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RÉSUMÉ

Trente malades (8 hommes, 22 femmes) dont l'âge varie entre 33-85 ans, souffrant de diverses formes cliniques de dépression, furent traités durant cinq semaines en moyenne dans un Hôpital Général où le milieu thérapeutique est différent de celui d'une institution mentale. Tous ces cas à l'admission auraient justifié l'emploi des électro-chocs avant l'introduction de l'Imipramine. Quatorze furent diagnostiqués psychoses maniaco-dépressives de forme dépressive, allant de la stupeur mélancolique jusqu'à l'agitation dépressive; trois dépressions névrotiques; cinq cas d'hypocondrie; une psychose puerpérale et sept psychoses séniles.

L'Imipramine fut utilisée généralement par voie orale à la dose de 50 mg. q.i.d. Dans certains cas particuliers et pour des raisons thérapeutiques la voie intra-musculaire ou intra-veineuse fut employée. La dose maximum d'Imipramine chez certains malades atteignit 600 mg. par jour sans apparition d'effet toxique. Dans ce rapport préliminaire la toxicité de l'Imipramine s'est révélée nulle. Cependant la majorité des malades se plaignirent d'une transpiration abondante. Les divers examens de sang et d'urine n'ont pas montré de changements attribuables au médicament.

Douze malades de cette série furent choisis pour un "double blind". Six reçurent de l'Imipramine et six du placebo. Le résultat de cette expérimence à la fin de deux semaines d'observation ne fut pas concluant. L'amélioration obtenue par le médicament ne fut pas supérieure à celle produite par le placebo.

En général les résultats obtenus par l'Imipramine durant cinq semaines d'hospitalisation sont assez encourageants: 80% des malades sont guéris et sont suivis à la clinique externe. Il est probable que cette thérapeutique doit être continuée pour une longue période de temps afin d'éviter les rechutes. L'introduction de ce nouveau produit dans l'arsenal thérapeutique psychiatrique présente un grand intérêt pour le médecin non spécialiste. Le médecin de famille peut actuellement grâce à l'Imipramine traiter les premiers symptômes de dépression et éviter l'évolution d'un tel syndrome. A.H.

IMIPRAMINE (TOFRANIL*): A SAFE, EFFECTIVE ANTI-DEPRESSANT DRUG IN PRIVATE PRACTICE

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SINCE THE ADVENT of "psychopharmacology", which began when chlorpromazine proved itself to be such a widely useful drug, there has been a mounting deluge of new drugs into areas of psychiatric interest, and a multitude of reports, papers, claims and counterclaims about the clinical effectiveness of these agents, together with many reports of their side effects and complications. An interesting by-product has also been the renewed emphasis on the difficulties of controlled clinical research in such a complex clinical field, where it is difficult to define diagnosis accurately, or to evaluate degrees of morbidity, and where the factors responsible for improvement or recovery in a given patient produce disagreement among the observing experts. Feldman[1] presented evidence that all research workers are not uniformly successful in their evaluation of the clinical effectiveness of new drugs, and he related this to the emotional bias and attitude of the investigator, as a determining factor in the results. This report came from the Menninger Clinic, where, under relatively standardized investigative conditions, the staff members obtained widely divergent results with the first clinical investigations of chlorpromazine. Attempts to objectify the investigation of drug results have led to the use of "blind" and "double-blind" techniques, or the development of rating scales of various sorts. The latter seem to this writer to be unwieldy, and add confusion to the interpretation of the results offered. Tuteur[2] has called attention to the pitfalls, fallacies and limitations associated with the double-blind study method. He has pointed out that in many investigators it leads to an unwarranted sense of security. An incidental development of much interest in this whole movement has been to focus attention again on the place of the placebo, and on other non-specific therapeutic elements in the hospital setting which foster a sick patient's improvement. Bartemeier,[3] in an interesting paper, pointed out that there is a need to evaluate again and again what milieu factors in the hospital environment have produced favourable modifications of mental illness in patients who recover in a hospital setting where there is a minimum of professional personnel and assistance. According to recent reporting[4] of a Conference on Tranquillizers in Montreal, called to consider the psychodynamic, psychoanalytic and sociological aspects of tranquillizing drugs, Dr. R. W. Hyde expressed the views of his committee that the milieu is most important, and the drug effect is relatively non-specific. The conference experts were said to have expressed widely divergent views about the reasons for the clinical effects of any drug, and disagreed about the ways in which improvement changes are effected. Paul Hoch[5] has succinctly stated recently: "Regardless of the

*Product of Geigy Pharmaceuticals.

methods you use today in psychiatry to observe behaviour changes, the only method which can be used despite its many shortcomings is the clinical one. Any attempt to replace it in the present state of our knowledge by all kinds of so-called scientific constructs is doomed to failure." My own view is precisely similar, in that I feel that careful clinical observation is invaluable in assessing a new drug. Any claim for results that are merely the product of the investigator's enthusiasm will be tempered, confirmed or rejected by the observations of other researchers.

