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# TOXICITY OF IMIPRAMINE: REPORT ON SERIOUS SIDE EFFECTS AND MASSIVE OVERDOSAGE*

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RECENTLY a new and potent agent has been introduced for the treatment of depressive illnesses. This compound, N-(3-dimethylaminopropyl)-iminodibenzyl hydrochloride (imipramine or Tofranil†), is similar in structure to the phenothiazine compounds, differing only in the introduction of a two carbon chain in place of the sulphur atom of the phenothiazine nucleus. From the neuropharmacological point of view, however, imipramine is decidedly different from these "tranquillizing" drugs. It has been found to be a powerful antidepressant, whose action seems considerably more reliable and of greater efficacy than that of any agent hitherto used for chemotherapy of the depressive syndrome.

It is the authors' belief that clinical experience to date has established to a reasonable degree the usefulness of this preparation in dealing with the classical "endogenous" depression and, to a lesser extent, the so-called "neurotic" or "reactive" depression.[2-4] Whether this initial enthusiasm will be followed by a later wave of discouragement, as has happened in the past with so many widely heralded "wonder drugs", remains to be seen. Certainly imipramine is not expected entirely to displace electroconvulsive therapy for the acutely ill, actively suicidal patient, but it is proving a most useful agent in the treatment of a fairly broad spectrum of depressive illnesses. Its success is also stimulating new lines of investigation and bringing about a reappraisal of the conceptual framework underlying this whole vast and somewhat amorphous field.

Thus far, imipramine has been handled principally by clinical investigators, but results would seem to justify its being made available for general use. Since depressive illnesses are so commonly observed as a part of everyday medical practice, one may assume that very considerable quantities of this drug will be dispensed on an office basis and that its widest usage will come, not from the psychiatrist, but from the general physician.

With the introduction of any new drug capable of modifying behaviour, two concomitant phenomena inevitably seem to accompany its wide acceptance: (1) overdosage, either intentional or accidental; (2) the occurrence of side effects of major or minor importance.

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## 1. MASSIVE OVERDOSAGE

With any drug prescribed widely for depressed patients, overdosage is much more likely to occur purposefully than accidentally. Deliberate overdosage may occur to produce intoxication or euphoria, or to attempt suicide. As imipramine has no euphorizing effect, widespread abuse of dosage level seems unlikely for this purpose, but there is always the possibility of its use in attempting suicide. The following is a report of such an incident. To our knowledge, it is the first such case of massive overdosage.

### CASE REPORTS

CASE 1.—Mrs. P., 21 years old and weighing 107 lb., was being treated on the in-patient service of the Department of Psychiatry of the Montreal General Hospital. The diagnosis was "depressive reaction associated with a character disorder". She was being given psychotherapy and tranquillizing agents, but had received no imipramine.

Having secretly stolen a bottle of one hundred 25-mg. tablets of imipramine from a doctor's office, the patient first ingested six 25-mg. tablets at about 7.45 p.m. She then had tea and toast with the other patients and at about 8.45 p.m. ingested the remainder of the pills, making a total intake of 2500 mg. of the drug. A few moments later she informed a nurse of what she had done. On initial examination at 9.15 p.m., she was slightly drowsy but able to recount what had happened. It was felt that the urgent need for gastric lavage precluded full examination at that time, and the lavage was accordingly carried out between 9.15 and 9.45 p.m. On insertion of the gastric tube, the patient began to vomit and the combined effect of the lavage and the vomiting gave us the impression that the stomach was effectively emptied. Inspection of the vomitus revealed no intact tablets. Since the vomitus was not saved for analysis, it is not possible to tell exactly how much of the ingested imipramine was actually absorbed. After the lavage, the patient apologized for causing trouble, thanked the doctor and walked unaided back to her room. Fifteen minutes later (10 p.m.) she became unconscious.

On examination at this time, colour was good, skin pale, warm and dry, but mucous membranes moist. Blood pressure was 90/50 mm. Hg (normal for this patient); pulse 120 per minute, full and bounding. Pulsations, both arterial and venous, were strikingly visible in the neck. Respirations were 32 per minute, deep and stertorous. The patient by this time was stuporous but responded to any stimulation by becoming restless. When her name was called she could open her eyes and stretch out her arms, with marked ataxia, but made no sound. She withdrew briskly from any skin stimulation. Any stimulus—sound, skin stimulation, even changes in the room lighting—would increase her restlessness. Pupils were dilated but responded to light with a brisk though small contraction. Deep tendon reflexes were all markedly hyperactive but were bilaterally symmetrical. It was our impression that bilateral Babinski responses were present, although this was difficult to ascertain because of the brisk withdrawal response.

