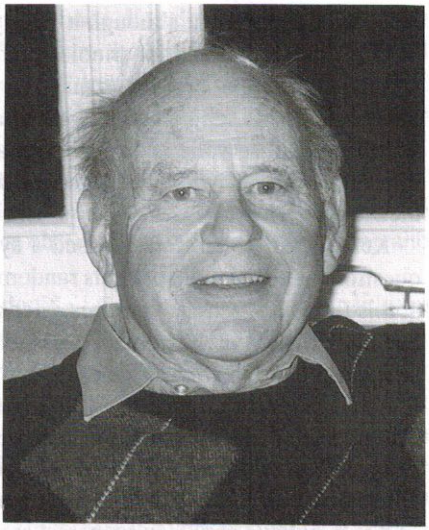
EARLY DAYS IN BIOLOGICAL PSYCHIATRY

Alec Coppen



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When I started my studies in biological psychiatry in the late 1950s, the field was pretty open since there had been very little work in the area, apart from studies in the genetics of psychiatric illness carried out in the 1920s and 1930s. So if one chose one's subject wisely, one was a bit like Lewis and Clarke in their exploration of the United States – wherever one went, one was certain to come across new and interesting discoveries.

When I started with the Medical Research Council (MRC) of the United Kingdom in 1960, I had certain principles in mind. I had selected the area of affective disorders as my field, and I was determined to concentrate on the biochemical abnormalities found in patients showing this condition. I decided that the basic requirement was a clinical research ward, where systematic and accurate measurements could be undertaken on rigorously selected patients under controlled conditions. This approach was rapidly agreed upon between the MRC and the National Health Service with the minimum of delay and bureaucracy. I also determined that patients selected for study should lose nothing by being admitted to our ward, so that they would have the best treatment and be followed up very carefully.

Our general plan of investigation was to study patients when they were depressed (or manic) and at various intervals after recovery. This basic facility is essential to biological studies in patients, and a close everyday interaction with them is a great stimulus to achieve what I consider the end point of all these studies: a reduction of their morbidity and mortality. Attached to the ward was a laboratory in which we were able to perform a wide range of investigations.

Another important approach was to collaborate with other specialist units. For example, when measuring whole-body electrolytes, we worked with the Radiological Protection Unit

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Coppen was elected a fellow of the CINP in 1968. He was a Councillor of the 12th, and served as President of the 16th Executive.

in Sutton, where they measured the K40 in our patients in a whole-body counter. We were also able to observe in our patients the fallout from the various nuclear bombs that were being exploded at that time by the USSR and the United States.

We identified three main areas of interest: electrolytes, monoamines, and endocrine changes. Our interest in endocrine changes was initially in the area of adrenal cortical activity, and we showed, even after allowing for admission to hospital (which has a marked effect on cortisol secretion), that there was increased activity both during and after recovery from an episode of depression, although it slowly subsided to normality after some weeks.

Our interest in the endocrinology of mood extended to changes that had been observed around the time of the menstrual period. About 1960, when Neil Kessell and I became interested in this subject, there were almost no systematic studies. Dalton had published her well-known observations on schoolgirls' performance, and Linford Rees had also published observations in this area, but in general there was little awareness of mood changes around the menstrual period.

Kessell and I therefore devised a systematic investigation of the problem by sending a questionnaire to sample patients randomly selected from general practitioners' lists. Working at this time had many advantages. Menstruation was still an amazingly taboo topic, and little had been written in the popular press, so that our subjects were being questioned about mood changes around the menstrual cycle for the first time. Secondly, this was before the introduction of the contraceptive pill, which in itself could have effects on the premenstrual syndrome. The results of this investigation were really quite dramatic. There was a syndrome of mood changes before the period severely affecting at least 10 percent of the population. Curiously enough, it took some time for news of our work to reach the general population because, hard as it is to believe now, newspapers were very coy about publishing anything on the subject of menstruation. I think that, in general, it was a great relief to many women to learn that they were not alone with regard to their symptoms, although at the time we could not suggest any very effective treatment.

Another interest of ours was in monoamines. This work received a great boost in 1963 when we were able to show that, in a double-blind trial, tryptophan very significantly improved the antidepressant action of MAOIs and tryptophan augmentation compared favourably to placebo augmentation. This action was so marked that for many years, it was a powerful instrument in treating patients who responded poorly to standard antidepressants. The reason that the practice was discontinued was that tryptophan was taken off the market because of problems with its production (which did not actually affect the tryptophan available in this country). It is interesting that these observations on tryptophan supplementation have recently been paralleled by studies on depressive patients subject to tryptophan depletion, which can cause a worsening of their symptoms. Our tryptophan and MAOI studies were the first positive evidence of a link between serotonin (5HT) and depression and led many groups to undertake a series of investigations into 5HT and its metabolite, 5-hydroxy-indole acetic acid (5HIAA) in depressive patients. We looked at CSF and brain concentrations, at blood concentration of total and free tryptophan, and at 5HT platelet transport. Our interest in 5HT was taken up by other European centres, but curiously enough, it was met by hostility in the United States. There was a rather absurd, but fruitful rivalry between the noradrenaline and 5HT theories of depression. Of course, there is no simple theory of depression, but evidence has accumulated over the years that 5HT does have a fairly central place in the disorder.

