Thomas A. Ban: Neuropsychopharmacology in historical perspective. Education in the field in the post-psychopharmacology era Collated 12

Samuel Gershon: Events and Memories

Samuel Gershon: Events and Memories

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 four 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 (1954 and 1955, respectively) confirming their findings in the large study by Noack and Trautner (1951), 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 and 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 and 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 and 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, Pennycuik, Morris 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 and 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.

References:

Blackwell B. Bits and Pieces of a Psychiatrist's Life. United States; XLibris Corporation: 2012.

Cade J. Lithium salts in the treatment of psychotic excitement. Med J Austr 1949;2:349-52.

Coats DA, Trautner EM, Gershon S. The treatment of lithium poisoning. Austr Ann Med 1957;6:11-5.

Gershon S, Trautner EM. The treatment of shock dependency by pharmacological agents. Med JAustr 1956;43:783-7.

Gershon S, Yuwiler A. Lithium ion. A specific psychopharmacological approach to the treatment of mania. J Neuropsychiat 1960;1:229-41.

Gershon S, Trautner EM. The treatment of shock dependency by pharmacological agents. Med J Aust. 1956;1(19):783-7.

Glesinger B. Evaluation of lithium in treatment of psychotic excitement. Med J Austr. 1954;41:277-81.

Margulies M. Suggestions for the treatment of schizophrenic and manic depressive patients Med J Austr 1955;1:137-43.

Noack CH, Trautner EM. The lithium treatment of maniacal psychosis. Med J Austr 1951;2:219-22.

Trautner EM, Morris R, Noack CH, Gershon S. The excretion and retention of ingested lithium and its effect on ionic balance in man. Med J Austr 1955;2:280-91.

Trautner EM, Pennycuik PR, Morris RJH, Gershon S, Shankly KH. The effects of prolonged subtoxic lithium ingestion in rats. Aust J Exp Biol Med Sci 1958; 36:305-21.

June 25, 2015

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 and Gershon 1953; Trautner, Gershon and Duerrheim 1954; Gershon and 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 and Duerrheim 1954) and psychotic depression (Gershon and 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 five days and sometimes for two successive five-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 and 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!

References:

Gershon S, Trautner EM. The Treatment of Depressive Psychosis with Sodium Succinate. Med. J Aust. 1954; 2:291-298.

Gershon S, Trethewie ER, Crawford M. The Use of Succinic Acid in the Treatment of Acute Carbon Monoxide Poisoning. Arch Int. Pharacodyn.1961; 134: 16-27.

Trautner EM, Gershon S, Duerrrheim GE. The Treatment of Schizophrenia by Combined Barbiturate-Succinate Therapy. Med. J Aust. 1954; 2: 181-188.

Trautner EM, Trethewie ER, Gershon S. The Analeptic Effect of Succinate in Coma and Confusional States. Med. J Aust. 1953; 2:848-865.

July 2, 2015

3. Bemegride

Compound 2 (succinic acid) was and still is puzzling in both its clinical effects and mode of action. One of its basic effects was as an analeptic in a variety of cases of CNS depressant induced drug effects and in different comas and confusional states. It demonstrated meaningful arousal in all cases and complete restoration of clear consciousness and normal motor activity in some. We did not proceed further because we had no lead to follow; looking back, this is a sorry admission as succinic acid produced some remarkable clinical effects without side effects in our dose range. So we studied a group of more specific drug antagonists, because we had a better idea of their actions as well as a source for the compounds and their analogues.

Bemegride was the first compound in this series we studied. Its structure and development suggested it would be a specific antagonist against barbiturates. We published three studies in barbiturate poisoning, the first in several animal species (Trautner, Shaw and Gershon 1956), the next in the treatment of barbiturate overdose in humans (Trautner, Shaw and Gershon 1957a) and the third an overall summary of the experiments in animals and the study in human overdose (Trautner, Shaw and Gershon, 1957b). In the 1950s and 1960s barbiturate poisoning was very common in suicide attempts and accidental overdoses, often causing death. We also noted in animals that pretreatment with Bemegride prior to barbiturate dosage would shorten sleeping time, the opposite of the effect seen with succinate.

Our results led to preparing a pill containing both barbiturate and Bemegride designed to diminish the lethality of barbiturate overdose. The pill was manufactured by a small pharmaceutical company and entered into animal studies followed by small clinical trials. These demonstrated a clear effect, diminishing the depth and duration of coma in animals and humans while reducing the death rate in animals. With the advent of the benzodiazepines public health policy strongly discouraged prescribing barbiturates for insomnia so manufacture of the combination pill and marketing ceased.

Bemegride was a lifesaving drug but when safer alternatives to barbiturates were available it became irrelevant. My future as a pharmaceutical tycoon took a turn for the worse!

References:

Trautner EM, Shaw FH, Gershon S. Bemegride in barbiturate poisoning. Lancet 1956;2:514.

Trautner EM, Shaw FH, Gershon S. Treatment of barbiturate poisoning. Brit med J 1957a;1:231.

Trautner EM, Shaw FH, Gershon S. Effects of Bemegride in barbiturate over dosage in humans. Brit med J 1957b;2:1509-14.

July 9, 2015

4. Morphine

We studied morphine side effects and the fact that it had a marked effect on histamine release. (Gershon and Shaw 1958a). Previously we mentioned in our studies that IV succinic acid exerted a rapid and dramatic antagonistic effect on morphine effects in animals (especially dogs) and humans, but we did not discover the mode of action.

It seemed obvious to try the effects of anti-histaminic compounds on morphinised animals; given IV to dogs these produced sedation but in the morphinised dog the opposite effect occurred with alerting effects.

As a result of this preliminary work we felt what would be of clinical value was a partial morphine antagonist. This would permit the use of doses of morphine to produce maximum pain control while the antagonist would preserve vital functions, such as respiration. There was considerable interest in this possibility following the emergency experiences with major wounds during World War II when Australia had troops posted all over the world in conditions of extremes of weather, isolated from specialized medical resources.

Our department had developed an excellent working relationship with the Army Medical section. My Chairman, Dr. Frank Shaw, had been working in this area for some time and the laboratory had selected a candidate partial morphine antagonist. This compound was amiphenazole (Daptazole) and animal work had been carried out with members of our department. Our first paper on this topic was entitled “Morphine Antagonism” (Shaw, Gershon and Bentley 1957). The first clinical effort was to obtain a normative profile of morphine effects. In the absence of pain it had a much higher incidence of side effects such as nausea and vomiting.

As mentioned with succinic acid, we could antagonize the CNS depressant effects of morphine in animals and man and improve vital functions with some loss of analgesia. So, with amiphenazole, we were looking to achieve full retention of pain control, but with antagonism of depressed vital functions.

These studies were pursued on one of the cancer units of a University affiliated hospital and published in the British Medical Journal. (Christie, Shaw, McCance et al. 1958b) followed by "Amiphenazole and Morphine in the production of Analgesia" (Gershon, Bruce, Orchard et al.1958c). As in prior work with barbiturates, we considered the development of a one pill mixture of two compounds to provide efficacy and safety which would ensure against over dosage with less risk of lethality. We again negotiated with a small pharmaceutical company and this combination was effective in achieving the goal of increased safety with adequate dosing of morphine and without causing decreased pain control. The product went on the market and was used fairly widely in Australia and England producing published results that were all positive. However, after a year or so, the sales diminished and it was taken off the market. Our efforts established efficacy; however the market determined the outcome and so we returned to the laboratory.

References:.

