

THE TREATMENT OF DEPRESSIVE STATES WITH G 22355 (IMIPRAMINE HYDROCHLORIDE)¹

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Depressive states can have very different causes, treatment varying accordingly. Until now only electroshock therapy for endogenous depressions and psychotherapy for reactive depressions really fulfilled requirements of effective treatment. The drawbacks of electroshock are well known. To mention only one of them—the occurrence of psycho-organic symptoms, which can be extremely unpleasant, particularly for the more intelligent person who has to do intellectual work. Furthermore the efficacy of electroshock therapy diminishes in many cases the more often it has to be repeated, and the methods employed to prevent incidents arising in the motor apparatus also impair its efficiency.

As regards psychotherapy for reactive depressions, everybody with experience in this field knows how tedious and difficult such treatment may sometimes be and how unsatisfactory the results often are. In any case, the present status of the treatment of depression is such that new efficacious medicaments are urgently required.

The effect of the psychopharmacologic drugs already known on depressive states is slight or indeed absent altogether. This applies particularly to chlorpromazine and its chemically allied substances and to reserpine. Stimulating substances which produce euphoria have at the most an extremely transient effect on depressions and in addition involve the risk of addiction. This also applies to amphetamine and similar substances. Many forms of depression possessed no really adequate treatment till now, and there was nothing much that could be done except wait till the disturbance cleared up on its own.

N-(gamma-dimethylaminopropyl)-iminodibenzylhydrochloride (G-22355) is a sub-

stance with markedly anti-depressive properties(1).³ Its mode of action remains for the present completely unknown. It may indeed in individuals who are predisposed give rise to a somewhat manic-like condition or even a manic state, i.e., it may act by stimulation and produce a sense of euphoria. But it is not a substance to be considered in general as a type of euphoriant. Only very few persons experience it as such, and as we have been able to show in hundreds of cases it does not lead to addiction.

The effect is striking in patients with a deep depression. We mean by this a general retardation in thinking and action, associated with fatigue, heaviness, feeling of oppression, and a melancholic or even despairing mood, all of these symptoms being aggravated in the morning and tending to improve in the afternoon and evening. From the external appearance alone it is possible to tell that the mood improves with imipramine hydrochloride. The patients get up in the morning of their own accord, they speak louder and more rapidly, their facial expression becomes more vivacious. They commence some activity on their own, again seeking contact with other people, they begin to entertain themselves, take part in games, become more cheerful and are once again able to laugh.

The patients express themselves as feeling much better, fatigue disappears, the feeling of heaviness in the limbs vanishes, and the sense of oppression in the chest gives way to a feeling of relief. The general inhibition, which led to the retardation, subsides. They declare that they are now able to follow other persons' train of thought, and that once more new thoughts occur to them, whereas previously they were continually tortured by the same fixed idea. They again become interested in things, are able to enjoy themselves, despondency gives way to a desire to undertake something, despair gives place to renewed hope in the future. Instead of being concerned about imagined or real guilt in their past, they become occupied

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³ Imipramine hydrochloride is supplied by the Geigy Chemical Corp. under the trademark of Tofranil.

with plans concerning their own future. Actual delusions of guilt, or of loss, or hypochondriacal delusions become less evident. The patients declare "I don't think of it anymore" or "the thought doesn't enter my head now". Suicidal tendencies also diminish, become more controllable or disappear altogether. Instead of the feeling of being ill patients experience a sense of increasing strength and health. An irritable, morose and resistant attitude gives place to a feeling of gratitude and affection for the doctor. Fits of crying and moaning cease. Where the depression was accompanied by insomnia sleep occurs again, in many cases spontaneously under the influence of imipramine hydrochloride, and the sleep is felt to be normal and refreshing, not fatiguing and forced as that so often produced by sleeping remedies.

Where during the depression there was marked inner or outer excitement and uneasiness, imipramine hydrochloride exerts a tranquilizing effect. Where the depression had led to loss of appetite, the appetite returns. Loss of weight during the depression is again made good. But patients do not actually become obese, as is apt to happen with chlorpromazine. In cases where the depression had led to constipation imipramine hydrochloride counteracts this. Feelings of inner tension and cramp are also relieved.

All these effects can occur almost suddenly after two to three days treatment and are then already fully developed. In other cases improvement occurs in about one to four weeks, sometimes suddenly, often little by little. Not infrequently the cure is complete, sufferers and their relatives confirming the fact that they had not been so well for a long time. It often turns out that the actual perceptible illness had been preceded by a very long prodromal phase with mild disturbances, which hardly appeared to be pathological at the time, and only on looking back after the cure is it seen to have been part of the illness. In many cases however, there is merely some degree of improvement, making the condition more bearable for the patient, and even permitting resumption of work, though at the cost of considerable effort. In other cases there is no effect at

all. If, in what is certainly a purely depressive state, treatment with imipramine hydrochloride has no satisfactory effect, a combination with electroshock is indicated. Imipramine hydrochloride, like chlorpromazine, probably has a shock-economizing effect. But the action is always purely symptomatic. As soon as the medicament is discontinued the illness breaks out again, usually with undiminished severity after a few days, and it can be cured again by repeating the medicament. It is thus possible experimentally in suitable cases to provoke or to cure the illness at will.