Having no precedent to guide us, we decided simply to observe the patient closely and treat whatever

symptoms developed. Vital signs were recorded every 15 minutes throughout the night.

The next hour (2-3 hours after ingestion) was marked by a decrease in the level of consciousness and an increase in sensitivity to stimuli. The patient was quiet unless disturbed by stimulation, and it was noted that the eyes were moving back and forth. At 11.10 p.m., during the course of physical examination, the patient had a clonic-tonic, bilaterally symmetrical, grand mal seizure lasting 10 seconds. This convulsion appeared to be directly related to stimulation during examination. Respiration, resumed immediately after cessation of the convulsion, was shallow for the first few breaths, then deep and regular. The patient was much quieter after the seizure. She was then given an intramuscular injection of amobarbital sodium, 7½ grains (0.5 g.), following which she was catheterized and about 200 c.c. of urine obtained. The room was then darkened and kept as quiet as possible.

The period of maximum depression of function was between midnight and 1 a.m., i.e. four to five hours after the first (small) dose of imipramine had been ingested. At 12.30 a.m., B.P. was 80/50 mm. Hg and the pulse rate had risen to 110 per minute, while the respiration rate had fallen to 20 per minute, excursions becoming more normal at this point. By this time the pupillary response to light was also of greater magnitude. At 2 a.m. (six hours after ingestion) the patient could open her eyes when called by name. By 3.30 a.m. (7½ hours after ingestion) the patient could move her arms and legs when spoken to, and by 6 a.m. she was fully awake, complaining that her arms were stiff and painful. She then asked for a drink and a cigarette, was given some juice, and complained of a sore throat.

The following day the patient was very drowsy and slept all day, but was easily roused, was well oriented (except as to the exact hour), and asked spontaneously whether the other patients knew what she had done. During that day, slight ataxia of the arms was noted, along with intermittent choreiform movements of the arms and a tremor about the mouth. She was given 1 grain of amobarbital sodium 3 times on that day. Temperature, not recorded during the acute phase, was noted on the day following the poisoning to be slightly above her normal base line, reaching a maximum of 99.4° F.

Thirty-six hours after ingestion of the drug, the patient appeared to have completely recovered. Her only complaint was of pain and tenderness in both biceps tendons, a complaint which may have been related to the seizure.

Questioned as to her recollection of events, the patient stated that her last clear memory was of telling the nurse she had taken the pills. She had no memory of subsequent happenings until the afternoon of the day following her suicidal attempt.

Urinalysis revealed the presence of free imipramine and a number of other abnormal constituents which were not clearly identified.

*Comment.*—It is impossible to say how much of the drug was actually absorbed in the above case, but it would seem safe to assume that it was a quantity much larger than the usual therapeutic dose. In large doses, imipramine is known to produce a mixture of central nervous system depression and stimulation, closely resembling intoxication with antihistamines.[1]

In our patient, the higher centres were depressed, while the vital centres were stimulated. Pulse and respiration increased in rate and magnitude. No fall in blood pressure was noted until after the administration of barbiturate, and even then the hypotension was only slight. This was surprising in view of the very frequent occurrence of hypotension as a side effect at therapeutic dosage level.

It should be noted that this was a young, physically healthy patient with no cardiovascular disease. The rapid, bounding pulse in this case gave us the impression of a much increased cardiac output. Had this been superimposed on an already strained cardiovascular system, the outcome might have been much more serious.

The other principal danger seen in this case arose from a convulsion. It would seem that important points to remember in the treatment of imipramine poisoning are:

1. Reduction of all external stimuli to a minimum, keeping the room quiet and dark, and if possible avoiding physical manipulation of the patient.
2. The use of barbiturates, where necessary, to prevent convulsions.