Christie G, Shaw FH, McCance I, Bruce DW, Gershon S. Treatment of certain side effects of morphine. Brit. Med. J. 1958b;1:675-80.

Gershon S, Shaw FH. Morphine and histamine release. J. Pharm. 1958a;10:22-9.

Gershon S, Bruce DW, Orchard N, Shaw FH. Amiphenazole and morphine in the production of analgesia. Brit. Med. J. 1958c;2:366-8.

Shaw FH, Gershon S, Bentley GA. Morphine antagonism. J. Pharm. 1957;9:666-71.

July 30, 2015

5. THA

The next opening was provided by a series of compounds synthesized by Prof. Adrian Albert at the Australian National University (ANU) in Canberra. He was synthesizing a series of acridine compounds in collaboration with the Chairman of Microbiology as antibacterial agents and possible use against tuberculosis. As the Department of Microbiology, in the next building to ours, was doing elaborate in vitro work, we planned to evaluate the pharmacologic properties of one compound in the series: THA, or 1,2,3,4 - tetrahydro - 5 - aminoacridine.

We started with little pharmacological knowledge of the compound, but had a very good dog model of morphine's effects. So we studied it as an analeptic. Given IV to a sleeping morphinized dog, THA produced an immediate arousal and return to clear consciousness.

Our interest in this compound expanded when we were contacted by the US Army to discuss our work with anti-hallucinogens. We arranged to have a detailed discussion with them together with colleagues at the University of Melbourne, who had developed different potential compounds. They were interested in our whole program, but particularly THA, because their main hallucinogenic compounds (referred to as incapacitating agents) were related to the pharmacology of Ditran (JB-329), a mixture of two structurally related isomers of an anti-cholinergic drug (Gershon and Olaria 1960). The following day, the colonel in charge turned up with a research grant for us to sign. After we published a number of papers on THA, I received a letter from a psychiatrist at the University of Pittsburgh asking permission to access my FDA submitted IND on THA (Bell and Gershon 1964; Bell, Gershon, Carroll and Holan 1964; Brinkman and Gershon 1983; Gershon 1960; Gershon 1965; Gershon, Naubauer and Sundland 1965; Gershon and Shaw 1958; Neubauer, Sundland and Gershon 1966a,b). He wished to administer THA to cases of imipramine overdose or poisoning, with or without other sedatives. I granted permission and he published papers on the success of the clinical observations. Apparently he also obtained patents for this use of THA, about which I was not fully informed (Soares and Gershon 1995).

Meanwhile, other investigators tried THA administration in Alzheimer's patients and also patented their findings. THA was then marketed as a treatment for the condition. Their observations amounted to replication of what we had shown previously; THA clearly produced arousal in many different drug-induced and clinical conditions. THA had a new life for several years as a highly touted treatment for Alzheimer's and it had a significant effect on the established

idea that Alzheimer's was untreatable. This gave rise to the introduction of other potential therapeutic agents and the field regained some therapeutic hope. My belief is that cholinergic antagonists have considerable therapeutic value and deserve further study. Still, great caution must be adopted because the disease has often been present for many years before treatment is attempted.

I must end this section with my belief that all these antagonists have considerable therapeutic value and deserve further study.

References:

Bell C, Gershon S. Experimental anticholinergic psychotomimetics. Antagonism of Yohimbine and Tacrine [THA]. S Med Exp 1964;10:15-21.

Bell C, Gershon S, Carroll B, Holan G. Behavioral antagonism to a new psychotomimetic—JB 329. Arch Int Pharmacodyn Ther. 1964;147:3-25.

Brinkman S, Gershon S. Measurement of cholinergic drug effects on memory in Alzheimer's Disease. Neurobiology of Aging 1983;4:139-45.

Gershon S. Blocking effect of tetrahydroaminacrin on a new psychotomimetic agent. Nature 1960;186:1072-3.

Gershon S. Behavioral effects of anticholinergic psychotomimetics and their antagonists in man and animals. Recent Adv Biol Psychiatry 1965;8:141-9.

Gershon S, Neubauer H, Sundland DM. Interaction between some anticholinergic agents and phenothiazines. Potentiation of the phenothiazine sedation and its antagonism. Clin Pharmacol Ther 1965;6:749-56.

Gershon S, Olaria J. JB-329, a new psychotomimetic, its antagonism to tetrahydroamino-acridane, and its comparison with LSD, mescaline and Sernyl. J Neuropsychiatry 1960;1:283-9.

Gershon S, Shaw FH. Tetrahydroaminacrin as a decurarising agent. J Pharm 1958; 10: 22-9.

Neubauer H, Sundland DM, Gershon S. Ditran antagonists in a mixed psychiatric population. J Nerv Ment Dis 1966a;142:265-77.

Neubauer H, Sundland DM, Gershon S. Sernyl, Ditran and their antagonists: Succinate and THA. Int J Neuropsychiatry 1966b;2:216-22.

Soares JC, Gershon S. THA – historical aspects, review of pharmacological properties and therapeutic effects. Dementia 1995;6:225-34.

August 6, 2015

6. Indole alkaloids

Yohimbine, Harmine and Ibogaine

Yohimbine

While still in Australia, before going to the University of Michigan, we started to study this group of compounds. They drew our attention from reports claiming they produced psychological, especially hallucinogenic, effects in humans. We also thought, after our studies with Ditran, that we might be able to find other models of such states. So we began to evaluate Yohimbine (YOH) in animal preparations including anesthetized rats, guinea pigs and dogs to establish pharmacological baselines. In all these animal preparations, YOH produced a fall in blood pressure as reported in the literature. We also injected the same dose intramuscularly to conscious dogs. The effect was arousal, increased activity and some distress with increased panting. We also heard the heart pounding strongly. These simple superficial observations did not seem to make sense. So we decided to plan studies in conscious beagle dogs to observe behavior and physiological effects.

We were fortunate that a group in the physiology department at the Florey Institute were working intensively with sheep. They had a technician, an immigrant physician, Ben, from Poland, who developed a preparation with an exteriorized carotid artery under a cover of skin to keep the animal viable after it had catheters inserted into the carotid artery. Ben also developed an exteriorized opening for the salivary gland and was assigned to help us get set up. This assistance and advice was given free with support from the Chairman. Ben became a friend to our group, ready to help at any time. I don't believe this sort of support, given to junior people, would be readily available today.

We could measure blood pressure from the carotid artery and inject the dose of YOH intravenously. The dog was either suspended in a leather harness with feet off the ground or free for behavioral observations in a large open mesh cage. In the conscious dog, intravenous YOH produced elevation of blood pressure with heart rate; blood pressure did not go down as usual in anesthetized animal preparations. Accompanying this finding was behavioral activation which became a central part of our interest in YOH.

At the lowest dose, we saw restless behavior, rise in blood pressure and increase in salivation. As the dose was increased, cardio-vascular and behavioral responses increased from restlessness to general bodily movements in the cage into what we considered to be anxiety and panic.

While I was at the NIMH funded unit at the University of Michigan, I worked under the supervision of Professor RW Gerard. I studied YOH effects in man and published extensive and detailed observations (Holmberg and Gershon 1961). The major finding was that the experiments presented us with a drug induced model of "anxiety." Now that our subjects could talk we documented all the behavioral and psychological features obtained by observation, physical recording and interrogation. With increased dosing, symptoms reached a "panic" state.

My colleague in these human experiments was Gunnar Holmberg from Sweden, a psychiatrist and physiologist. We became friends and maintained a relationship long after we returned to our home countries. These physiological, behavioral and psychological studies established early bench marks for developing drug induced models for psychological disorders.

