Arizona

HISTORICAL EVOLUTION OF ANTIDEPRESSANT DRUGS

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When I started on my medical career as a student, the treatment of depressed patients had progressed no further than the treatments available to Emil Kraepelin when he introduced the concept of manic-depressive disease toward the end of the 19th century. Kraepelin had labeled the disease manic-depressive psychosis because in his time, psychiatrists were working almost exclusively in mental hospitals, and depressed patients who were hospitalized in those days were only the most severe type - endogenous depressions and what we then called involutional melancholias - and usually psychotic. Less extreme cases of depression were not even identified as being really ill. Perhaps they were seen by a family doctor who might give them a tonic and prescribe "rest" or a trip to help them see things in a better light. Or - antitherapeutically - they were admonished to count their blessings and look at the brighter side of life. A few would receive psychotherapy of very questionable efficacy.

One retrospective study of the outcome of depression in the late 30's, before the introduction of any antidepressant treatment including ECT, reported on 100 patients diagnosed as depressed. The duration of their episodes ranged from three months to 11 years. Only one in three recovered within a year. One out of four took more than 2 years to recover.[1] Other authors have reported complete, spontaneous recoveries occurring as long as 13 years after onset.[2] It is noteworthy that even then about 15% remained chronic and did not recover at all - the same percentage as today.[1] Apparently, all of today's treatments have served only to reduce the frequency, duration and severity of

symptoms and the mortality by suicide, but have not been able to touch the "hard core" 15 per cent. What most of us do not realize today is that during those years depressed patients often reached a pitiful state and stayed there for a long time. Emaciated, pale, stuporous, mute and motionless, they blended in with the vegetating chronic schizophrenics who populated the backwards of mental hospitals. Their final diagnosis often was dementia. There are, of course, no epidemiological data available for the millions below the tip of that iceberg, whose depressions were not diagnosed in those days, that is until the 1940's.

One time-honored treatment that often gave a little relief to depressed patients then was tincture opii, starting with a few drops a day and increasing the dose gradually over weeks or months. This treatment allayed some of the worst distress and agitation - perhaps for a few weeks. It also would produce stubborn constipation. It would, unfortunately, have no effect on the depressed mood, psychotic manifestations or suicidal tendencies. Interestingly, in the patients I treated, I never observed the development of dependence on opium and eventually, the patients could be easily, though gradually, weaned from the drug without withdrawal symptoms.

Among other early attempts at pharmacotherapy we tried photosensitizing hematoporphyrin[3], dinitrile succinate[4], methedrine[5], testosterone[6] and nicotinic acid[7], for which claims as antidepressants had been made - but, as always, the results were disappointing.

Other treatments recommended included nitrogen-induced anoxia[8] and X-ray irradiation of the skull[9]. We tested the idea that inhalation of nitrous oxide -"laughing gas" - might work as an anitdepressant, and made some interesting observations. It produced instant dreams, leading to interesting speculation on dynamics, but no cure for depression.[10]

In the early 1950's, the medical world was dazzled by the discoveries of ACTH and cortisone. ACTH was also suggested as a therapy for depression,[11] because it was widely believed at first that adrenocortical function was reduced in depressed patients. I had the opposite intuition - that the adrenocortical system was, in fact, hyperactive in depressed states - and as we all know today, research in recent years has proved that to be the case. The important point is that ACTH was not an effective treatment for depression.

The concept of convulsive therapy was first conceived in 1936 by Meduna, the Hungarian psychiatrist who had the courage to translate the concept of convulsive treatment into practice by the only means available to him at the time: intramuscular injections of large doses of camphor dissolved in oil. That produced convulsions alright, but the trouble was that it took many minutes, sometimes more than an hour, before they occurred - without warning, and it happened often when the patient was no longer lying down.

This therapy was soon replaced by intravenous injections of metrazol which took only a few seconds to produce a convulsion. However, during this short period, until a sufficiently high concentration of metrazol had reached the brain, to produce

unconsciousness, the patient suffered indescribable agony and abject terror. Many patients had to be pulled out from under beds and other hiding places when they were scheduled for follow-up treatment. One of our patients, a schizophrenic, anticipating his third metrazol injection, actually committed suicide, leaving a note saying that he could not go through the experience again.

By the time Cerletti and Bini started to induce convulsions by electricity and ECT emerged, two years later, guilt - or at least ambivalence after having witnessed patients' reactions to metrazole - had driven me to a firm stand against having an "electric chair" in our hospital. However, it was soon becoming clear that convulsive treatment was indeed dramatically effective in cases we had been virtually unable to treat before, in particular involutional melancholias. Only when I was convinced that patients did not suffer from the new version of convulsive treatment, did I manage to overcome my reluctance. But now another discouraging complication came to light: fractured thoracic vertebrae, as a result of the convulsions - a complication which made us wonder whether we should abandon ECT altogether.