Side effects are relatively slight. In over 500 cases we have treated with the preparation, we have never met with a serious complication. Even patients who have been treated for over two years without interruption have shown no severe side effects.

Often there is a feeling of dryness in the mouth, tachycardia and a tendency to sweating coming on in attacks. The blood picture in about 2/3 of cases reveals a slight increase in eosinophils, but we have never seen a marked eosinophilia. Particularly at the commencement of treatment there is occasionally transient erythema. Only in one case did we see severe allergic exanthems, necessitating interruption of treatment. Stomatitis, however, sometimes occurs, probably due to inhibition of salivation, and is easily relieved. Allergic reactions in the nursing staff have never been seen. As in the case of chlorpromazine, but to a less marked extent, photosensitization may also occur.

The blood pressure is scarcely affected by imipramine hydrochloride. If however there is arterial hypertension, then in many cases imipramine hydrochloride lowers it slightly. We have seen differences of up to 70 mm. As long as the preparation is being given the blood pressure remains low, but it rises at once again if treatment is interrupted. We observed collapse phenomena only very exceptionally with the current method of carrying out treatment. But we make a practice of getting all patients out of bed regularly, even if they receive high doses of imipramine hydrochloride, by injection. We saw thrombosis in two cases only, embolism never.

We have not seen disturbances in the

gastrointestinal tract. Patients who have a tendency to be constipated, and when this is not attributable to the depression, generally complain of increased constipation under treatment and require aperients regularly. Icterus, which could be attributed with any degree of certainty to imipramine hydrochloride, has not been observed so far as we are aware.

In some cases, particularly in certain forms of organic diseases and in schizophrenia, a state of agitation arises after from one to several weeks. This can occasionally be considered as an exacerbation of the psychosis. Sometimes it appears to be an acute toxic psychosis of the acute exogenous reaction type. Occasionally such psychoses subside again, but often they necessitate interrupting treatment and it is possible that afterwards a remission occurs or substantial tranquilization, which persists at least for some time after the end of treatment. Such episodes only occur seldom, in pure depressive states.

Then there are a number of side effects which are only observed rarely. During the first few days of treatment there may be giddiness shortly after taking the substance, occasionally there are complaints of paresthesia, now and then of unpleasant sensations in the precordium, sometimes of headache. In older people disturbance in accommodation can be a nuisance and may necessitate prescribing glasses.

The *dosage* of imipramine hydrochloride is not entirely simple. Generally it is of the same order of magnitude as that of chlorpromazine. On the whole when giving it by injection we have not exceeded 150 mg. a day, and by oral administration not substantially above 300 mg. a day. Elsewhere however, considerably higher doses have been given and the preparation has also been given intravenously. But it is important to know in many cases, particularly in very young patients and adolescents who suffer from symptoms of neurovegetative lability and in elderly patients with severe vascular disturbance lower doses are indicated. We make a point then of not exceeding 20-30 mg/day and as far as possible split up the dose. In such cases the effect is usually the same as that of higher doses in other patients.

If however these patients are given higher doses, unpleasant states of tension and agitation occur and the tension may under particular circumstances find an explosive outlet.

The most important problem in the treatment of depressive states is that of finding the correct indication for the drug. Here lie the greatest difficulties and the whole success of treatment depends on the right indication being chosen. The main indication for imipramine hydrochloride is without doubt a simple endogenous depression, possibly presenting the rather frequent depressive delusions and suicidal urges. Every complication of the depression impairs the chances of success of treatment. In marked manic-depressive psychosis, *i.e.*, if the depressions are easily and frequently replaced by manic-like phases or actual manic states, the reaction is less favorable. Such depressions seem to respond less well and the tendency arises for the depression to switch over into a manic phase. Imipramine hydrochloride is certainly not the drug of choice for mania and it may even reinforce the manic agitation.