## 2. Major Side Effects and Untoward Reactions

Side effects, if minor, need not necessarily detract from the therapeutic effectiveness of the drug, and may indeed be unavoidable by the very nature of the compound concerned, being only something of a nuisance to the patient. With imipramine, these minor side effects are very common and need not be detailed here.[2-4]

However, the presence of more serious reactions – reactions which may temporarily or permanently damage or incapacitate the patient – is certainly a phenomenon which carries with it the extreme necessity for:

1. Awareness of such a possibility.
2. Great caution in prescribing the agent in susceptible individuals.
3. Close and continuous personal supervision by the physician of all patients for whom the drug is prescribed.

In the cases detailed below, we do not feel that it is possible to trace a direct causal linkage between administration of the drug and the serious manifestations observed. It may well be that the conditions thus produced are only coincidental and that one cannot exclude other etiological possibilities. Nevertheless, it is felt that imipramine should be held suspect until disproven, or until the drug has been given a much wider usage without such cases being reported, i.e., we feel it is wiser to err on the side of caution and conservatism. It should be noted further that these are the most serious reactions to date in a series of some 150 cases at the Montreal General Hospital. Proportionally, therefore, the number of these reactions

is not great, but the severity is such that close scrutiny should be given to them at our present level of knowledge of this drug's action.

CASE 2.—Mr. F.G., a 63-year-old successful business man, was in good health until three weeks before admission, when he developed an acute depressive reaction with marked agitation. Symptoms were typical and classical for this type of illness. Functional inquiry did not reveal any significant findings in relationship to any of the organ systems.

He was a well-developed, well-nourished man, looking considerably younger than his stated age and in very obvious emotional distress. Blood pressure was 130/80 mm. Hg, pulse rate 80, showing a mild sinus arrhythmia. These findings were confirmed by a consultant in internal medicine, who noted that this man appeared physically about 10 years younger than his actual age. The patient was initially given three electroconvulsions to deal with his acute suicidal depression and agitation. Simultaneously, he was given imipramine, 200 mg. per day. Results from the combination of these two treatments were excellent. Depressive symptoms cleared remarkably well within three weeks of admission. The patient was making plans to return home when, on July 27, he began to complain of pain over the 10th to 12th ribs, two inches from the midvertebral line, increased on deep breathing. Physical examination at that time revealed tenderness in the above-mentioned area along with impaired aeration at the left base and the presence of numerous rales in the left base area. No pleural rub was noted. Temperature was 99° F. at this time. Radiographic findings were consistent with a pneumonia at the left base. Antibiotic treatment was immediately instituted, and imipramine therapy continued at the same dosage level.

The patient seemed to be recovering from this "pneumonia" when, on August 5, he complained of more chest pain than usual and spiked a fever of 100.4° F. He was seen again by a medical consultant who noted dullness, and in view of the recently developed hæmoptysis and the physical findings, made a diagnosis of multiple pulmonary emboli. He was immediately transferred to the medical service and anticoagulant therapy was initiated. On August 5, the radiographic findings suggested "an increased pleural effusion with small right pleural effusion which has appeared since the last examination". Imipramine therapy was discontinued on this day.

The patient's temperature subsided during the next five days with the continuation of antibiotic and routine anticoagulant therapy, and general symptoms continued to improve steadily. Anticoagulant therapy was gradually discontinued and finally stopped on August 14. On this date imipramine, 150 mg. per day, was recommenced. The patient began graduated activity, and it was considered that he could leave hospital in the near future. On August 22, having been thought ready for discharge that day or the next, he was found dead in his chair.

An autopsy was performed. Pathological findings included massive pulmonary embolism with: (a) loose thrombi in right ventricle, (b) bilateral lower lobe pulmonary infarct, marginally organizing.

Associated conditions were: (1) lower lobe pulmonary congestion, bilateral; (2) left pleural effusion (100 c.c.); (3) aortic atherosclerosis, moderate; (4) diffuse colloid goitre; (5) remote appendectomy with paracæcal adhesions.

A source of embolism was not demonstrated. The emboli suggested an origin in large veins but the lower limbs, in which there was no external evidence of phlebothrombosis, could not be explored.

