LITHIUM IN PSYCHIATRY: HISTORICAL ORIGINS AND PRESENT POSITION

There are few specifics in medicine. The specific antimanic effect of the lithium ion is one. It was not an accidental discovery. It was the inevitable though unforeseen product of an hypothesis and of a series of experiments to test that hypothesis.

The hypothesis was crude and the experimental methods were primitive. The work was done single-handed in a chronic mental hospital.

A reasonable assumption regarding the etiology of manic-depressive psychosis is that it is analogous to thyreotoxicosis and myxoedema, mania being a state of intoxication by a normal product of the body circulating in excess, whilst melancholia is the corresponding deprivative condition. If this is so, the key to the problem lies in the study of the manic patient, who might be expected to excrete this product in the urine. (Cade 1947).

With no knowledge at all of the properties of such a substance, one would need to use the crudest kind of biological test as a preliminary screening device. And crude it was — the intraperitoneal injection of guinea pigs with fresh urine from manic, depressive and schizophrenic patients and from normal controls. Early experiments quickly showed that urine from manic patients was far more toxic than urine from non-manics and normal subjects. The mode of death was the same in all animals. After a latent period of a quarter to half an hour they would first become tremulous, ataxic and quadriplegic, soon to exhibit myoclonic twitching and then, after a few minutes, develop a major fit and die in status epilepticus.

It was at this stage necessary to discover what particular toxic substance was responsible. The obvious first choices were the end-products of protein metabolism — urea, uric acid and creatinine.

Urea quickly proved to be the culprit. The next step then was to determine what was responsible for the quantitative differences. Why was manic urine more toxic? Urea concentration tests showed that it could not be explained by a simple excess of urea. Manic patients’ urine is not more highly concentrated than manic-depressive psychosis is that it is analogous to thyreotoxicosis and myxoedema, mania being a state of intoxication by a normal product of the body circulating in excess, whilst melancholia is the corresponding deprivative condition. If this is so, the key to the problem lies in the study of the manic patient, who might be expected to excrete this product in the urine. (Cade 1947).

With no knowledge at all of the properties of such a substance, one would need to use the crudest kind of biological test as a preliminary screening device. And crude it was — the intraperitoneal injection of guinea pigs with fresh urine from manic, depressive and schizophrenic patients and from normal controls. Early experiments quickly showed that urine from manic patients was far more toxic than urine from non-manics and normal subjects. The mode of death was the same in all animals. After a latent period of a quarter to half an hour they would first become tremulous, ataxic and quadriplegic, soon to exhibit myoclonic twitching and then, after a few minutes, develop a major fit and die in status epilepticus.

It was at this stage necessary to discover what particular toxic substance was responsible. The obvious first choices were the end-products of protein metabolism — urea, uric acid and creatinine.

Urea quickly proved to be the culprit. The next step then was to determine what was responsible for the quantitative differences. Why was manic urine more toxic? Urea concentration tests showed that it could not be explained by a simple excess of urea. Manic patients’ urine is not more highly concentrated in this respect. Could it be that the other end-products of nitrogen metabolism were the quantitative modifiers?

Creatinine was injected intraperitoneally in high concentrations with negligible effects. When added, even in low concentrations, to solutions of urea it had a high protective effect against the convulsive toxicity of urea. So much so, that it was tentatively tried in epilepsy but on such a limited scale that the results though promising were inconclusive. It is interesting in this context to note the similarities in chemical structure of creatinine and phenytoin. This field still awaits further exploration.

What about uric acid? If anything, it appeared to enhance the toxic effect of urea but its insolubility was the problem. This naturally led to a trial of the most soluble salt, lithium urate. It was because of this solubility that lithium salts had been prescribed in the treatment of gout in the nineteenth century.

Then came the great paradox. Lithium urate injected with urea was less toxic. The next step was inevitable. Lithium urate solutions were found to be tranquilizing to guinea pigs. Those who have played with, and experimented with, these animals know to what degree a ready startle reaction is part of their make-up. It was even more startling to the experimenter to find after lithium that they could be turned on their backs and that, instead of their usual frantic righting reflex behaviour, they merely lay there and gazed placidly back at the experimenter.

Again, the next step was ordained. Which ion was it? Lithium carbonate in 0.5% aqueous solution injected by itself produced results similar to, or better than, the urate — a highly tranquilized but by no means sleepy animal. (Cade 1949).

It may seem a far cry from tranquillized guinea pigs to manic humans but indeed it was an express return journey. Even on the outward trip there were few stops. How to proceed? Primum non nocere. The older pharmacopoeias did not describe any toxic effects of lithium salts but was that good enough? There is always the number one experimental animal, oneself. Single and repeated doses of lithium citrate and lithium carbonate in the doses contemplated for human use produced no discernible ill-effects.