Then came curare, looked upon then as a rather mysterious, exotic arrow poison from the jungles of the Amazon River. As near neighbors to the Montreal anaesthetist who introduced curare as a medical intervention, we were among the first to use this substance to attenuate the muscular contractions brought on by ECT. Curare - and later succinylcholine - eliminated spinal fractures and, in combination with barbiturate anesthesia,

atropine and oxygen-bagging rendered ECT quite safe.

ECT thus became the first really effective treatment for depression and, strangely enough, it still is the treatment to fall back on in those cases that call for our heaviest artillery. But the strange - and somewhat scandalous - thing is that, after almost half a century of clinical use, we still do not know how or why it works.

Of course, the dramatic remissions of ECT do not always last and sudden, unexpected relapses may be dangerous. In the early days of ECT, we profited from the insight into endocrine mechanisms we had gained from the study of cortisone and we developed a test - today we would call it a biological marker - that would warn us of an impending relapse. The test was then the "state of the art" but would be considered today very primitive. Since we had at that time no method to measure cortisone levels directly, we used the indirect method of counting eosinophils in the blood. We established a rule that depressed patients had to remain in the hospital for at least two weeks after their last ECT and could then be discharged only, if the eosinophil count had reached a certain level which indicated that their adrenocortex was no longer hyperactive.[12] (Fig. 1)

The period of futile therapeutic trials was over. The era of the heroic, but still controversial, convulsive treatment was in full swing. We were now impatiently awaiting the age of antidepressant chemotherapy. We had just witnessed the utterly surprising breakthrough of the antipsychotic drugs. I argued often with detail men and research directors of pharmaceutical companies that, since we now had drugs to suppress hallucinations

and delusions - something not even dreamed of a couple of years earlier - there must be some drug to counteract depression. After all, depression is usually self-limited, and therefore even more likely to have a biological substrate than psychosis.

In 1957 I attended, along with hundreds of others, The 2nd Congress of the World Psychiatric Association in Zurich. The meeting was dominated by discussion of existential psychiatry, with enthusiastic response from European psychiatrists and considerable bafflement on the part of our American colleagues. The highlight of the congress was one of Carl Jung's last public appearances. A modest presentation by the Swiss psychiatrist Roland Kuhn of the first public report on the antidepressant effects of imipramine, produced by Geigy, was attended by an audience of "barely a dozen people" - not including myself.

Actually, an internal report had been made a year earlier to Geigy which was ignored. On my flight back to Canada I read Kuhn's paper, just published in a Swiss medical journal, and was very impressed by his results. As soon as I arrived home I phoned the Canadian representative of Geigy to tell him I wanted to work with the new drug. But in Montreal nobody at Geigy's had heard of imipramine, although Kuhn had told the company a full year earlier that his observations indicated the antidepressant potential of this drug as being "of the utmost practical importance." Apparently, this message did not get through.

After a flurry of telex and cable messages, a supply of imipramine arrived and we immediately began a clinical trial in Montreal, with 84 patients.

Actually, Kuhn had been exploring possible antipsychotic or hypnotic effects of imipramine because of the similarity of its chemical structure to chlorpromazine, the archetype of the antipsychotics. He found it had neither antipsychotic nor hypnotic properties - but, being a brillant clinical observer, he did note that it exerted a consistent antidepressant action, giving not merely fleeting symptomatic relief.

At that time, 1957, there were barely any governmental restrictions on the use of new drugs - nor any institutional review boards.

The ethics, the responsibility and the clinical competence were the bailiwick of the clinician who undertook the trial. There were no special criteria to ensure rigorous homogeneity of the sample. Thus unfettered, I wanted to cast a wide net over most depressive conditions and included in my first clinical trial with imipramine 39 manic-depressives (both unipolar and bipolar), 12 patients suffering from involutional melancholia, 11 schizophrenic and schizoaffective patients with depressive symptoms, 7 depressed patients with senile dementia and cerebral arteriosclerosis, 6 personality disorers of the cyclothymic type, 5 neurotic depressive reactions and 4 patients diagnosed as mixed psychoneurosis with dominant depressive symptoms.