The tranquillizers have signally failed to be of help in dealing with depressed reactions. As a matter of fact, these agents have been described as fostering the development of depressed reactions in many patients *by inhibiting motor activity through which agitation and tension would be discharged to some degree.* Those drugs which have been in common usage as pharmacological agents for relief of depressed states have been singularly ineffective. Amphetamine, dextroamphetamine, pipradrol, methyl phenidate, methamphetamine and Deprol (meprobamate and benactyzine) are generally of limited value in the hands of most psychiatrists in aiding the clinically depressed patient. Marsilid (iproniazid) was first used in the treatment of tuberculous patients, and was observed to produce a euphoriant effect, but proved unsuited for psychiatric use because of severe toxicity.[6] The only persistent, reliable and effective way of influencing the course, duration and severity of a depression has remained the judicious use of electroshock treatment, when supported by other appropriate measures and carried out in a psychotherapeutic setting.[7]

Recently, the first few reports have appeared about a new antidepressive drug, called imipramine (G22355 or Tofranil). Kuhn[8] described his experiences with the treatment of more than 500 patients over a three-year period with this drug. He described the drug as having a potent antidepressant action, best results being obtained in the group of endogenous depressions. Side effects in his series were slight with the usual dosages up to 300 mg. a day. The precise mode of action was unknown. Azima and Vispo[9] reported on 63 patients treated either as private patients or outpatients. Of their depressed patients 83% were significantly improved. This was emphasized as a rather notable result, since these patients were described as having intractable depressive states. Perhaps on this account, they advised the long-continued usage of the drug, otherwise there was a tendency to relapse when the drug was discontinued too early. Lehmann, Cahn and DeVerteuil[10] also reported the treatment of depressive states with imipramine. Of 84 patients in their hospitalized series 60% were recovered or much improved after eight weeks. They described it as a relatively nontoxic drug in doses under 200 mg. a day. The drug was described as a new chemical agent, having primarily an inhibitory action on the central nervous system. Wortis,[6] in summarizing the psychiatric drug advances of 1958, describes imipramine as an iminodibenzyl derivative, with the same side-chain as chlorpromazine but a different ring system, and says, "It is said to be very effective in depressions." Jaundice has been reported, also photosensitivity and visual disturbances due to its atropine-like action, but the general toxicity is claimed to be low. Thus far, there are only three reports on this drug in the literature, though many more will surely follow as it becomes released for more general use.

PERSONAL EXPERIENCE

My present impressions of imipramine have been based on the observation of 26 patients from my private practice to whom this drug was given. After approximately six months of experience, it is my feeling that imipramine is the most effective and the most promising drug ever to appear for the treatment of depressive conditions. The dosage schedule was rather lower than that already reported for patients in hospital. The starting dose given was 100 mg. per day in four divided doses. In all but two cases, this appeared satisfactory, and in these two the dosage was increased only to 150 mg. per day. In the others, it was possible to reduce the dose after improvement was noted, and to taper the dose before the drug was discontinued altogether. The time of improvement varied from the second day on the drug in one patient, to the more average onset of improvement between 10 to 14 days after starting.

Perhaps because of the low dosage used, the only side effects complained of were attacks of sweating in five patients, which disappeared on a lowered dosage schedule. Five patients discontinued the use of the drug within the first few days because of complaints related to atropine-like effects, such as "haziness", uncomfortable head feelings, or listlessness. Since this is an ambulatory patient population, it was not possible to persist with the drug in these instances by introducing suitable modifications. No complications were noted in this series. A mild transient leukocytosis occurred in several patients, also a minor reduction in blood pressure. Laboratory studies were not energetically pursued, but where spot checks were done, there was no disturbance or change evidenced in renal or liver function. No allergic reactions developed. The drug did not interfere with sleep.

