Biographies
(Autobiography)
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Events and Memories
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2. SUCCINIC ACID

Work on succinic acid took place during my psychiatric residency (1952–1956). I was single, working for long periods in several different mental hospitals throughout Victoria, where I read a lot of articles in *Current Contents*. These included reports on mescaline's psychedelic effects in man and the observation they could be resolved, or antagonized with intravenous (IV) succinic acid, returning the subject to clear consciousness.

My colleagues and I decided to study this and sought physician referrals of patients with barbiturate overdose, morphine, and comas from other causes. In all cases there were varying degrees of lightening of coma or increased clarity of consciousness. In animals, we explored these findings in more detail. Using a Beagle dog we could induce sleep with a barbiturate and after 15 minutes we would wake the dog with an IV dose of Succinic acid. However, if we gave the dose of succinate prior to the barbiturate we increased sleep time. We were not been able to explain this but we published three reports on different uses of succinate in different psychiatric populations. These three reports on succinate happened to be my first three papers published; (Trautner, Trethewie & Gershon, 1953), (Trautner, Gershon & Duerrheim, 1954), (Gershon & Trautner, 1954)

The first paper involved trial and error experiments to profile the scope of succinate's analeptic effect in animals and man. These studies did not involve a random, double-blind design, the best proof of an experimental effect. However, in most cases, the effects were replicated in several experiments. We stumbled on observations which were considered real and important but not explained by our own findings or described in the literature. An example, in dogs administered

barbiturates, was that a dose of succinate would produce a clear change in sleep duration, but in another experiment, when the substance was given in mid-sleep time, the dog would wake up and either stay awake or drowse and could be raised by voice. However, if we gave the IV succinate first, followed by the barbiturate, sleeping time would be increased or even doubled. With other sedative drugs we only studied the analeptic effect and arousal occurred each time. We also had the opportunity to do trials in patients after overdose, post anesthesia or in some confusional states. This analeptic paper was an example of an inexperienced investigator going far afield after chance observations. The findings remain interesting and could be further investigated in a number of clinical conditions.

The second paper was in a schizophrenic population, stimulated by experience on insulin coma therapy (ICT), at Royal Park Hospital, when my resident colleague (Neil McConaghy) and I raised questions about its value. These treatments were given to a large number of schizophrenic patients in the morning and, when adequate duration of coma had been attained, they were roused with intra-gastric glucose. After a set number of treatments they were evaluated and released from hospital. However my colleague and I considered very few, if any, improved. Also, not all woke after the glucose, some had protracted comas, some died and others developed neurological impairments. In summary, this treatment was dangerous and had not been established anywhere in the world as effective treatment for schizophrenia. Yet it was used universally as the best treatment available in Australia, England, Russia and Israel. Then, in 1959, a group at the Maudsley published a control study of barbiturate sleep vs. ICT and showed no difference between treatments; neither produced improvement. We were all witnesses to a worldwide delusion. Even in the world of modern psychiatry we are at similar risk. This is an important reason for putting the history of our discipline at the forefront of educational programs. Alas, if we do not, I fear in the near future we will repeat our mistakes.

This is a preamble to the use of succinate in the treatment of schizophrenia (Trautner Gershon & Duerrheim, 1954) and psychotic depression (Gershon & Trautner, 1954) described below.

SCHIZOPHRENIA STUDY

This study was undertaken following the finding that succinic acid could antagonize hallucinations due to mescaline and other drugs. We wished to evaluate its effects on hallucinations in schizophrenic subjects as well as on prolonging barbiturate sleep time leading to a lower dose and increase in safety. Thirdly, we wanted to assess possible therapeutic effects of these two procedures on the schizophrenic illness itself.