*Comment.*—This 63-year-old man, previously organically quite sound, developed during the course of imipramine therapy small multiple pulmonary emboli which responded to treatment, concurrent with the discontinuation of imipramine. After discontinuation of anticoagulant treatment, imipramine therapy was resumed and the patient eventually died of a massive pulmonary embolus. It is worth noting that this was one of our patients who showed a very pronounced hypotensive effect with the initial administration of imipramine. One wonders whether the hypotensive effect in this case might possibly have precipitated thrombus formation with subsequent embolic development.

CASE 3.—Mrs. A.B., a 35-year-old housewife, was admitted to hospital on July 18, 1958, with a diagnosis of "depressive reaction". Chief complaints were of sleep difficulty, excessive fatigue, anorexia, and weight loss of 30 lb.

Functional inquiry was essentially negative. Of her bowels, she said "they go too much — it's not quite diarrhœa" (three bowel movements a day). Before the presenting illness her bowels had moved regularly once a day.

She was a thin, attractive little woman in no acute distress. The only significant finding was a very flaccid abdomen with a midline Cæsarean scar.

The patient was started on imipramine on the usual dosage schedule with a maximum of 200 mg. per day. Routine laboratory examinations, including alkaline phosphatase determination, urinalysis, white cell count, and fasting blood sugar determination, gave results within normal limits.

The patient progressed favourably on imipramine and subcoma insulin therapy from the time of admission until some four weeks later (August 15). On this day, for the first time, she had no bowel movement. The next day she required an enema, but still had no spontaneous bowel movement until August 23.

Medical consultation on August 18 revealed abdominal distension with moderate right lower quadrant tenderness. The rectum was empty. The next day, a consulting surgeon noted the presence of a supraumbilical hernia which was tender and could be reduced. A non-tender mass, about 5 cm. by 2 cm. in diameter, was also noted in the right lower quandrant.

The patient was carefully observed over the course of the next few days. Radiographs of the abdomen in the supine and upright positions showed the presence of considerable gas and fluid within the small and large bowel, and the possibility of a bowel obstruction was raised but not considered likely.

Laparotomy was performed on August 23. A pocketing of peritoneum into the posterior wall of the abdomen on either side of the linea alba was noted. The excess of stretched linea alba in this area was excised and the epigastric hernia was reduced. Exploration of the abdomen showed that the colon was filled with scybalous fæcal material. Diagnosis was made of

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"epigastric supra-umbilical hernia". The postoperative course was uneventful, and the patient was discharged with her surgical condition cured and her psychiatric condition much improved.

*Comment.*—This patient had no previous history of constipation, and one may presume that the constipating effect of the imipramine was a factor in precipitating her partial intestinal obstruction. It is postulated that the increase of intra-abdominal pressure may have thus made evident a defect in the already weakened abdominal wall. The pattern of this patient's constipation was the most severe of that noted in any of the patients studied, although constipation was one of the commonest side effects seen.

CASE 4.—Mrs. R.E., a 52-year-old French Canadian with lifelong emotional difficulties, was admitted to the Montreal General Hospital on November 19, 1958, with a diagnosis of depressive reaction. Weight on admission was 100 lb. In addition to the psychiatric difficulty, she described mild shortness of breath for the past 10 years, especially when under severe stress and strain. She noted difficulty in walking into the wind, but reported no difficulty in walking up to a religious shrine equivalent to climbing some 10 flights of stairs. She reported occasional mild swelling of her feet in hot weather, but there was no mention of orthopnœa or paroxysmal nocturnal dyspnœa.

Physical examination at that time revealed no facial or ankle œdema. There were scattered moist rales at both bases. The heart rate was 88 per minute, periodically irregular with multiple extrasystoles. Blood pressure was 118/80 mm. Hg. Five days after admission her weight was 95 lb. On November 29, 10 days after admission, the patient was started on imipramine in a dosage schedule of 50 mg. 3 times a day intramuscularly, gradually increased to 200 mg. per day in divided doses by mouth. Two days after the initiation of imipramine therapy, the patient's weight was 102 lb. Imipramine had produced increased agitation, activity and apprehension to such an extent that by December 3, dosage was reduced to 25 mg. 3 times a day for two days, and the drug was discountinued on December 5.

On December 8, the patient was in acute congestive failure. The medical consultant stated that the striking physical findings were marked dyspnœa, orthopnœa, distension of the jugular veins, a huge heart with a mitral systolic murmur, crepitations at both lung bases and possibly a large right pleural effusion. The liver was enlarged, there was marked ankle œdema, and by this time the patient's weight had reached 112 lb.