The next question was to establish the etiology of the effects of YOH in animals and man. Patients with a baseline of clinical anxiety were sensitive to the YOH injection and developed high

levels of anxiety with a smaller dose. Without detailing the effects at this time, by chance, we also came up with an observation that suggested a possible screen for antidepressant agents.

Later Developments

The key finding of the effect of YOH in producing a physiological and behavioral model of anxiety in humans was followed up intensively by the Yale group. Some years later, at NYU, I learned from Don Kline of the effects of intravenous lactate infusion as another agent for inducing anxiety in man. Don's work attracted considerable attention but, unfortunately, neither of us did any direct comparison of the two models. More recently, neuroscientists have reported the presence of a gene and its relationship to basal high and low levels of anxiety. Other compounds have a reverse effect to YOH; Anandamide has an anti-anxiety effect and low levels are present when the patient has high anxiety. It has also been postulated that cannabinoids have an anti-anxiety effect, as do benzodiazepines. In the light of these findings and lack of a synthesis, we suggested possible modes of action for YOH (Holmberg, Gershon and Beck 1962a). Later the Yale group reported that with varying basal levels of clinical anxiety, the dose of YOH could be graded, low basal levels of anxiety required larger doses of YOH.

To proceed with investigations of YOH and its interaction with other psychoactive drugs, our first test compound was imipramine (Gershon, Holmberg, Mattson et al. 1962). With this extensive collection of data in man we went back to more detailed studies in the conscious dog. These studies showed that the physiological and psychological effects of YOH were increased by the tricyclic antidepressants, the early SSRI's and 5 HTP (Lang and Gershon 1963a).

We also conducted similar experiments with anti-anxiety agents and proposed a screening method for them (Lang and Gershon 1963b) .

With these and other experiments, we concluded that part of the effects of YOH was mediated by serotonin, confirmed later in our synthesis inhibitor studies at NYU. Looking at all our data, we found all antidepressants we administered with YOH produced a picture of increased arousal and anxiety up to the occurrence of panic state with increased autonomic effects. We then did the opposite set of experiments with antianxiety agents such as Librium and Valium. In all of these trials, the compounds modulated and reduced the behavioural and physiological effects to

baseline. We had now accumulated enough evidence to claim we had a model of anxiety and panic states in humans and dogs, confirmed by the actions of antidepressants and antianxiety drugs, consistent with the clinical effects in patients.

Harmine and Ibogaine

Our work in Australia and America also included two other indole alkaloids, harmine and ibogaine. Harmine was first reported to reverse catatonia in the 1920s and ibogaine was used as a hallucinogen for therapeutic purposes by Shamans in South America to treat addictions and other problems.

My work on these compounds was collaborative in both countries. In Australia, I became Acting Chairman of Pharmacology and initiated a one year fellowship as an elective for talented third year medical students. Four fellows worked with me on the indoles and all later had significant academic careers. Included were Barney Carroll, who became Chair of Psychiatry at Duke University in America and Ian Gust, who became Director of the Virology Institute at the University of Melbourne.

I also collaborated with Bill Lang, first as a post-doc in Melbourne, and then as a visiting fellow at the Missouri Institute of Psychiatry. Shortly after he returned to Australia, he died of a blood cancer and I lost a friend and collaborator.

Our results with these other alkaloids, sometimes separately and sometimes with YOH, are referenced below. Both harmine and ibogaine produced similar effects to YOH with strong alerting and arousal effects against a large variety of compounds and depressed clinical states. Harmine has been reported by others to also have selegiline like effects inhibiting both forms of MAOI.

References:

Bell C, Gershon S, Carroll B, Hogan G. The analeptic activity and EEG effects of some indole alkaloids. Psychiat Neurol 1963;146:276-85

Bell C, Gershon S, Carroll B, Hogan G. Behavioral antagonists to a new psychotomimetic- JB 329. Arch Int Pharmacodyn 1964;147:3-25.

Garfield S, Sletten I, Sundland D, Ballou SR, Gershon S. Chemically induced anxiety. Int J Neuropsychiat. 1967;5:426-33.

Gershon S. Yohimbine analogues exhibiting differential pharmacological responses., Med. Pharmacol Exp 1966;15(1):24-34.

Gershon S, Bell C. A study of the antagonism of some Indole alkaloids to the behavioural effects of Ditran. Med Exp 1963;8:15-27.

Gershon S, Holmberg G, Mattson E, Mattson N, Marshall A. Imipramine Hydrochloride; its effects on clinical, autonomic and physiological functions. Arch Gen Psychiat 1962;6:96-101.

Ho A, Hoffman DB, Gershon S, Loh HH. Distribution and metabolism of tritiated Yohimbine in mice. Int Pharmacodyn Ther 1971;194(2):304-15.

Holmberg G, Gershon S., Autonomic and psychic effects of Yohimbine Hydrochloride. Psychopharmacology 1961;2:93-106.

Holmberg G, Gershon S, Beck L. Yohimbine as an autonomic test drug. Nature 1962;193:1313-4.

Lambert GA, Lang WJ, Friedman E, Mellor E, Gershon S. Pharmacologic and biochemical properties of isomeric yohimbine alkaloids. Europe. J Pharmacol 1978;49:39-48.

Lang WJ, Gershon S. Effects of psychoactive drugs on yohimbine induced responses in conscious dogs; a study of antidepressant drugs. Med Exp 1963a;7:224-31.

Lang WJ, Gershon S, Effects of psychoactive drugs on yohimbine responses in conscious dogs. A proposed screening procedure for anti-anxiety agents. Arch Int Pharmacodyn 1963b;142:457-72.

Lang W Gershon S, Hogan G. Some antagonists of atropine-like psychotomimetics. J Pharm Pharmacol 1963;15:831-40.

Sanghyi I, Gershon S. Similarities between the behavioural and pharmacological actions of yohimbine and 5-hydroxytryptophan in the conscious dog. Europ J Pharmacol 1970;11:125-9.

August 20, 2015

The Etiology of Bipolar Disorder: A Biochemical Puzzle

7. Acetylcholine, Norepinephrine and Serotonin

We pursued an answer to this puzzle for almost 15 years in Australia and America. I hope these pieces of the puzzle will induce new thinking about current beliefs concerning neurotransmitters and their effects on bipolar disorder beyond the unitary effect of any one transmitter alone.

1. Acetylcholine

Like so many scientific findings, serendipity played a role in our first step. The Chair of our Department in Melbourne was contacted by the Commonwealth Scientific and Industrial Research (CSIRO) concerning a problem. In one laboratory, many staff scientists were reporting sick, seen first by general physicians and then, in most cases, referred to a psychiatrist. Of these a total of 16 patients were diagnosed with either depression or schizophrenia. The following case study presents the clinical picture:

> *A man of 43 had been exposed to organo-phosphorous insecticides over a 10-year period. He complained from time to time of nausea, vomiting, excessive perspiration, giddiness and muscular incoordination. He became tired, had difficulty sleeping and worried about impaired mental abilities. In 1959, he consulted a psychiatrist with complaints of severe depression. He was restless, miserable, had nightmares and insomnia. He was irritable, cried occasionally and was unable to carry on at work or at home. He was given sedatives at night and treated with multiple antidepressants including a MAO inhibitor but with little effect. By December 1960, eight months after toxic exposure ceased, he was no longer depressed, slept well, while memory and concentration returned to normal and he felt like his former self.*

Of the 16 cases we saw, seven were diagnosed as depression, five as schizophrenic and the remaining four were not clearly defined. But all had impaired memory and concentration. Gradual recovery was related not to treatment but to natural restoration of choline acetylase. We first drew attention to these effects in an article published in the Lancet (Gershon and Shaw 1960).