One of the great developments during the 1960s was the realization that mood disorders were not single episodes, but were largely a recurrent and chronic condition that required long-term treatment. Jules Angst was very influential in showing this fact, and careful evaluation of the outcome of our own patients brought it home to us. My own interest in lithium resulted from my early work in electrolytes, where we showed an increase in residual (mainly intracellular) sodium in patients when they were depressed.

This topic brought me into contact with Mogens Schou about 1960, and we met many times to discuss the best way of testing long-term treatment in mood-disorder patients. We did not find any effect of lithium on the abnormality of sodium distribution, but we did find subsequently that lithium normalized the decreased 5HT transport in depressive patients. However, these results stimulated our interest in the long-term treatment of mood-disorder patients, which has been the most important development in this area in the last fifty years. Schou's early trials were rather convincing, but were flawed in terms of modern standards of testing treatments. But it should be recalled that randomized, placebo-controlled retrials were a relatively new development at the time when the first observations were made by Schou and his co-workers.

I saw the importance of carrying out a prospective double-blind trial of prophylactic lithium in the late 1960s. This we did with three other centres, and we were able to show two things: both unipolar and bipolar illnesses without long-term treatment have a very poor outcome; and long-term maintenance treatment can considerably improve these patients' long-term outlook. Later on, we carried out a second randomized, double-blind trial on the continuation treatment by lithium of patients who had received ECT. The results were striking. ECT is the most effective treatment for depression: its onset of improvement is rapid, and it is useful in a very broad spectrum of patients. Its main drawback is that there is a very frequent occurrence of relapse: over 60 percent of patients relapse within one year if they receive a placebo. On the other hand, patients who receive maintenance/prophylactic treatment with lithium show a very low relapse rate during this time. In fact, ECT and maintenance/prophylactic treatment with lithium together represent by far the most effective treatment of the condition. Studying the mode of action of antidepressant drugs has led to many hypotheses about the pathology of depression. It is tantalizing that we have so little information about the mode of action of ECT.

We had set up a mood-disorder clinic for administering lithium and other long-term treatments. One lesson we learned is that simply prescribing treatment is not effective. Patients must be informed about the nature of their illness. They must be seen at regular intervals and their compliance ensured by, if possible, plasma monitoring. As the patient becomes accusomed to the regime, the follow-up intervals can be lengthened or the patient devolved to the general practitioner. By now we must have known about the recurrent nature of unipolar depression for thirty years, but I would be surprised if the number of patients who receive adequate maintenance treatment represents more than 2 or 3 percent. The most common cause of suicide is depressive illness, and we have shown that maintenance treatment can reduce suicide by 70 percent. Not to treat recurrent depression is a serious medical mistake.

During the early years of drug development, we came across the problem of dosage. We found, for example, that patients metabolized drugs at very different rates so that a standardized dosage could produce a fourteen-fold difference in the steady state of plasma concentration. The question arose whether there was a plasma concentration of a tricyclic drug that was optimum – the so-called therapeutic window. The existence of such a "window" was alleged for nortriptyline. We examined the position for amitriptyline, and after a lot of work, including

an international investigation that I organized for the World Health Organization, we concluded that 150 mg of amitriptyline was adequate for most adult Europeans. However, in other ethnic groups, such as the Japanese, the rates of metabolism are so different from those in people of European origin that we cannot extrapolate results from one group to another. After a lot of experience in this area, we carried out what I feel was the definitive investigation on lithium dosage. This, I can say, is the dose, on a once-a-day regimen, that would produce a twelve-hour plasma level of 0.5-0.7 mmol/l. More than this is counter-productive. The investigation showed that higher levels produced poorer response, probably because of the effect on the thyroid. Lithium now is one of the best established of all the psychotropic compounds. John Davis has reported twenty-six randomized, double-blind trials on lithium prophylaxis, all showing a very marked effect on the course of mood disorder.

Neurochemistry and psychopharmacology have become elaborate and complex, and the number of publications on any one topic increases year by year. Because of this development, I feel that we are in a similar position to the one outlined by John Maddox in an editorial published in *Nature* entitled "Finding the Wood among the Trees." Maddox was commenting on molecular biology, but his remarks are also highly appropriate to our field. "Is there a danger," he asked, "where there are grants for producing data but hardly any for standing back in contemplation ... [that] the accumulation of data will get so far ahead of its assimilation into a conceptual framework that the data will eventually prove an encumbrance?" It seems to me that, in general in psychopharmacology, the treatment of mood disorders has not improved very much overall in the last twenty years, in spite of an explosion of new data.