The typical change reported by improving patients was that there was no special response felt to the individual dose, no lift of mood, no spurt of energy, but as the days passed, the depressive symptoms were rapidly relieved and the patient simply got well. This effect is the more dramatic, as some of the patients in this series were suffering from severe agitated depressions, which

TABLE I.—SUCCESSFUL CASES

Case	*Sex*	*Age*	*Diagnosis*	*Previous history and treatment*	*Daily dose*	*Results*	*Side effects*
1	M	69	Agitated depression	Hospital and E.S.T. twice before	100 mg.	Recovery	Sweating
2	F	53	Agitated depression	Hospital and E.S.T. + drugs	100 mg.	Recovery	None
3	F	64	Agitated depression	Hospital and E.S.T. + drugs—4 previous occasions	100 mg.	Recovery	None
4	F	58	Retarded depression	Hospital and E.S.T.—3 previous occasions	100 mg.	Recovery	None
5	M	47	Agitated depression	Hospital and E.S.T. twice before	100 mg.	Recovery	Sweating
6	M	49	Obsessional-ruminative depression	Hospital and E.S.T. twice; suicidal attempt	100 mg.	Recovery	None
7	M	40	Reactive depression	Repeated examination and sedation + psychotherapy	100 mg.	Recovery	None
8	F	75	Arteriosclerotic depression	Variety of drugs + hospitalization	150 mg.	Recovery	None
9	F	56	Circular M.D. depression	Hospital and E.S.T. Considered for lobotomy after 11 years	100 mg.	Recovery	None
10	F	58	Involutional depression	Hospitalization + insulin + drugs	100 mg.	Recovery	None
11	F	51	Recurrent depression	6 previous attacks. Hospital and E.S.T.	100 mg.	Recovery	None
12	F	57	Obsessional neurosis: repeated depression	Hospital and E.S.T. 3 times + drugs to addiction + psychotherapy	100 mg.	Recovery	None
13	M	60	Depression; glaucoma	Hospital and E.S.T. 3 times	100 mg.	Recovery	None
14	M	54	Depression: irritable colon	Hospital and E.S.T. psychotherapy + drugs	100 mg.	Improvement	None
15	F	63	Circular M.D. depression	E.S.T. 6 times + interval E.S.T.	50 mg.	Improvement	None
16	M	46	M.D. depression	E.S.T. 4 times before	150 mg.	Improvement	None
17	F	29	Schizo-affective	Hospital and E.S.T. + drugs + prolonged psychotherapy	100 mg.	Recovery	None
18	F	44	M.D. depression, hypothyroidism	Hospital and E.S.T. + drugs + prolonged psychotherapy	100 mg.	Improvement	Sweating
19	M	43	Schizo-affective	Somatic complaints. Drugs + psychotherapy	100 mg.	Improvement	None
20	F	56	Circular M.D. depression	Hospital and E.S.T. 3 times + drugs + psychotherapy	100 mg.	Recovery	None
21	F	40	Circular M.D. depression	Hospital + drugs and prolonged psychotherapy	100 mg.	Improvement	Sweating

TABLE II.—UNSUCCESSFUL CASES

Cases	*Sex*	*Age*	*Diagnosis*	*Previous history and treatment*	*Daily dose*	*Results*	*Side-effects*
1	F	37	Severe obsessive depression	Hospital and E.S.T. in 2 previous attacks	100 mg.	Stopped 3 days	Listlessness
2	M	53	Severe obsessive depression	Hospital and E.S.T.	100 mg.	Stopped 7 days	Listlessness
3	F	42	Schizo-affective	Hospital and E.S.T. twice	100 mg.	Stopped 3 days	Listlessness
4	F	39	Mixed psycho. depression	Drugs and prolonged psychotherapy	100 mg.	Stopped 3 days	Listlessness
5	F	63	Schizo-affective paranoid	Hospital + E.S.T. twice	100 mg.	Stopped 4 days	Listlessness, dry mouth

in identical attacks in the past had necessitated hospital admission, electroshock and other supportive measures. Illustrative cases will be briefly presented below to demonstrate the kind of case material in the study.

RESULTS

A quick glance at Tables I and II indicates that a total of 21 patients out of the 26 recovered from their depression or were vastly improved. This gives a recovery and improvement rate of approximately 80%, which is similar to that already claimed in the few published reports on this drug. The five patients who did not improve all stopped the medication prematurely, claiming unpleasant listlessness, "hazy feelings", or dry mouth. Persuasion to modify and continue the schedule failed to lead to resumption of the drug. It is worth noting that in at least three of these five patients the use of any other drug was equally hesitant and anxiety-laden, because of intense fears of any change in reality assessment and fears of loss of control.

ILLUSTRATIVE CASES

CASE 4.—This 58-year-old woman had a history of four episodes of retarded depression during which she became anorexic, lost weight and sleep, could not think, was regressed and lost interest. Filled with suicidal preoccupations. First attack 24 years ago after failure of her marriage. She was then in an institution for 13 months before recovery. Second attack in October 1955, reactive to problems in a second marriage. She was admitted to a psychiatric service in a general hospital, received E.S.T. and recovered in six weeks. Her third attack was in April 1957, with identical complaints, which again responded to hospital care and E.S.T. in six weeks. In October 1958, she was again depressed, "vacant", "no thoughts", "like wires in the head", "can't sleep", "no memory", etc. Started on imipramine 100 mg. daily—she felt im-

proved by the third day and after 10 days all her symptoms were gone. The drug was continued two weeks longer on a reduced dose, then stopped. The patient continues quite well to the present.