We followed up this study with a field survey in two fruit growing regions in Victoria, where physicians reported that rates of depression were elevated after the spraying season. The results of our study and the survey were published the following year (Gershon and Shaw 1961).

After publication, we received letters from investigators in other countries reporting similar observations in farming communities and several from Europe sent reprints of their work. It also had wider ramifications. A well-known murder mystery author quoted our paper and used insecticides as the murder weapon, while Rachel Carson's popular book exposed the health risks associated with widespread spraying of foods by insecticides. As often happens, in preparing our findings for publication, we found earlier work of a similar nature conducted a decade earlier by researchers at the Maudsley Hospital in London (Rowntree, Nevin and Wilson 1950). They used the same irreversible cholinesterase as in our studies, di-isopropyl-fluoro-phosphate (DUFLOS). This was given to 17 schizophrenic and nine manic-depressive patients for from 7 to 37 days. In six schizophrenic patients, psychosis was activated and florid symptoms that characterized the onset of illness were reactivated. Consciousness was not impaired and this was not a delirium. In manic depressives, mania lessened while depression, insomnia and dreaming increased. These changes in mental state persisted for several months after drug administration.

Observations in 10 normal control subjects were also informative; they developed a characteristic picture of depression, irritability, lassitude and apathy. They looked dejected, miserable and unhappy. These findings were essentially similar to our Australian cases and the EEG changes reported in London were similar to the one case of our own, where we had an EEG. In our sample, DUFLOS induced or reactivated both depressive and schizophrenic forms of illness and these effects lasted for from 6 to 12 months after exposure, despite any treatment interventions. This recovery time was dictated by the body manufacturing new acetyl cholinesterase.

In America, at NYU, we communicated and collaborated with Davis and Janowsky over their findings with manic-depressive patients administered physostigmine, a reversible acetyl cholinesterase inhibitor with effects lasting only up to 24 hours. Administered in the manic phase, this produced a marked diminution in all symptoms, including behavior, speech and thought often with a full reversion to baseline and even some symptoms of depression. My colleague, Burt Angrist, and I discussed these findings and decided they were related to our own work on induction of depression by insecticides. The patients we were seeing at Bellevue, admitted as emergencies, were probably more severe than those available to Davis and Janowsky in a State Hospital, so we

invited them to join us in a collaborative study. Together, we interviewed selected patients, recorded their clinical picture and rated them on a mania scale. Our visitors injected physostigmine and the patients gradually became calmer, speaking in a more rational way and, after about an hour, were well behaved, talking sensibly and restored to a euthymic state. One patient began to show depressive symptoms with an increasing dose until administration was terminated.

This collaboration confirmed consistent findings with reversible and irreversible acetyl cholinesterase inhibitors and supported the role of acetylcholine in the biochemical etiology of both schizophrenia and bipolar disorder. It also demonstrated a level of scientific collegiality we currently miss (Shopsin, Janowsky, Davis and Gershon 1975).

2. Norepinephrine or Serotonin?

From the mid 1960's on, biochemical speculation about etiology of the major psychiatric syndromes began to focus on the catecholamines. In 1965, Shildkraut proposed the "catecholamine hypothesis of affective disorders" (Shildkraut 1965) and in 1970 Axelrod and his team won the Nobel Prize for their work on the uptake of catecholamines in humans.

This theory held that decreased levels of norepinephrine (NE) and its metabolites existed in the brain and cerebrospinal fluid in depression while elevated levels were present in mania. New antidepressants were introduced at a rapid rate and we had access to many of them at NYU for clinical trials and animal experiments. In our clinical trials, some of them were ineffective for depression but had fulfilled the animal requirements for this hypothesis. It was not long before experiments with synthesis inhibitors and treatment response to the SSRI antidepressants began to reconcile this anomaly and shift the focus to serotonin.

We now became involved at NYU with experiments in animals and humans using synthesis inhibitors of both amines, norepinephrine and serotonin. Patients with depression, successfully treated with imipramine and in remission, were treated with AMPT, a NE synthesis inhibitor or PCPA, a serotonin synthesis inhibitor. Only the serotonin inhibitor caused a return of depressive symptoms; its withdrawal led to return of remission. This clinical demonstration was preceded by numerous animal experiments to justify the logic and safety of conducting the experiment in patients (Shopsin, Gershon, Goldstein et al. 1975).

Closely related to our studies, was the pioneering work of our colleague Dr. Michael Stanley, showing reduced imipramine binding (serotonin transporters) in the brain of individuals who had committed suicide, published in Science (Stanley, Virgilio and Gershon 1982).

This record of research conducted between 1960 and 1975 reveals the shifting sands of biochemical speculation about the etiology of bipolar disorders, from acetylcholine to norepinephrine to serotonin. As so often in neuroscience research, the brain produces more puzzles than definitive or singular answers. How do we reconcile our earlier findings with acetylcholine and more recent ones with serotonin? One could suggest that our experiments with these two sets of neurotransmitters are classical examples of translational neuroscience, we hope may be followed up to clarify their roles.

References:

Gershon S, Shaw FH. Psychiatric sequela of exposure to OP insecticides. Lancet 1960;1:1371-4.

Gershon S, Shaw FH. Psychiatric sequelae of chronic exposure to organophosphorus insecticides. Lancet 1961;1:1371-4.

Rowntree DW, Nevin S, Wilson A. The effects of diisopropylfluorophosphonate in schizophrenia and manic depressive psychosis. J Neurol Neurosurg Psychiatry. 1950;13(1):47-62.

Shildkraut JJ. The catecholamine hypothesis of affective disorders; a review of supporting evidence. Am. J. Psychiatry 1965;122:509-22.

Shopsin B, Gershon S, Goldstein M, Friedman E, Wilk S. Use of synthesis inhibitors in defining the role of biogenic amines during imipramine treatment in depressed patients. Psychopharmacol Commun. 1975;1(2):239-49.

Stanley M, Virgilio J, Gershon S. Tritiated imipramine binding sites are decreased in the frontal cortex of suicides. Science 1982;216:1337-9

September 24, 2015

8. Neuropathology

Adverse Effects of Antipsychotic Medication

Since our earliest reports (Mackiewicz and Gershon 1964; Singer, Sanghvi and Gershon 1971), perhaps a hundred new antipsychotic compounds have been introduced. Each reports a lengthy list of side effects; many are direct actions on the brain, others may be caused via other neuronal mechanisms. Well publicized CNS effects include tardive dyskinesia, Parkinson's syndrome, neuroleptic malignant syndrome and serious neurotoxicity along with drug interactions, including irreversible effects with lithium. A detailed compilation of these adverse effects should cause more concern than seems to be the case. Furthermore, increasing proposals to treat younger and younger children should arouse more alarm in our present state of ignorance.

Neuropathology

Our early study on rabbits treated with chlorpromazine showed neuropathology and nerve loss (Manckiewicz and Gershon 1964). More recently, rats treated with haloperidol showed similar neuronal changes in the substantia nigra and striatum (Mitchell, Cooper and Griffith 2002). Here is the crux of the problem: we do not know the etiology of the psychotic disorders we are treating, we cannot label them reliably and the treatments are almost certainly harmful to the brain and other organ systems. Yet we blithely persist as if there were no problems.