The first patient was a little, wizened, chronic manic, middle-aged man, dirty, mischievous, rubbish gathering, interfering, destructive, amiable and challenging, who had enjoyed pre-eminent nuisance value in a back ward for many years. After three days — no effect. Fourth day — the optimistic therapist thought he saw some change for the better but acknowledged that it could have been his expectant imagination. The nursing staff were non-committal but loyal. Fifth day — yes, more settled, tidier, less distracted. From then on, no doubts. Within three weeks, he was enjoying the unaccustomed and quite unexpected amenities of a convalescent ward. These observations were multiplied and were reported in September 1949. It may seem strange that they attracted relatively little attention. There were various reasons. First, lithium chloride, at that time and for some time past, was being used in a quite uncontrolled way as a substitute for sodium chloride in the treatment of the
oedema of congestive cardiac failure and a number of deaths were reported in the American medical press. Unfortunately, too, in a proportion of cases of chronic or relapsing mania, the therapeutic and toxic doses appeared to overlap and lastly, of course, phenothiazines were just over the temporal horizon.

It has become increasingly clear over the years that provided lithium salts are used with discretion—that is, provided the patient is observed daily as an in-patient during saturation dosage; that he has an adequate sodium chloride intake; that during maintenance dosage he has one rest day a week; and that either he or his relatives are intelligent and co-operative enough to recognize toxic symptoms so that he can promptly cease intake and report to his doctor—then no serious trouble is likely to arise.

PERSONALITY TRAITS AND CORONARY HEART DISEASE

Dunbar (1943), Arlow (1945) and Gildea (1949) claimed that patients with coronary heart disease have a specific type of personality pattern. Weiss et al (1957) suggested that gradually mounting stress of emotional origin may be a significant factor in the aetiology of the disease. Roseman et al (1961, 1963, 1964) reported that patients who suffer from coronary heart disease exhibit a particular type of behaviour which they called Behavioural-pattern A. They found that subjects with this Behavioural-pattern had higher incidence of coronary heart disease and suggested that Behavioural-pattern A has an aetiological relationship to coronary heart disease. Russek and Zohman (1958) reported that the young coronary patient was "an aggressive, ambitious individual who had lived beyond his normal capacity and tempo".

Cleveland et al (1962) conducted psychological tests and clinical interviews on 25 young males hospitalised for recent infarction and compared the results with those of 25 males awaiting serious surgery. They found that the coronary patients revealed a pattern of personality characteristics, including "chronic restlessness, underlying passivity, and suppressed hostility" and suggested that these personality features might have had a bearing on the propensity for coronary disease. Bruhn et al (1966) reported that educational mobility, educational discrepancy between husband and wife, and total Cornell Medical Index score distinguished coronary heart patients from normals.

Psychiatric interviews, a detailed social inventory, and a battery of psychological tests were carried out upon a group of 46 young men with coronary heart disease and upon 49 healthy control subjects, by Miles et al (1954). When the two groups were compared in specific personality traits, they found that the differences were not significant. Culpan and Davies (1959) compared a group of 21 patients with myocardial infarction with a matched control group and found no significant differences in personality patterns between the two groups. Keith (1965) compared 3 groups of subjects with regard to behavioural patterns. These groups consisted of 76 patients with coronary heart disease, 51 patients with peptic ulcer and 62 controls without any disease. Ratings of behaviour patterns were made without prior knowledge of the medical diagnosis. He found no significant differences between the 3 groups.

Thus a review of literature shows that there are conflicting reports on the relationship between personality traits and coronary artery disease. A critical evaluation of the above studies shows that there is no substantial evidence for the hypothesis that emotional stress and a particular personality type are aetologically related to coronary heart disease. The studies which suggest the above hypothesis are deficient in two important respects. The selection of patients was not consecutive or random. Secondly, very subjective psychological assessments were often made by those who knew the diagnosis of the patients they were characterising. The inevitable intrusion of preconceived ideas into the psychological assessment makes many studies in this field difficult to interpret.

The above criticism was substantiated by observations in a study on chest pains after myocardial infarction, the details of which are reported elsewhere (Verghese, 1966). This study was conducted on 106 Australian or U.K.-born male subjects, all of whom had had a myocardial infarction from 6 months to 3 years previously. It was found that the Eysenck Personality Inventory scores (neuroticism and extroversion) and the Cornell Medical Index scores of the coronary group of patients were similar to those of a normal group of Australian-born workers as reported by Kidson (1966).

It was also perceived that the coronary group of patients studied did not form a homogeneous group. They could be classified into different groups accord-