CASE 9.—This 58-year-old woman had a history of circular manic depressive psychosis of 11 years' duration, since the beginning of her menopause. The manic excitement was difficult but manageable with heroic doses of sedative. The depressions were severe, and becoming more prolonged and unresponsive to any treatment. She had had several courses of electroshock, subconvulsive shock, hospital admissions and drugs of every variety, including a prolonged fruitless trial of Marsilid. She is mentally borderline, and never available to psychotherapeutic exploration. Her last hospital admission was three months in duration without improvement. Lobotomy is considered as a therapy in reserve. She was started on imipramine 100 mg. a day and began to improve after 10 days. She has been continued on a maintenance dose of 50 mg. a day for the past three months and is enjoying the first interval of improved health since the first onset of the illness.

DISCUSSION

The clinical results in these cases are most gratifying. While this represents a small series, it is noteworthy that imipramine gives every promise of being a drug which can be safely prescribed in office practice. Furthermore, this drug is effective in those cases which previously have given only a barren response to the use of other drugs. It is my impression that imipramine will help to reduce the number of patients who will require electroshock treatment and hospital care. I would emphasize most emphatically that imipramine, or any other drug or single therapeutic aid, should only be utilized as part of a larger psychotherapeutic program. It is an illusion to look for the magic pill which will represent the final solution to the problems of mental illness.

Imipramine deserves the extensive clinical appraisal and testing it will undoubtedly receive. The indications at present are that it is most effective in relieving depressed states, but it may have a much wider range of usefulness in the relief of pain, in geriatric cases, in organic confusional states, etc. In this small series of patients the results were poorest in those patients who manifested marked schizoid features in the total picture of the illness.

The mechanism of action is not clear. From the clinical response alone, imipramine appears to behave more like a sedative than a stimulant. As previously noted, it does not interfere with sleep, and can in fact be taken at or near bedtime. It resembles chlorpromazine in certain respects, but without the reduction in motor function or the general inhibition seen with the ataraxics. Imipramine behaves like a sedative, but characteristically appears to facilitate verbal flow and general motor activity. The problem of addiction cannot be assessed until this drug is used over a much longer period of time.

SUMMARY

Imipramine (Tofranil) is described as a safe, effective antidepressant drug.

Clinical observations are reported on its use in 26 depressed patients from private practice. A recovery or marked improvement rate of 80% is obtained in this series.

No significant toxic side effects were seen. Imipramine appears to be safe in doses which are clinically effective.

Extensive clinical trials are warranted. It appears to the author to be the most promising drug ever to appear for the relief of states of depression. The development of specific indications for its use, and proper selection of patients, will reduce the need for hospital admission, electroshock and other ancillary measures.

The Tofranil was kindly supplied for investigation by Geigy Pharmaceuticals.

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RÉSUMÉ

L'auteur décrit les résultats que donna l'imipramine (Tofranil *marque déposée*) dans le traitement de la dépression chez 26 cas de ville. Une forte amélioration fut obtenue dans 80% d'entre eux. Il n'observa aucune manifestation toxique. L'imipramine peut être employée sans danger en doses thérapeutiques. Bien que ce médicament doive encore être l'objet de recherches cliniques étendues il semble à l'auteur que, dans le traitement des états dépressifs, ce soit le produit le plus efficace qu'on ait obtenu à date. Lorsqu'on aura déterminé les indications précises de son emploi ainsi que le genre de malades auxquels elle convient le mieux l'imipramine diminuera le nombre d'admission aux hôpitaux, le besoin de recourir aux électrochocs ainsi que l'application des mesures accessoires.

ASPIRIN STATISTICS IN THE SPACE AGE

"According to the U.S. Department of Commerce, production of acetysalicylic acid in 1958 reached an all-time high of 20 million pounds. At the rate of 7000 grains to the pound, five grains to the tablet, this could be translated into about 28 billion aspirin tablets or 14 billion aches. From the present state of the world, we would guess this to be a conservative estimate. For additional arithmetic doodling, a standard aspirin tablet would be seven-sixteenths of an inch in diameter and one-sixth of an inch thick. End-to-end, then, our billions of aspirin tablets would circle the world just about eight times. One on top of the other they would make a very unstable column reaching more than one-fourth the distance to the moon."—*Drug and Cosmetic Industry*, January 1959.