Laboratory findings during this period were as follows: urinalysis negative, fasting blood sugar 80 mg. %, alkaline phosphatase 4 units per 100 ml., blood urea nitrogen 12 mg. %. On December 9, the hæmogram showed 13,600 white blood cells with a shift to the left.

The patient was transferred to the medical service, where investigation of her heart disease showed it to be of a rheumatic type. A mitral commissurotomy was performed and the patient is now well.

*Comment.*—The close temporal relationship between the initiation of imipramine therapy and the onset of the congestive failure would indicate that this condition might well be a complication of imipramine therapy, although we are aware that such conditions can be precipitated by emotional stress *per se*. Further, consideration should be taken of the fact that in an agitated depression, under any form of treatment, one of the chief dangers is acute cardiac failure from overactivity and exhaustion. Nevertheless the imipramine therapy would seem to us to be implicated in the onset of this condition.

CASE 5.—Mr. J.R., a 59-year-old retired chef, was admitted to the medical wards of the Montreal General Hospital on September 12, 1958. His complaints were multiple, but the most prominent symptoms were "burning and boiling" in his abdomen, nervousness, loss of appetite, bad taste in his mouth, weight loss, insomnia, and low back pain. His ill health dated back about 12 years. At that time he had noticed a gradually increasing shortness of breath. The patient then developed a chronic cough which had continued for 10 years. He had had severe low back pain relieved only when he sat hunched over in a chair. He had felt markedly worse three years before admission when his wife, 20 years his junior, became very ill at confinement and lost one baby of a set of twins. After this he became so depressed and worried that he was unable to work and in fact has not worked since that time. During the three years before admission, in addition to the above-mentioned gastro-intestinal complaints, he had suffered from a feeling of despondency, loss of appetite, and difficulty in sleeping. There was a progressive weight loss, more marked in the last six months (35 lb).

He stated that in the three-year period before admission he had been seen by at least 50 different physicians, receiving huge quantities of various medications, and it was felt that admission for thorough investigation of his complaints was indicated.

Despite his decreased exercise tolerance, the patient had neither orthopnœa nor paroxysmal nocturnal dyspnœa. He was able to walk two blocks or ascend several flights of stairs before becoming short of breath, and denied swelling of his ankles. On admission, he was nervous and jumpy but in no respiratory distress. No jaundice, cyanosis or lymphadenopathy was present. Pulse was 86 per minute and regular; blood pressure 160/90. No cardiac abnormality was found. The antero-posterior diameter of the chest was increased and expansion decreased. There was no dullness on percussion. Breath sounds were normal. The liver was palpable two fingers' breadths below the right costal margin, firm and non-tender; the spleen was not palpable. Laboratory examinations were essentially negative; fasting blood sugar 89 mg. %, blood urea nitrogen 10 mg. %, bilirubin 0.3 mg. %, alkaline phosphatase 5 units, cephalin flocculation negative. A chest radiograph was reported as normal, as were the cholecystogram and intravenous pyelogram. The electrocardiogram showed a right bundle branch block.

The patient was seen by the psychiatric consultant, who stated that: "The patient is suffering from a disabling amount of anxiety and depression which, I feel, is affecting his physical condition. Sedation and supportive psychotherapy are indicated. I suggest a trial of imipramine. Diagnosis: depressive reaction."

Imipramine therapy was started on October 7, 1958, with an initial dose of 50 mg. per day orally, increasing over four days to 50 mg. 4 times a day. He was discharged from hospital on October 10, 1958.

The patient was followed up in the psychiatric outpatient department and showed slight improvement. His depression appeared to be lifting, but he was becoming more anxious. Chlorpromazine, 50 mg. 4 times a day, was started on October 24. On November 7, it was stated that "the patient is scarcely recognizable to me today. He appears physically ill in some way. His eyes are bulging, his lips blue, and he is so nervous he can barely talk, and can walk only a few faltering steps. He says he feels much worse than before and is ready only for his grave."