Although we had almost no restrictions to cramp our rather carefree research style then, we also received no additional funding or staffing to carry out clinical trials. As I had done 4 years earlier, with the first large-scale North American trial of chlorpromazine, I had to fold the research operation into the ongoing service functions at Douglas Hospital. It was our good

fortune - mine and that of my co-workers Dr. C.H. Cahn and R.L. DeVerteuil - that there was an experienced, enthusiastic and cooperative medical and nursing staff at the hospital.

Having now an antidepressant drug for which the appropriate dosage had to be established and which could possibly have some toxic properties, I realized that I also needed an instrument that allowed us to measure quantitatively depressive symptoms and their response to treatment. At that time there were only mood rating scales in the literature, but none that could measure the whole syndrome of clinical depression.

We then constructed what, I believe, was the first depression rating scale ever published. It rated mood, facial expression, retardation, agitation, feelings of guilt and worthlessness, sleep and weight loss. Having established acceptable interrater reliability, this scale was administered to our patients on imipramine at intervals of two weeks.

We started with an open trial, but halfway through it, we converted it, for a two-week period, into a placebo-controlled double blind trial with 21 patients in each group. This rather unorthodox switch nevertheless yielded quite decisive results: 60% of the patients on active drug were rated as recovered or much improved after eight weeks of treatment.[13] While this does not appear overwhelmingly favorable today, it was really remarkable in view of the fact that about half of our sample were chronic patients who had previously proved refractory to virtually every available mode of treatment, including ECT, over a number of years.

Fig. 2 represents the course of one chronically depressed woman over a ~~two~~ three-year period during which time she received a large number of ECT's as well as experimental treatments with chlorpromazine, iproniazid and even reserpine, until her depressive episodes were finally brought under control with imipramine. Although we had used doses from 100 to 600 mg of imipramine initially, we soon established 100 to 200 mg as the most appropriate dose range.

However, all other imipramine-like antidepressant drugs then and now had one big drawback: they required two to three weeks before their antidepressant action became significant. This was one of the reasons why our group at Douglas Hospital continued to search for new ways to treat depression. Before we had learned much about the action mechanisms of the tricyclics - which are even today far from clearly understood - I suspected that the therapeutic time lag of imipramine was because of its imperfect ability to cross the brain-blood barrier. Fever was known to lower this barrier temporarily, and so we devised a method which, though somewhat cumbersome, resulted in producing therapeutic responses in depressed patients who previously had not improved within 3 weeks of imipramine treatment. The method consisted of producing artificial hyperpyrexia by means of typhoid vaccine injections. Although this treatment never acquired great popularity and its action mechanism is probably quite different from what it originally had been thought to be, it did produce the desired clinical results.

Imipramine was soon followed by other tricyclic antidepressants. One of these was trimipramine which Rhone-

Poulenc had developed and with which my collaborator Thomas Ban and I worked extensively in the 1960's. At that time we still had no inkling of the action mechanism of tricyclic antidepressants and were looking in many directions for it. One of the more exotic experiments is presented in Fig. 3: The effects of trimipramine on the construction of spider webs. Tables 1 and 2 show the effects of trimipramine, as scored on our rating scale, over time, in comparison to amitriptyline, and the differential therapeutic efficacy of trimipramine in various diagnostic groupings.[15]

Finally, I would like to add to these recollections a bold and partly successful - though never confirmed - attempt I made to use promising but "taboo" drugs to fight severe depressive conditions that did not fit into our diagnostic catechism, for example, existential despair. We started these trials in what appeared to be certain hopeless depressions in the elderly, and later used the same therapy in a few depressed and persistently suicidal young adults who could not be readily diagnosed within the framework of the traditional categories of clinical depression. The treatment consisted in the combined use of oral dextroamphetamine (10mg) and intramuscular meperidine (pethidine; Demerol) (50mg) on alternate days, given six times within two weeks. The euphoric action of dextroamphetamine is well known and, of all opiates, the synthetic opiate meperidine is most frequently observed to produce euphoria. Evans had found that a combination of opiates with amphetamines enhances need achievement[16] which points to an effect of such a combination

of drugs on reinforcement contingencies, i.e. on psychological mechanisms which are thought to be deficient in depressive states. Furthermore, both amphetamines and meperidine increase available cerebral norepinephrine. I also had a theory that certain atypical depressive states occurred in persons who, for various reasons, had "unlearned" (or viscerally forgotten, so to speak) how to feel well, and that for them repeated, chemically induced states of euphoria might reactivate their ability to experience pleasure and enable them to free themselves from their hopeless anhedonia. Be that as it may, the treatment was effective in some 20 depressed patients and by design, nobody became dependent on the drugs under the conditions that guided the administration of the treatment. Our results were published, but to my knowledge, never systematically retested by anyone.[17]