The prognosis is also considerably less favorable if the depression is complicated by schizophrenic features or if it is merely a depressive state arising in the course of a schizophrenic process. This means that all cases where hallucinations are present, apart from the depressive state and any delusions attributable to this state, react less well or not at all to imipramine hydrochloride. The same applies to cases where catatonic blocking or other signs of an actual dissociation occur in addition to the depressive retardation of thinking and to cases of negativism. In certain cases, it is true, very striking effects can be obtained in relation to the schizophrenic features, which in some respects resemble those obtained with chlorpromazine and reserpine. Thus under particular circumstances it may be possible to break through a catatonic stupor. One patient, for years unable to think or speak, was suddenly able to do so freely with the aid of imipramine hydrochloride, and had the impression his thought disorder had become resolved. It may happen that the 'voices' get quieter, no longer seem so menacingly

close, and sound as if they come from a distance. There are cases in which the patient becomes indifferent regarding the content of his hallucinations and his schizophrenic delusions of persecution, ill-treatment and 'foreign influence.' In such cases the dissociation in thinking also usually gets less pronounced and affective rapport is considerably improved. In other cases of schizophrenia we see a depressive state accompanying the schizophrenia disappear, while the schizophrenic features persist entirely uninfluenced, or perhaps become more prominent, no longer being masked by the depression. But in the majority of cases of schizophrenia there is no effect at all or the patients become more agitated. This applies particularly to acute states of agitation. Here imipramine hydrochloride is certainly not indicated. On the other hand it may be possible to cure acute depressive phases such as are seen particularly at the commencement of a schizophrenic process in young persons, and also stuporous forms of acute psychoses in a very short time with imipramine hydrochloride alone. Strangely enough, however, we have even seen stupor develop in acutely ill patients during treatment with this drug. It is of course hardly possible to decide whether in these cases the stupor might not have occurred spontaneously and the imipramine hydrochloride were merely unable to influence it in its spontaneous course. In schizophrenic patients the combination of imipramine hydrochloride with chlorpromazine, less frequently with reserpine or electroshock has proved particularly good. It is interesting that there are patients who do not respond to any of these methods of treatment when given singly, but respond well to a combination of them.

The complication of depression with organic brain disease offers unfavorable prospects for treatment. If anything, good results may be expected when the organic component is mainly vascular in nature and has not yet led to extensive destruction in the brain. In relatively early stages of organic brain disease, which are often accompanied by depressive states, imipramine hydrochloride may act very well, particularly if hypertension is present. Then anxiety states, pain, hypochondri-

acal fears and agitation at night often respond too. When, however, vital parts of the brain are already functionally inefficient due to organic causes, particularly in processes involving cerebral atrophy, then imipramine hydrochloride usually has no effect even in severe depressive states. Practical experience has shown that cerebral atrophy is extraordinarily easily overlooked, unless pneumoencephalography is regularly carried out. With pathological EEG findings the possibility must always be borne in mind that such widespread interference with cerebral function may exist as to render imipramine hydrochloride ineffectual.

Depressive states in epileptics appear not to respond at all to imipramine hydrochloride. In a few cases however we have observed a good reaction in epileptoid twilight states accompanied by agitation. But this effect only occurs as quite an exception.

In a case of Wilson's disease we observed a distinct improvement in the extrapyramidal motor symptoms and in the psychotic phase of excitement.

States of agitation in severe forms of mental deficiency respond usually little or not at all to imipramine hydrochloride. On the other hand, quite striking results have sometimes been seen in the endogenous depressions of mental defectives.

While on the one hand the range of indications for imipramine hydrochloride in depressive states is somewhat limited, it is on the other hand very much increased when it is remembered that very varied psychopathological symptoms may be caused by an endogenous depression or a depressive state of some other origin, and the depressive state may often be overlooked because of some more striking psychopathological findings. Almost any neurotic symptom can be caused by a depressive state or be maintained because of the simultaneous occurrence of a depression. There are undoubtedly patients who present the picture of an obsessional condition, and typical psychogenic connections may possibly be demonstrable and some degree of improvement be attained by psychotherapy, and yet an endogenous depression is present. In such a case, treatment with imipramine hydrochloride can bring a com-

plete change in the situation within a few days, which could not be achieved by intensive prolonged psychotherapy. As regards the prognosis, of course all the well known unfavorable factors must be considered. Nevertheless, imipramine hydrochloride under particular circumstances can appreciably facilitate psychotherapy.

The same applies to certain hysterical symptoms, anxiety states and phobias of apparently neurotic origin and to physical functional disorders, which tend today to be placed in the field of psychosomatic medicine. In this manner, for instance, we were able within 4 weeks to cure completely a severe impotence in a 40-year-old man, which had lasted almost 2 years and was endangering his marriage.

Imipramine hydrochloride appears to us to have a great practical significance in cases in which accidents with bodily injuries lead to obstinate pain and depression, preventing resumption of work and causing trouble to the insurance companies. But even in severe illnesses with a fatal outcome this drug can bring great relief in the terminal stages. It has not yet been determined whether imipramine hydrochloride exerts such an effect through an apparent analgesic component or whether less attention is paid to the pain due to change in mood. We are here merely at the threshold of studies which very probably will considerably extend the range of indications for imipramine hydrochloride.