The Risk-Benefit Dilemma

Psychiatrists, like physicians in the rest of medicine, informed by the Hippocratic Oath to, "First, do no harm," struggle with the task of balancing benefits against risks. Perhaps the best example was when insulin coma was deemed the best and most effective treatment for schizophrenia, a worldwide pandemic delusion. Insulin coma was accompanied by protracted or irreversible coma, degrees of dementia, and occasional death. When a colleague and I questioned its efficacy based on patient follow ups at John Cade's hospital in Melbourne, we were attacked

as irresponsible, ignorant and punished. Our claim it was not effective was validated by the Maudsley study comparing insulin coma with barbiturate induced sleep, showing no difference between treatments (Ackner, Harris and Oldham 1957; Bourne 1953; Fink, Shaw, Gross and Oldham 1958)**.** Yet insulin coma continued worldwide until the antipsychotics arrived in 1954. Whatever perceived benefits insulin coma bestowed were probably due to the care and attention devoted to the treatment of patients in coma.

The situation with the anti-psychotics has been more nuanced and complex but also slow to evolve and clarify. The initial benefits appeared revolutionary, and within a decade, the old asylums were closing and "deinstitutionalization" was underway. The drugs primarily stifled the acute and disturbing features of schizophrenia that required institutionalization; hallucinations, delusions, paranoia and aggression (the so called positive symptoms).

Only later did we fully appreciate the obverse side of the risk-benefit coin. Patients, often alone and bereft of family, living in an unwelcoming community and sometimes on the streets, became victims of side effects and stopped taking the drugs, relapsed and were re-hospitalized (the so-called revolving door). This was aggravated by an increasing awareness among patients and prescribers that anti-psychotic medication often did little to benefit the cognitive difficulties, social skill deficits, apathy and poor motivation that combined to complicate earning a living and thriving in community (the so called negative symptoms).

The similarities between these two historic events, insulin coma and antipsychotic medication, are disturbingly similar; the benefits were overinflated and the risks underestimated. We seem unable to assimilate that lesson and pass it along. What is needed is a textbook on the neurological and neuropathological effects of anti-psychotic drugs, coupled with the clinical skill and knowledge to use them wisely in both a hospital and a supportive community setting.

References:

Ackner B, Harris A, Oldham AJ. Insulin treatment of schizophrenia. Lancet 1957;1:607-11.

Bourne H. The insulin myth. Lancet 1953;2:964-8.

Fink M, Shaw R, Gross G, Coleman FS. Comparative study of chlorpromazine and insulin in the therapy of psychosis. JAMA 1958;166:1846-50.

Mackiewicz J, Gershon S. An experimental study of the neuropathological and toxicological effects of chlorpromazine and reserpine. J. Neuropsychiat. 1964;5:159-69.

Mitchell IJ, Cooper AC, Griffith MR. Acute administration of haloperidol induces apoptosis of neurons in the striatum and substantia of rats. Neuroscience. 2002;109(1):89-99.

Singer G, Sanghvi I, Gershon S. Exploration of certain behavioral patter ns induced by psychotropic agents in the rat. Psychopharmacol. Bull. 1971;7:32

November 5, 2015

9. Model Psychoses:

Amphetamine

I came to NYU in early 1963 from St. Louis and quickly saw that Bellevue Hospital had a very different mix of patient populations. The most conspicuous groups were drug users and abusers in large numbers (Angrist and Gershon 1967a,b).

The variety of agents was almost limitless and hallucinogenic properties were attributed to many strange products. So we had a dilemma; what substances produced abnormal behavioral effects and were they due to an active substance or group belief and individual expectations?

In about 1964, a young psychiatrist came to see me after training with Don Klein. In his introduction, Burton Angrist told me he had learned a great deal of psychopharmacology from Dr. Klein but was looking for an area of study that was different and more in line with the clinical populations he was interested in. This turned out to be the psychopharmacology of psychotomimetics and drugs of abuse, including the fads that changed from year to year in the

addict population. So we mutually agreed to this area for study, believing it was both important and could contribute to scientific knowledge.

We started with a simple question; what was myth and reality among drug abusers? Burt noted a popular practice in the culture at that time was smoking the baked inner white layer of banana peel. That was a real conundrum to begin with. Surveys of users recorded its purported hallucinogenic effects so he had to find colleagues who could determine the chemical nature of the constituents. At NYU that was Arnold Friedhoff, Schweitzer and me. We were very good at chromatographic analysis and the sacrifice of many bananas was the clear answer. There was no chemically active product and what we found was mostly carbon, a cheap and safe pharmacologically inactive substance (Angrist, Schweitzer, Friedhoff and Gershon 1967).

This small experiment taught us a lot about mass drug abuse and the reliability of reported effects. In this case, they were the expectations of guru users passed on to their acolytes. The sobering results caused Burt to examine compounds with a better provenance.

Burt's next step was to examine the pattern and effects of amphetamine abuse in New York City (Angrist and Gershon 1969). A cross sectional picture revealed its use was widespread and in some cases devastating. We heard about many psychotic features upon interviewing those who mixed drugs with alcohol. Many were unemployed, including some physicians who had lost their license. This group with their impairments formed the population for the next phase of our work, including carefully planned clinical and chemical studies that yielded over 30 publications, mostly in five years (1967-1972), among them clinical findings, (Angrist and Gershon 1970; Angrist, Schweitzer, Friedhoff et al. 1969; Angrist, Schweitzer, Gershon and Friedhoff 1970; Angrist, Shopsin, Gershon and Friedhoff 1970) and basic science studies in animals predominantly examining amphetamine, its stereoisomers (Angrist and Gershon 1971; Angrist, Shopsin and Gershon 1978; Wallach, Friedman and Gershon 1972) and its metabolites (Angrist, Schweitzer, Friedhoff and Gershon 1970; Angrist, Shopsin, Gershon and Wilk, 1972; Schweitzer, Friedhoff, Angrist and Gershon 1971).

This body of work demonstrates what a principal investigator with a clear concept can accomplish in making a truly translational impact on neuroscience and clinical research.

Background Events and Findings

It was well known for many years that abuse of amphetamines could produce psychotic episodes (Angrist and Gershon 1967a,b). This was demonstrated more dramatically during the Second World War when the Japanese military used amphetamine for increasing alertness and working longer hours. After the war ended, we gained considerable evidence that psychoses sometimes resulted and most recovered fully. In the English literature, there were reports that some psychoses resembled schizophrenia, while others insisted they were more like a delirium or a disorganized hyperactive state, akin to mania.

This was a primary question in the first stage of our studies. Burt began by admitting such patients to our research ward and recording their symptoms and behavioral profile until aberrant features subsided. He was a superb, sensitive and highly observant psychiatrist, who carefully noted the changing clinical state over the duration of their stay. We found the patterns fitted well with the different clinical pictures observed and reported in schizophrenia. We decided to test this hypothesis by comparing the profile we saw in nature with that we obtained in a research setting (Angrist and Gershon 1970). These experiments were essential because many investigators held that the symptoms of schizophrenia were different from the amphetamine-induced behaviors observed in addicts. After experiments with different doses of amphetamine over varying durations, Angrist and I concluded that, compared with the spectrum of naturally occurring schizophrenic disorders, administration of amphetamine to normal subjects produced pictures that were indistinguishable.

Once we had demonstrated this finding, we decided it would be profitable to examine the underlying pharmacological effects of amphetamine.

