Biographies
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# Events and Memories
# Samuel Gershon

## 1. LITHIUM

I have been pressured by my colleagues in INHN to write about some of the events and memories of my professional life in psychopharmacology. Barry Blackwell has written a memoir titled "*Bits and Pieces of a Psychiatrist's Life*", a complete account of his personal and professional accomplishments. I could not do that but Tom Ban suggested I contribute an account of each of the drugs I helped develop- *'bits and pieces'* - if not a full memoir. I have accepted the challenge and will stick mainly to professional aspects told through work events and scientific episodes.

I graduated from medical school at the University of Sydney in 1950 and then did a rotating internship. During 1951, I took a rotation through the psychiatric inpatient facility at the Royal Prince Alfred Hospital attached to the University. The psychiatrist in charge of the institute was a very liberal fellow, not convinced he knew all the answers and willing to admit we had very few. Australia at that time was a fairly isolated place, but we heard a lot about Dr. Cade including his talks in 1948 and article in 1949 on lithium treatment of mania and the enormous success he reported (Cade, 1949). So, it was possible to use lithium therapeutically during this elective. In the few cases I treated, lithium seemed effective, using it cautiously over 7-10 days, since deaths from lithium had been reported by others in Australia.

The next year, 1952, I transferred to the University of Melbourne and joined the Department of Mental Health. I was assigned to the Royal Park Mental Hospital in Melbourne, where Cade was

the Superintendent. At the same time, I enrolled at the University where mandated courses in psychiatry were given and exams over the next 4 years were administered. Unlike the boards in Psychiatry in the US, we had to pass every subject in the curriculum each year or do it again.

Royal Park Hospital was the acute receiving hospital for Melbourne. So this seemed the greatest place in the world to actually study lithium - the first significant discovery in psychiatry.

At this point, I only wanted to evaluate and understand its therapeutic profile, clinical effects and process of improvement. So, I asked senior colleagues who I should speak to about getting supervision. They told me this was not a good idea as Dr. Cade had banned lithium in the hospital because of the deaths and serious toxicities that had occurred, including one of his own patients in the original 1949 report. This was not a great start and, after a lot of psychological turmoil, I decided I would have to find another route.

At this point, I only thought of personal observation of lithium's effects and course of treatment; I had done no research and did not know of anyone doing research. My choice of action was born of desperation; I contacted a Professor at the University of Melbourne known as approachable to students and faculty. This was Professor Wright, Chair of Physiology. I went without an appointment, a young dopey kid, but he was nice and kind. He elicited what I wanted to do and evaluated me carefully. After further questioning and discussion, the meeting ended when he said, "Well, you should go up and see "Trautie". So I went upstairs and found Dr. Trautner, in his lab with a couple of doctoral students… I had found my research mentor and a future friend.

Trautner was an elderly, wrinkled gentleman with a heavy German accent. I am ashamed to say I have no photo of him. We had a general discussion about his published 1951 study of 100 hospitalized psychiatric patients treated with lithium. An important feature was that it was the first lithium study in the world in which patients had their lithium assays monitored, and no patients had died. Also, this was the first study to use flame photometry to monitor the plasma levels of sodium and potassium, the result of Dr. Victor Wynn's first use of the assay. Dr. Wynn was also a faculty member in the Department of Physiology at the University of Melbourne so

the University faculty played the main role in a broad range of studies on the physiology of lithium. They established the procedures for safe use of lithium in humans, keeping it alive in psychiatry. As I mentioned, Cade banned the use of lithium in his hospital and Roberts and Ashburner at two other state hospitals in Victoria reported deaths of a patient at each hospital and that was the death knell for lithium therapy in Australia. However, two other psychiatrists (both new immigrants) in two other states in Australia also contacted Trautner and he advised them to carry out their own mania studies. Both Glesinger and Margulies, published papers confirming their findings in the large study by Noack and Trautner, both used plasma assays and had no untoward effects.

Thus, my encounter with Trautner generated enthusiasm for how one might treat and understand at least one psychiatric disorder. As a novice, I had no research funds or assistants but was encouraged and supported with help and advice by colleagues at the University of Melbourne, who gave their knowledge and time unconditionally.

The first major Lithium project (Trautner, Morris, Noack & Gershon, 1955), was on the differential retention and excretion between manic and non-manic phase patients. We found that classic manic bipolar 1 patients would retain more of the lithium ion ingested over a one week period than normal or control subjects, whose retention and excretion was more in daily balance. When the manic phase remitted, they excreted the retained lithium, exceeding their daily dose until they reached homeostasis. This new and exciting finding was state and trait dependent.

This study also gave us clues about other ionic effects, including sodium and potassium losses. This was time consuming, taking a couple of years, but provided the ground work for later studies. Our findings also dictated we develop a treatment plan for lithium toxicity. Again, we went to our colleague at the University of Melbourne, Dr. Douglas Coats, an expert in electrolyte and renal physiology who agreed to work with us on this urgent and important topic. Our paper (Coats,Trautner&Gershon,1957) offered an explanation of the aberration in water and electrolyte balance found in bipolar disorder and proposed a treatment plan, that followed logically from the previous study. We had occasion to use our results to help other psychiatrists deal with toxic patients to obtain positive outcomes.

The next lithium report came after I arrived in the U.S. at the University of Michigan, on a scholarship awarded after an Australia-wide competition; it had a large grant to establish Schizophrenia and Psychopharmacology Research projects. This paper summarized laboratory and clinical experiences to date (Gershon &Yuwiler, 1960). Art Yuwiler was head of the biochemistry research division. The views presented are still those I hold today. After an additional 55 years of study and observation, Lithium is one of the few examples of psychopharmacological specificity in psychiatric treatment.

During this period, we established the efficacy of Lithium in mania, demonstrated the effect of lithium on water and electrolyte physiology, reported the differential retention and excretion of lithium in the manic phase, elucidated the therapeutic range for treatment of mania, and also studied the clinical picture of lithium toxicity as well as demonstrated an effective treatment plan for it.

The next issue we thought urgent was potential toxic effects to the embryo. Now that safe clinical usage was possible, we realized special risk could exist in pregnant women, but the best we could do was an animal study on the results of prolonged sub-toxic lithium in rats (Trautner et al, 1958). All animals went through pregnancy with good weight and general health. On examination of the uterus near term, the one finding was that lithium treated rats retained fewer intact fetuses than controls, indicating that some toxic effects would have to be studied in higher species. This was the case in humans, where a low incidence of some cardiac defects occurred. The authors were all University of Melbourne colleagues.

Our next study may seem esoteric by current standards. However, it demonstrated important findings. Maintenance ECT was used in many cases of patients who suffered from recurrent depression, recurrent bipolar disorder and resistant schizophrenia unresponsive to other treatments;. This study examined the use of lithium in bipolar cases and found that it could provide a maintenance medication to replace the use of recurrent treatments with ECT (Gershon & Trautner, 1956).

In Australia, we also did some experiments in Trautner's lab using Warburg brain biochemical techniques. With the simple belief mania had an increase in brain cell activity, we embarked in our first experiment. We also knew that we could increase brain slice energy activity with DNP [di-nitro-phenol]. Would the addition of lithium have an effect on this system? After a non-toxic concentration of lithium was added to the DNP activated system we consistently found a decrease in metabolic activity. This was an exciting finding but due to the usual "circumstances beyond our control" we never continued with these experiments.

All of the studies cited were conducted without grants or research funds, contributed to by the faculty and the meager resources of their labs. They were all unblinded because we could not afford elaborate designs.

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