The question arises what happens in reactive depressions, and here we find a very confused situation. In a patient with an endogenous depression who was under treatment with imipramine hydrochloride we witnessed a severe reactive depression which developed in connection with a disappointment in love. Both the reactive and the endogenous depression responded very well to imipramine hydrochloride during the further course of treatment. We have seen excellent results with imipramine hydrochloride in several cases of apparently purely reactive depression. In other cases, where difficult neurotic problems predominated, we had the impression that imipramine hydrochloride was unable to develop its effect until these problems had to some extent been dealt with. In a num-

ber of cases we witnessed considerable improvement in the psychotherapeutic treatment with the use of imipramine hydrochloride and the medicament was found to exert an increasing effect on the endogenous component, which was not amenable to psychotherapy, and this again benefited the purely reactive factors. In any event in reactive depressions which do not, as they should normally, disappear within a relatively short time, treatment with imipramine hydrochloride is absolutely indicated. We shall not enter upon the extremely difficult problem as to what extent endogenous and reactive depressions differ clinically from one another and what the significance may be of the striking similarity of the clinical pictures of these two diseases with apparently different etiology.

In this connection, a question of great general importance presents itself, namely, whether, and to what extent, imipramine hydrochloride influences healthy impulses of conscience, consciousness of guilt and resistance against criminal or immoral actions. The seriousness of the moral and social implications involved in this question cannot be ignored. It is essential that investigation of this matter should be undertaken on a wide scale. For the time being perhaps the following can be stated: Undoubtedly the possibility exists of influencing people's ethical and moral behavior by administration of particular substances. The best known example is alcohol. It is therefore certainly within the realm of possibility that newly discovered medicaments may exert a similar effect. Furthermore, it should be remembered that in certain individuals suffering from depression, and in whom manic phases occur, their whole moral structure may altogether deviate from the normal. This does not mean that such factors belong to the characteristics of the psychosis. But it is known that manic states particularly may give rise to criminal actions and to the absence of inhibition or moral scruples. If then a medicament such as imipramine hydrochloride exerts an effect on the mood and possibly provokes manic-like reactions, then it must be expected that in certain persons their moral structure may be imperiled. The inhibition

against committing suicide must also be seen in this light ; just as in the spontaneous course of a depression, phases occur in which resistance against suicide is lessened, during the course of imipramine hydrochloride treatment there may be an increased risk of suicide. It is essential to take this into account, and in spite of the possibilities which imipramine hydrochloride offers, to commit to an institution patients who are endangered in this way.

In the course of the treatment we have carried out to date, we have not seen any particularly striking signs of interference with ethical or moral standards. In one case we treated a patient with depression who was about to appear on trial in court for homosexual offences against a youth. The depression practically disappeared. The self-reproaches, hysterical collapse with crying and moaning disappeared completely within 3 days. But there was absolutely no evidence that the patient's own moral condemnation of his actions had suffered. The depressive phase gave place to a perfectly adequate sense of his own moral failure and to a natural reaction of repentance. The homosexual desires became strikingly less prominent during treatment.

Clinically it could be shown that the homosexual tendencies had become noticeable in connection with a depression of several years' duration and that they had replaced a previous heterosexual attitude. One must of course avoid drawing too far-reaching conclusions from a single case. But it at least appears as if substances such as imipramine hydrochloride need not necessarily seriously impair a patient's moral attitude and sense of judgment.

An important field of research opens up here, rendered accessible for the first time by the recent development of psychopharmacology, and touching not only problems of psychiatry but also those of general psychology, religion and philosophy.

SUMMARY

Over a three-year period, more than 500 psychiatric patients of various diagnostic categories were treated with imipramine hydrochloride. It was demonstrated that the compound has potent antidepressant action. Best responses were obtained in cases of endogenous depression showing the typical symptoms of mental and motor retardation, fatigue, feeling of heaviness, hopelessness, guilt, and despair. The condition is furthermore characterized by the aggravation of symptoms in the morning with a tendency to improvement during the day. Treatment with imipramine hydrochloride resulted in full or social recovery in a high percentage of the patients. As a rule, the initial response was evident within 2 to 3 days, while in some cases 1 to 4 weeks of therapy were required. In view of the symptomatic nature of the action of imipramine hydrochloride, therapy must be maintained as long as the illness lasts. The side effects noted were relatively slight, and with the exception of one case of severe allergic exanthema necessitating discontinuance of treatment, no serious complications were encountered. In some cases of depression, particularly those associated with organic brain damage or schizophrenic psychosis, transitory states of agitation or exacerbation of the psychotic features were noted. These observations suggest the importance of a proper selection of the patients as to type and etiology of depression. While in a number of instances, neurotic, schizophrenic or other depressions were also benefited by the drug, particularly when used in combination with chlorpromazine, electroshock or psychotherapy, it is concluded that imipramine hydrochloride is primarily indicated and effective in the treatment of endogenous depression.

BIBLIOGRAPHY

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