Amphetamine blocks the reuptake of dopamine and to a lesser extent norepinephrine and serotonin. Our data suggested that antipsychotic drugs, which also block dopamine receptors, would antagonize amphetamine-induced psychotic states. We used haloperidol to mitigate or terminate schizophrenic symptoms in our amphetamine induced psychotic subjects; the findings demonstrated a similar antagonistic effect but the blocking effect was more rapid and greater in degree for drug-induced cases compared to that seen in chronic schizophrenic patients. Discussion persists as to whether you need a predisposed substrate for amphetamine to induce a psychosis or if it is being produced *de novo* with a *restituto ad integrum* on full elimination of the drug. Our data supports the latter assumption. Patients with a sub-syndromal profile of schizophrenia seem to be sensitive to sub-threshold doses that produce a psychosis.

Another use of this research was to employ amphetamine induced effects in animals as a screen for psychoactive drugs. Amphetamines produce motor hyperactivity in rats and mice and this behavior can be used to screen for antipsychotic and anti-manic agents, although this does not apply reliably to all compounds. For example, it is not modified by lithium or valproate, only by most antipsychotics and sedatives. Therefore, we extended our studies to amphetamine-induced stereotypy in rodents to dogs (Angrist and Gershon 1972; Rotrosen, Wallach, Angrist and Gershon 1972; Wallach, Angrist and Gershon 1971) and cats (Wallach and Gershon 1972) where many antipsychotics antagonized this behavior. Clozapine, an atypical antipsychotic, antagonized stereotypy but not hyperactivity. This discrepancy, together with differences on dopamine effects, led others to suggest clozapine was not an effective antipsychotic. In our own early clinical studies on clozapine, we found it a very interesting and effective antipsychotic. It was also unique with a very low incidence of EPS and a therapeutic action on treating tardive dyskinesia caused by other antipsychotics. Clozapine use has suffered from the dispute over its different effects on dopamine neurotransmission but this has been shown irrelevant to its therapeutic activity.

All the studies in this broad arena were created by a talented group of scientists working collaboratively in a supportive academic setting. This form of interaction is less frequent now and I believe science has suffered a loss.

References:

Angrist BM, Gershon S. Drug-induced psychoses. Part 1. Hospital Practice1967;11:36-9.

Angrist BM, Gershon S. Drug-induced psychoses. Part 2. Hospital Practice 1967;11:50-3.

Angrist BM, Schweitzer J, Friedhoff AJ, Gershon S. Banana smoking: Chromatographic analysis of baked skins. NY State J. Med 196715:2893-5.

Angrist BM, Gershon S. Amphetamine Abuse in New York City 1966-1968. Seminars in Psychiatry 1969;196-207.

Angrist BM, Schweitzer J, Friedhoff AJ, Gershon S, Hekiminian L, Floyd A. The clinical symptomology of amphetamine psychosis and its relationship to amphetamine levels in urine. Int. J. Pharmacopsychiat. 1969; 2:125-39.

Angrist BM, Gershon S. The phenomenology of experimentally induced amphetamine psychosis; preliminary observations. Biol. Psychiat. 1970;2:95-107.

Angrist BM, Schweitzer J, Gershon S, Friedhoff AJ. Mephenteramine psychosis; misuse of the Wyamine inhaler. Am. J. Psychiat. 1970;126:1315-17.

Angrist BM, Schweitzer J, Friedhoff AJ, Gershon S. Investigation of P-methoxyamphetamine excretion in amphetamine induced psychoses. Nature 1970;225:651-2.

Angrist BM, Gershon S. A pilot study of pathogenic mechanisms in amphetamine psychosis utilizing differential effects of D and L amphetamine. Pharmacopsychiatrie Neuro Psychopharmacologie 1971;4:65.

Angrist BM, Shopsin B, Gershon S, Wilk S, Metabolites of monoamines in urine and CSF after large dose amphetamine administration. Psychopharmacologia 1972;26:1-9.

Rotrosen J, Wallach MB, Angrist BM, Gershon S. Antagonism of apomorphine induced stereotypy and emesis in dogs by thioridazine, haloperidol, and pimozide. Psychopharmacologia. 1972;26(2):185-94.

Schweitzer J, Friedhoff AJ, Angrist BM, Gershon S. Excretion of P-methoxyamphetamine administered to humans. Nature 1971;229:133-4.

Wallach MB, Angrist BM, Gershon S. The comparison of stereotyped behavior-inducing effects of D and L amphetamine in dogs. Comm. Behav. Biol. 1971;6:93-6.

Wallach MB, Friedman E, Gershon S. 2,5-dimethoxy-4-amphetamine (DOM), a neuropharmacological examination. J. Pharmacol. Exp. Therap. 1972;182:145-54.

Wallach MB, Gershon S. The induction and antagonism of CNS stimulant-induced stereotyped behavior in the cat. Eur. J. Pharmacol. 1972;18:22-6.

December 3, 2015

Comment by Burton Angrist

1. Studies of amphetamine psychosis: Clinical aspects

When I began my residency training, Psychiatry was more or less overwhelmingly dominated by psychoanalytic thought. I was excited and couldn't wait to begin healing the sick with my clever psychotherapeutic insights. The only problem was that the sick were inconsiderate enough not to get better.

I was using medications but my supervisor, recognizing his own limitations in this area, suggested I consult with Don Klein, our hospital's research psychopharmacologist. Don generously reviewed my patients in detail and made suggestions for many about changes in dose, drug, etc. They all improved! (Some a lot, some less, but all were better to some degree). I was floored and decided to get postdoctoral training in psychopharmacology.

I went to Jerome Jaffe, one of my Pharmacology professors in medical school, for advice and Jerry steered me to Sam Gershon, who had recently started a Psychopharmacology Research Unit at NYU/Bellevue.

I liked Sam immediately. He was gracious, utterly without pretense, and often hilariously funny. Over time. this fondness continued to grow but I also recognized some of his other qualities, his remarkable astuteness and clarity of thought and a real wisdom complementing his enormous knowledge base.

I began working on some of the ongoing clinical trials on the unit, learning to do some ratings, and saw some of the patients in Sam's study of lithium vs. chlorpromazine in acute mania that led to the introduction of lithium in the US.

Soon, however, in order to stimulate my enthusiasm, Sam sat down with me and asked about my own specific interests in Psychiatry and Psychopharmacology. Rather than naming a specific area, I said that I was interested in fine-grained clinical assessment as a clue to biologic substrates. For example, we lump together as "paranoid" both patients who are hyper-aroused, fearful and diffusely referential, and those who calmly and with little affect say they simply have "known" for years that the government, mafia or CIA has been spying on them. Surely, there must be a different biologic basis to these clinical presentations. I remember Sam's response, "That's very commendable. Why don't you have a look at the similarities and differences between amphetamine psychosis and schizophrenia? Kety and others have been saying that it's an excellent pharmacologic model."

I was skeptical and excited – skeptical that any drug psychosis could model the rich, complex symptoms of schizophrenia but excited because I already had an interest in substance abuse and Bellevue had many patients with extraordinarily heavy and varied substance abuse histories. (It was the mid-1960s and I was a bit of a hippie.) I began reading up on amphetamine psychosis and interviewing patients admitted to Bellevue after using the drug.

The literature review at first seemed surprisingly sparse. From 1938 when it was first reported (Young and Scoville 1958) to 1958, only about 20 reports described about 30 cases of amphetamine psychosis. In 1958, however, Connell's monograph alone concisely and clearly described 42 patients with amphetamine psychosis (Connell 1958). The first, clinical section of the monograph ended with 17 conclusions, three of which will be repeated here:

1. Psychosis associated with amphetamine usage is much more common in this country than would be expected from reports in the literature.
2. The clinical picture is primarily a paranoid psychosis with ideas of reference, delusions of persecution, auditory and visual hallucinations, in a setting of clear consciousness.
3. The mental picture may be indistinguishable from acute or chronic paranoid schizophrenia.