Imipramine was discontinued at this point. He was admitted to the psychiatric ward on November 17, 1958, with marked blueness about his lips, earthy colour, and laboured respiration with a short inspiratory phase and a prolonged expiratory phase. The liver, palpable four fingers' breadths below the right costal margin, was smooth and slightly tender. Heart sounds were distant, blood pressure was 160/95 mm. Hg, rate 72, regular. The patient had "two pillow" orthopnœa, pitting œdema of the right ankle and leg, and pitting œdema of the left ankle. In short, he was obviously in congestive heart failure. An electrocardiogram showed right bundle branch block (no change from previous admission). The patient's congestive failure was treated with the usual measures: digitalis, diuretics, and low salt diet, and his heart failure cleared.

*Comment.*—This patient undoubtedly had preexisting cardiovascular disease. He tolerated 200 mg. of imipramine for some time, but it seems likely that the combination of imipramine and chlorpromazine with their combined hypotensive effect may well have overstrained his already shaky cardiovascular system. In addition, a sodium-retaining effect may have been a factor in this case.

## DISCUSSION

We have detailed in this paper certain severe reactions associated with the use of a promising new antidepressant drug. This does not, of course, exhaust the range of individual untoward reactions from this agent. It may well be that future controlled studies will disclose an increasing number of conditions under which this drug should be contraindicated or prescribed with exceeding caution. There is some clinical evidence to suggest the possibility of imipramine's having an influence on sodium and water retention and also of its being involved in the production of certain cardiac arrhythmias, in cases not mentioned here. Further, there is the as yet unanswered question of its effect on the convulsive threshold, especially in patients with latent epilepsy.

On the basis of our experience to date, we do not feel entirely safe in prescribing imipramine for any patient with definite cardiovascular disease, especially where the possibility of the patient's developing congestive failure is present.

Hypertension without marked systemic effects does not appear to be a contraindication; in fact, imipramine has appeared to be of considerable benefit in certain severe cases. However, the possibility of a precipitous blood pressure fall in such individuals must be continually kept in mind. Even more does this apply to cases in which both imipramine and phenothiazine derivatives are being used, the latter to control anxiety and agitation.

Our chief purpose in presenting these unfavourable reactions is to make a plea for a reasonable amount of discrimination in the prescription of this new drug. Properly used and with close and careful supervision of patients, it has great potential. This drug—or its related successors—may well have inaugurated a whole new era in the treatment of the depressive illnesses. It would be a pity to see its therapeutic promise dissipated by over-eager use without due regard for its limitations and hazards.

It behoves us to remember that the use of an antidepressant presupposes a depressed patient; the danger of suicide is always present and not always easily discernible. Imipramine treatment should not be instituted unless the patient can have the benefit of the doctor's own personal and continued appraisal of progress, without which the use of drugs to influence behaviour becomes meaningless.

## SUMMARY

Overdosage with suicidal intent and serious side effects are seen as almost inevitable concomitants of the widespread use of any drug introduced for the treatment of depression.

Case histories are presented in which imipramine, a new and potent antidepressant, was associated with attempted suicide, onset or aggravation of cardiovascular complications, and the production of a partial intestinal obstruction with herniation.

The need for careful selection and evaluation of patients before prescribing this drug is stressed.

Imipramine is felt to hold considerable therapeutic promise, but toxic reactions of alarming severity may be noted unless the drug is used subject to the physician's careful supervision of his patients.

The presence of definite cardiovascular disease (apart from hypertension) would seem at least a relative contraindication for the use of this drug.

A method of management of massive overdosage is described.

We wish to thank Dr. A. E. Moll, Chairman, Department of Psychiatry, Montreal General Hospital, for permission to publish.

### REFERENCES

1. BENSLEY, E. H. AND JORON, G. E.: Handbook of treatment of acute poisoning, E. & S. Livingstone, Ltd., Edinburgh, 1958, p. 59.
2. KUHN, R.: *Am. J. Psychiat.*, 115: 459, 1958.
3. LEHMANN, H. E., CAHN, C. H. AND DE VERTEUIL, R. L.: *Canad. Psychiat. A. J.*, 3: 155, 1958.
4. MANN, A. M. AND MACPHERSON, A. S.: *Ibid.*, 4: 38, 1959.