Almost simultaneously, the monoamine oxidase inhibitors (MAOIs), another type of antidepressant medication, was being investigated by Nathan Kline. For some time I had heard rumors of mysterious developments in the field of antidepressants going on with Kline's team at Rockland Research Institute (now the Nathan Kline Institute) in New York. Drug detail men had told me about the intensely secretive attitude surrounding this project, so we did not learn any of the details. But soon afterward, Nate and I became very close friends and remained so until his untimely death three years ago. Nate had discovered the antidepressant action of MAO inhibitors. He often described to me his early tribulations in trying to establish these effects. He had been excited by animal experiments that he had seen in the Warner laboratories in New Jersey. Rats that were given

iproniazid prior to reserpine became hyperactive, indicating that the sedating effect of reserpine had been counteracted by iproniazid. Nate had already been working with reserpine as an antipsychotic and had become interested in the strange, euphorizing effects of iproniazid which were observed in patients suffering from tuberculosis who were receiving the drug experimentally for its antibiotic effect. It was already known that iproniazid had monoamine inhibiting effects. Nate now put things together and developed his theory of the antidepressant action of monoamine inhibition. He presented his preliminary clinical findings, on 17 regressed and retarded hospital patients and 9 depressed patients he had seen in private practice, at a Regional Research Conference of the American Psychiatric Association at Syracuse in April 1957. These proceedings were not published until 1958.

Kline knew that Gaddum and Kwiatkowsky, in 1938, had theorized that ephedrine produced its stimulant effect by acting as an amine oxidase inhibitor.[18] Integrating theory and practice, the MAOI's had now become the second family of antidepressant drugs and, together with the cyclic antidepressants, derived from imipramine, and ECT, they still constitute part of our main armamentarium of somatic antidepressant treatment.

Nate also played an important role in introducing lithium into the pharmaceutical industry, after Mogan Schou had made Cade's discovery, in 1944, of lithium's anti-manic effect clinically applicable. Kline was at first greeted with great

indifference in the US industry which was not eager to invest in the production of a drug for which they could not obtain patent rights. But in his typical, irresistable fashion, he did manage to persuade two companies to produce lithium medication and put it on the U.S. market. This happened only after a group of American, Canadian and British clinicians, including myself, had set up a two-year trial, using double-blind, multi-hospital studies as the means of demonstrating the effectiveness and safety of lithium.

Interestingly, at the end of the first year of the study the conviction of the investigators was so unanimously in favour of the drug that it was deemed to be unethical to continue the trial under double-blind conditions. In fact, I had broken the code because of some suicide attempts among my patients, and refused to continue the study under blind conditions when it was clearly demonstrable that the experimental (lithium) group did so much better than the controls.

Let me review briefly the avalanche of events with the tricyclic antidepressants after Kuhn had published, in 1957, the clinical effects of imipramine. Sigg, in 1959, observed in Geigy laboratories the potentiation of noradrenalin by imipramine. In 1961, Brodie and his team at the National Institutes of Mental Health (NIMH) introduced the reserpine syndrome as a model for depression. At about the same time Axelrod and his co-workers at NIMH discovered the reuptake blocking of noradrenalin by tricyclic antidepressants. In 1965 Schildkraut, Bunney and Davis introduced the catecholamine hypothesis of affective disorders. In 1969 Carlsson and his collaborators at the Karolinska

Institute discovered the reuptake blocking of serotonin in presynaptic neurons by tricyclic antidepressants, which served as the basis for the serotonin hypothesis of depression. In 1975, Vetulani and Sulser, at Vanderbilt University, reported the down-regulation of the noradrenalin receptor system in the brain following chronic administration of tricyclic antidepressants. In 1979, Langer and Associates, in Paris, discovered the high-affinity imipramine binding sites in animals and man.

These were very exciting times. We were uncovering the first agents in medical history that showed any hope of alleviating the oldest, most devastating, frustrating and universal mental disorder. The field was wide open and new discoveries were being made at a rapidly accelerating rate. This was all happening against the backdrop of the thrilling pro-research Sputnik era. The findings constituted a veritable Rosetta Stone: we had discovered, empirically, a host of new dramatic clinical effects, for which no cause was yet known and no theory existed. The challenge of deciphering the action mechanisms opened up an entirely new era for the neurosciences.

Today we have two generations of antidepressant drugs in our armamentarium, both based on quarter-century old models and both still limited in many ways in effectiveness and safety.

We now await a third generation of drugs based on the sophisticated new insights and imaginative rationales that are emerging from modern neuroscientific research.

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