensable for "inert psychasthenic states" who do not respond to E.C.T. and give the impression of being neurotic personalities. Alexander's description does fit some of the atypical depressions we have tried to distinguish in this paper as being specifically helped by iproniazid when all else has failed, but, as we have particularly stated, symptoms of overreactivity are often present. Saunder *et al.* (1959) show that iproniazid has helped patients with a long history of anxieties and compulsions, and they also describe the successful use of iproniazid in stopping cyclic depression.

We have tried to show that the clinical response to iproniazid is not necessarily proportional to the amount of obvious endogenous depression present; rather the opposite. It may be that there is really no basic distinction between the groups we have differentiated, apart from the presence of a more reactive and labile nervous system, which is therefore more easily restored to normal. But we are not entirely satisfied with this explanation, and it would seem that further attempts to differentiate these groups biochemically, and in other ways, might provide further proof of the existence of different types of depressive syndromes with differing aetiologies and treatments. For at least one of these groups iproniazid seems almost a specific treatment where other therapy has failed, just as E.C.T. is often so specific in true involutional depressions.

*Three supposedly non-hepatotoxic substitutes for marsilid are at present under trial in this department, but it is too early yet to say how efficient they will prove to be.

Summary

Iproniazid has been found to be of particular value in treating a group of "atypical" depressive illnesses. Some of these patients appeared to be suffering from phobic anxiety states with secondary depression, while others had been regarded as suffering from "anxiety hysteria" or dismissed as being merely "inadequate." Most, however, had had good previous personalities before the illness started. Iproniazid helped when other therapy, including E.C.T., had failed.

In this group the dose of iproniazid for maximal therapeutic response had to be adjusted for each individual patient.

Iproniazid was found to have a less rapid and less complete effect in some typical endogenous depressive illnesses. In addition, some cases of recurrent depressive attacks are described in which the patients appear to have had their expected attacks of depression prevented or modified by taking iproniazid regularly over a long period. The value of iproniazid in sometimes preventing relapse into depression again after improvement with E.C.T. is also reported.

The complete remission of Raynaud's phenomenon in one woman treated with iproniazid is reported.

The toxic effects and dangers of iproniazid are emphasized: it should be used only in persons severely disabled by their illness who are not thought likely to respond to other treatments.

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