Finding newly admitted patients and seeing them quickly, before their symptoms cleared might have been enormously difficult in a hospital the size of Bellevue were it not for a research screening program previously set up by Dr. Arnold Friedhoff. In this program, a research nurse reviewed the prior 24 hours' admission notes and listed the patient name, ward and chief complaint (or gave a description of the circumstances of admission if no complaint was offered, i.e., "Found wandering nude in Central Park," etc.) If amphetamine was mentioned or if presenting symptoms were obviously those of an acute paranoid psychosis, I'd go interview the patient on the ward and, sometimes transfer them to Sam's research ward.

In this way, I was able to identify and interview 60 patients with amphetamine- related admissions to Bellevue in a little over a year. Connell's first conclusion, "psychosis associated with amphetamine usage is much more common - than would be expected from reports in the literature," was certainly correct.

Of these 60 patients, more than half (32) had paranoid or paranoid-hallucinatory symptoms. (Auditory and visual hallucinations were most commonly seen but less frequently olfactory and

tactile hallucinations were encountered. Thus, Connell's conclusion that "the mental picture may be indistinguishable from acute or chronic paranoid schizophrenia" also was supported). Other presentations also were seen and included: emotional lability, tearfulness or anger, suicide attempts (cutting), potentially suicidal behavior (a patient jumped from a third story and sustained a leg fracture to escape persecutors). Unprovoked assaultiveness or bizarre behavior (a patient who took down a chain link fence and "played drums" on garbage cans) were also encountered (Angrist and Gershon 1969).

If the patients seen on other wards acknowledged amphetamine use and were willing, they were transferred to the research ward where symptoms were rated daily and urine was collected. In this way we intended:

1. to confirm the presence of amphetamine;
2. to determine the duration required for psychotic symptoms to clear; and
3. To examine any relationships between symptoms and urine amphetamine levels. These levels were determined in Dr. Friedhoff's laboratory by Dr. Jack Schweitzer.

However, the design of our studies also raised some important and troublesome problems. We didn't know our patients' pre-drug status and schizophrenic patients also sometimes took amphetamine. Thus, if a patient showed thought disorder, bizarre delusions or psychotic symptoms that did not resolve rapidly (as most did) did that imply pre-existing schizophrenia or rather did it mean that amphetamine could cause such effects in normals? What was due to the drug and what was due to substrate? I obsessed about the questions over and over and finally came to Sam with the problem. He smiled at me and said, "Doctor! You're trying to decide whether the chicken or the egg came first." That of course was the answer. The question was logically insolvable.

For a partial, perhaps imperfect solution, I fell back on Kraepelin's concept that recovery, in schizophrenia in not a full *restitutio ad integram.* When no longer psychotic, schizophrenic patients still show some residual symptoms such as blunted affect, diffuseness in line of thought and association, and perhaps, some mild delusional ideation. I decided to have patients seen by three senior psychiatrists (Drs. Gershon and Friedhoff and our research ward senior clinician Dr. Leon Hekimian), not when acutely ill but when apparently fully recovered, prior to discharge. Patients were then assigned to two groups, one who showed complete clearing and another with residual schizophrenic psychopathology (C & RSP). The study then showed that

1. amphetamine was present in all patients' urine;
2. psychotic symptoms cleared rapidly and this clearing paralleled the curve of declining amphetamine levels;
3. Not all patients reported hallucinations initially, but in those who did, hallucinations were invariably the first symptoms to clear; and
4. there were only trivial and clinically insignificant differences in the rate of clearing between patients who cleared completely and those who, when no longer psychotic, showed residual schizophrenic psychopathology (Angrist, Schweitzer, Friedhoff et al. 1969).

As this study was nearing completion, Griffith and coworkers reported a new approach to the study of amphetamine psychosis -- the prospective experimental induction of the condition by administration of the drug to screened non-schizophrenic volunteer-abusers. This stronger design enabled the researchers to observe the development of the psychosis uncontaminated by the possible use of other drugs or by pre-existing Axis I disorders.

Dextroamphetamine 5-10 mg per hour was administered orally. Blood pressure, pulse rate and temperature were checked before each dose. EKGs were done at baseline and if any change in cardiac rhythm was noted. This was done around the clock for as long as subjects tolerated it. Four subjects participated (Griffith, Oates and Cavanaugh 1968).

As noted in more detail in a subsequent report (Griffith, Cavanaugh, Held and Oates 1972), all four subjects became paranoid. Some felt they were being secretly photographed or described on TV. One felt that the entire study was a subterfuge. Another felt an assassin had been hired to kill him. Yet another became aware of a "giant oscillator" hidden in the ceiling that both controlled his thoughts and the behavior of others.

We pursued similar studies with the same safety measures Griffith, Cavanaugh, Held and Oates had devised, but slightly changed the drug and dosing regimen. Racemic amphetamine tables were used and dosing was made more flexible and potentially somewhat more aggressive (0-50 mg per hour could be given with the dose determined by the blood pressure and pulse rates determined immediately before) .

The first study involved four patients (Angrist and Gershon 1970). The first developed a characteristic syndrome that occurred each time he took amphetamine or related drugs (mephentermine inhalers) (Angrist, Schweitzer, Gershon and Friedhoff 1970) and which had led

to many prior hospitalizations at Bellevue. He began to smell a "vile" smell that he thought was caused by the drug being excreted in his perspiration. He would then feel that he was so offensive to others that they or some "gang" would "clean me up" or kill him. Often voices would reinforce these fears. In this case (after a cumulative dose of 230 mg), he began to take one of several showers. Later, lying in bed and still preoccupied with ideas about smelling, he heard other patients (who were on a separate part of the ward at the time) discussing him: "He's stupid. Why is he doing it? He's not doing anything. He's just staying up." He saw someone working in a laboratory across the street and felt he had been "planted" to observe him.

The second subject in this series began to feel that he had received special enlightenment from God and became "a prophet." He began writing his "revelations" frantically, then stopped and stood preaching them loudly to the world at large:

> "My consciousness in the form of what you know as human. My feeling which I receive from Him. I bring the answer to the unknown and yet. In my human form, He might let me act human, for the rest must still wonder at my actions, which make them doubt my having been used to <u>enlighten</u>. Every thought that stops me from accepting <u>all knowledge</u>, more than man has ever known. It is just part of the supreme game to make you wait until it is time for you to receive everlasting good. It is not mine to give. I am His. I bring His will, call it prophet."

Of the other two subjects, one became withdrawn and irritable and described a momentary episode of "terror" (feeling someone was behind him). The other became emotionally labile, infantile, provocative and hostile. She frequently glanced to the side with alarm, but denied visual hallucinations. Probably, neither could be described as formally psychotic.

In subsequent studies (Angrist, Shopsin, Gershon and Wilk 1972), florid psychotic states conforming precisely to prior descriptions of amphetamine psychosis were seen.

One subject, after 465 mg racemic amphetamine over 23 hours, saw "colored haloes" around lights, then "heard" a gang coming on the ward to kill him. His suspicions included the experimenter, who he assumed "set up the trap" and he lunged, but was able to stop himself. He rejected explanations that his experiences were drug induced with sardonic mock agreement (e.g., "Oh? Hah! So that's the way it's going to be?"). At other times, he became tearful and begged the

experimenter to explain "what was really going on." He had visual hallucinations of gangsters and doors opening and closing in the shadows and visual illusions (e.g., paper on a bulletin board "turned into" a gangster in a white raincoat). He jumped at the slightest sound, assuming it was the gang coming to "get" him.

What Does Amphetamine Psychosis Model?