In normal subjects succinate produces redness of the face and other parts of the skin, accompanied by a feeling of heat. Similar effects are seen with nicotinic acid, also claimed to have therapeutic effects in schizophrenia. The effect of IV succinate on hallucinations was evaluated in non-blind studies of schizophrenic patients. In most cases the injection reduced the potency of the hallucinations on the patient's behavior, modified by the type of hallucination. A positive effect would last from four to five hours. The ability to enhance barbiturate sleep with succinate pretreatment also created a safer procedure.

Due to the uncontrolled nature of our studies we could not reach any reliable conclusion about the long term therapeutic value of this treatment on the schizophrenic process. However, all three psychiatrists recorded improvement ratings after 7-10 days of the combined succinate barbiturate procedure. The patients were more relaxed, calmer, less distressed by hallucinations, eating and participating well in work assignments.

DEPRESSION STUDY

We followed this study in schizophrenia with a trial in long term hospitalized inpatients in a State Hospital with major depressive disorder. IV succinic acid was administered daily for 5 days and sometimes for 2 successive 5 day sequences. We observed a decrease in depressive symptoms, improvement in eating and measurable increases in weight. The research design caveats mentioned in the schizophrenia study apply here as well. We have not subsequently seen

any similar reports to confirm our observations but are convinced they merit further exploration and might improve current treatment.

We published another paper on the analeptic effect of succinic acid in acute carbon monoxide poisoning. (Gershon, Trethewie & Crawford, 1961). In this study we extended the range of possible efficacy beyond the usual group of chemical agents used for sedation and overdose. These experiments were in cats. A measured amount and time of exposure to carbon monoxide was administered when the animal would become comatose and lie on the floor of the cage. IV succinate was administered producing immediate arousal so the animal could stand up and walk in and out of the cage. On some occasions the animal would, after about an hour, become drowsy again and a repeat injection would restore full sustained consciousness.

Overall our experiments established parameters for the efficacy of succinate as an analeptic and anti-hallucinogen. As an analeptic the arousal effect was exceedingly wide ranging and seemed beneficial in a number of CNS depressant conditions, including carbon monoxide poisoning, without offering any clue to its mode of action. This was why we went to the extreme by trying it against carbon monoxide. To summarize, anti-hallucinogenic activity was seen against mescaline, LSD and possibly Sernyl but not Ditran. As an analeptic it appeared to demonstrate a very broad range of arousal activity in a variety of conditions.

On a travel scholarship I visited others doing related work. At the University of Vienna I met with Professor Arnold who published papers on the antagonistic effects of succinate against LSD in humans. He and his colleagues also had no explanation for the mode of action. On that visit I also met Peter Berner, the next chairman of psychiatry and was invited to the Austro-German Biological Psychiatry winter meetings each year. A second, very significant meeting was with Professor Hans Krebs at Oxford who identified the Krebs carbohydrate cycle. I wrote to Professor Krebs and told him of our work with succinate, asked to meet him and was profoundly grateful when he agreed to do so. In a leisurely and encouraging style he asked me to tell him what I found interesting about our findings. He patiently listened to my story, asked very few questions and, at the end, I enquired what he thought could be an explanation of some of these effects. He was very tentative about moving into the clinical area and said basic investigation in the neurosciences would have to be the route for answers to such questions. I felt honored to

have spent time with him. Subsequently I was amazed how on this, and every other occasion I sought to discuss findings with very famous scientists, I was never turned away, ignored or denied their fullest attention.

Dr. E.M Trautner (Trautie) became my mentor in 1952 and a close friend during my work with succinic acid from 1952-56. 'Trautie', often spent time in the student cafeteria at coffee time where he met many of the young female students [more than I did!]. One day he told me he had met a very special young lady who he kept suggesting I might marry. At the same time he was giving similar advice to the young lady, Lisl Wilder. He then took it upon himself to invite both of us to dinner. This experiment succeeded and we married in 1955. Thus my wife approved of my friend and my friend approved of my wife. After 59 years of marriage, work and travels together this experiment begun long ago suggests other experiments in our field may have merit!

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