RÉSUMÉ

C'est le sort presqu'inévitable des médicaments communément employés dans le traitement des états dépressifs, de servir un jour ou l'autre d'instrument de suicide. Ce risque s'ajoute aux autres incidents du traitement, souvent graves, qu'ils peuvent présenter. On relate les faits cliniques de cinq cas dans lesquels l'imipramine, un nouvel agent antidépressif puissant, a servi dans une tentative de suicide, a provoqué le début ou l'aggravation de complications cardiovasculaires et a donné lieu à une occlusion intestinale partielle avec herniation. Il importe donc de bien choisir les malades à qui on prescrit ce produit. L'imipramine semble posséder un avenir thérapeutique prometteur mais elle peut entraîner des réactions toxiques d'une gravité alarmante si le médecin n'exerce une surveillance étroite de ses malades. A part l'hypertension, une atteinte cardiovasculaire bien établie semblerait une contre-indication au moins relative. Les auteurs indiquent la conduite à suivre en présence d'intoxication par doses excessive.

# BISACODYL (Dulcolax) IN PROCTOLOGY

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THE CLINICAL EVALUATION of a new laxative compound is of interest to the medical profession in general but is of the utmost interest to the proctologist. In proctology, the complete evacuation of the bowel is essential for a thorough examination. Endoscopy requires the emptying of the colon without irritation of the rectal mucous membrane. Thus at the present time the usual procedure for preparation for a proctosigmoidoscopy is to give an evacuating enema with plain boiled water. However, very often the enema must be repeated in order to clean the sigmoid out completely. Incomplete preparation of the colon or alteration of the mucous membrane may lead to errors in diagnosis.

Pharmacological studies of the new contact laxative bisacodyl or Dulcolax* [Bis(p-acetoxyphenyl)-2-pyridylmethane] were carried out by Schmidt,[2] who showed that bisacodyl acts directly on the colonic mucosa, stimulating peristalsis. The drug does not depend for its action on systemic absorption and has little effect on the small intestine. The usual toxicity associated with absorbed substances is not encountered. Our interest in this drug was stimulated by reports in the literature on the use of this drug in preoperative and postoperative cases,[1, 7] in preparation for x-ray examinations,[3, 4, 6, 8] and in geriatrics.[9] In addition, our constant search for a simplified means of emptying the bowels before sigmoidoscopy without accompanying irritative production of mucus, prompted us to initiate a clinical investigation of bisacodyl.

## METHOD

Eighty-six patients took part in our clinical investigation of bisacodyl. The diagnoses included pruritus ani, fistula, fissures, hæmorrhoids and polyps. A variety of tablet-suppository combinations were prescribed in order to determine the most effective combination. Tablets were administered on the night preceding the examination, and suppositories were administered on the morning of the examination. Six different groups were set up according to the method of administration as follows:

Group I: 17 patients (2 suppositories, 2 tablets)
Group II: 11 patients (1 suppository, 2 tablets)
Group III: 2 patients (2 tablets)
Group IV: 10 patients (2 suppositories)
Group V: 12 patients (1 suppository, 1 tablet)
Group VI: 34 patients (1 suppository)

Adequacy of bisacodyl medication was judged according to both objective and subjective factors. Objective evidence of adequacy was given in terms of thoroughness of colonic emptying and absence of hyperæmia. Subjective adequacy was in terms of freedom from cramps and other distress. The following criteria incorporate all these points:

*Excellent.*—When examination confirmed that the colon was thoroughly emptied, and that the mucous membrane was free of all erythema, such as might result from irritation of tissues following the use of an irritating laxative or a distressing intestinal evacuation.

*Satisfactory.*—When examination confirmed a thorough emptying of the colon, but there were traces of mucus or erythema, or the patient complained of cramps or sensation of intestinal burning.

*Incomplete.*—When some factors unrelated to the laxative prevented completion of the examination.

## RESULTS

Results are summarized in Figs. 1 to 6. Groups V and VI show excellent results. Group V patients received one suppository and one tablet; Group VI received one suppository only. The reason for the rather high incidence of less than excellent results in those groups receiving two suppositories was the presence in some of slight mucosal alteration. Therefore, in cases where it is especially important that the mucosa show no artificial alteration, we prescribe a single suppository. For most purposes, however, we prefer to administer two suppositories, since in an occasional case the administration of a single suppository will not result in complete evacuation.

*Registered trade name, Geigy Pharmaceuticals.