Connell's fourth conclusion was "the mental picture may be indistinguishable from acute or chronic paranoid schizophrenia." Some controversy exists, particularly with respect to affect and thought disorder in amphetamine psychosis.

In his review of Connell's monograph, Slater (1969) commented that the two disorders may differ with respect to "the brisk emotional reactions usually in the direction of anxiety". In contrast, Griffith and co-workers (1972) noted that "subjects who were previously quite verbal and relatively trusting became quite taciturn and reserved and negativistic, and described their affect as "cold" and "detached." Bell did a study in which methamphetamine was given intravenously in doses individualized to raise blood pressure 50% and observed psychoses while subjects were still acutely elated. (Bell 1973). He commented that "the relatively slow oral administration of the drug in their (Griffith and co-workers) study probably "confused the issue" (Bell 1973).

Our own experience may support Bell's assessment. We clearly have seen dysphoric and blunted affect in some subjects but I don't recall ever seeing this response until subjects had been taking the drug overnight at least, a time at which there might have been some admixture of fatigue and "crashing" (Warning! This observation is from memory of studies done about 40 years ago).

Thought disorder in amphetamine psychosis is also somewhat controversial. It was not noted in the studies of Griffith, Cavanaugh, Held and Oates (1972) and Bell explicitly noted that this sign was not seen in amphetamine psychosis (Bell 1965). We've seen some examples which, although relatively mild, are, I believe, recognizably schizophreniform. Two examples are:

1. In response to the proverb "people who live in glass houses shouldn't throw stones" – "If you throw stones you risk your life. Living in a glass house would shatter your whole being."
2. In a patient who had received 430 mg of l-amphetamine in a study and been asked how he felt, "agitated and annoyed"; (Why?) "It's a ridiculous thing! Like the marijuana laws.

> That's totally ridiculous! It's like a thunderstorm in the forest. It affects young trees. There's a balance of nature. You mess with the balance of nature you lose buffalo, you lose birds. For man, you lose philosophies" (Angrist, Sathananthan, Wilk and Gershon 1974).

In addition to schizophrenia another condition that amphetamine psychosis models quite faithfully is psychotic mania. Post (1975) noted that the response to increasing doses of CNS stimulants progresses in a continuum from activation and euphoria through dysphoria to psychosis. A similar longitudinal evolution occurs in an episode of psychotic mania (Carlson and Goodwin 1973). Fibiger (1991) noted this and proposed that amphetamine psychosis be considered a model of psychotic mania.

So, which is it – schizophrenic or psychotic mania? I think the two often cannot be distinguished in the acute phase at a single point in time. The distinction is made longitudinally and based on interphase functioning and deficits when "well." In this, amphetamine psychosis with its usual tendency toward a *restitutio ad integram*, more closely models psychotic mania.

References:

Angrist BM, Gershon S. Amphetamine abuse in New York City 1966-1968. Seminars in Psychiat. 1969;195-207.

Angrist BM, Schweitzer J, Friedhoff AJ, Gershon S, Hekimian LJ, Floyd A. The clinical symptomatology of amphetamine psychosis and its relationship to amphetamine levels in urine. Int Pharmacopsychiat 1969;2:125-39.

Angrist BM, Gershon S. The phenomenology of experimentally induced amphetamine psychosis – preliminary observations. Biol Psychiat. 1970;95-107.

Angrist BM, Schweitzer J, Gershon S, Friedhoff AJ. Mephentermine psychosis: misuse of the Wyamine inhaler. Am J Psychiatry 1970;26:1315-17.

Angrist BM, Shopsin B, Gershon S, Wilk S. Metabolites of monoamines in urine and cerebrospinal fluid after large dose amphetamine administration. Psychopharmacologia (Berlin) 1972;26:1-9.

Angrist BM, Sathananthan G, Wilk, S, Gershon, S. Amphetamine psychosis: behavioral and biochemical aspects. J Psychiatric Res 1974;13-23.

Bell DS. The experimental reproduction of amphetamine psychosis. Arch Gen Psychiatry 1973;29:35-40.

Bell DS. A comparison of amphetamine psychosis and schizophrenia. Br J Psychiatry 1965;3:703-6.

Carlson, GA, Goodwin, FK. The stage of mania. Arch. Gen. Psychiatry 1973;28:221-8.

Connell PH. Amphetamine psychosis. Maudsley monographs number 5. London/New York/Philadelphia: Oxford University Press; 1958.

Fibiger HC, The dopamine hypothesis of schizophrenia and mood disorders: contradictions and speculations. The mesolimbic dopamine system: From motivation to action. Chichester (England): John Wiley & Sons: 1991, pp. 615-37.

Griffith JD, Oates JA, Cavanaugh J. Paranoid episodes induced by drugs. J Am Med Assoc 1968;205:39.

Griffith JD, Cavanaugh J, Held J, Oates JA. Dextroamphetamine evaluation of psychotomimetic properties in man. Arch Gen Psychiatry 1972;26:97-100.

Herman M, Nagler SV. Psychosis due to amphetamine. J Nerv Ment Dis 1954;130:268-72.

Post RM. Cocaine psychosis a continuum model. Am J. Psychiatry 1975;132:225-31.

Slater E. Review of amphetamine psychosis by P.H. Connell. Br Med J 1959;1:489.

Young D, Scoville NB. Paranoid psychosis in neurology and the possible danger of Benzedrine treatment. Med Clin N Am 1978;22:637-46.

December 31, 2015

Comment by Burton Angrist

2. Studies of amphetamine psychosis: Biological aspects

The clinical similarities between amphetamine psychosis, on the one hand, and acute schizophrenia, psychotic mania or other unspecified acute psychotic states, on the other, suggested the possibility of common biologic substrates. Pioneering work on the mechanism of action of amphetamine and the biologic basis of its effects (particularly at high doses) was done in the laboratory of the Danish pharmacologist Axel Randrup and co-workers Munkvad, Scheel, Kruger, Schorring and others.

These workers found that in animals, high dose stimulant treatment (i.e., in the dose range usually associated with psychosis in humans) led to constricted, repetitive stereotyped behavior in which elements of normal behavior such as grooming and eating were completely excluded. The type of behavior varied with species. As doses increased, rats sniffed, licked or chewed the cage. Cats moved eyes or head from side to side. Monkeys repetitively moved the body limbs or hands. Some human abusers also reported prolonged cleaning, self-washing, sorting items from a purse or dismantling clocks or other mechanical objects (Randrup and Munkvad 1967).

The pharmacology of this stereotyped behavior was studied intensively. The findings converged on the conclusion that this behavior was mediated by dopaminergic hyperactivity in the striatum. For example, the behavior could be induced by microinjections of amphetamine, apomorphine, p-hydroxyamphetamine or dopamine itself into the striatum and was antagonized by striatal microinjection or systemic administration of neuroleptics (Randrup and Munkvad 1970).

These studies were well known and influential. Thus we recognized that our own biological studies would probably focus on the effects of amphetamine on catecholamine neurotransmitters, particularly dopamine. We did four such studies, which are described briefly here.

1. Studies of Paramethoxy Amphetamine (PMA) in Humans

The first of these studies, however, did not address effects of amphetamine on neurotransmitters. Rather, it was suggested in discussion at a meeting in which J.R. Smythies proposed that amphetamine psychosis might not be related to effects of amphetamine per se but rather was due to the formation of paramethoxy amphetamine (PMA) from the amphetamine previously taken.

This idea was an extension of concepts previously expressed in an influential prior paper, in which it was hypothesized that abnormal methylation might produce psychotoxic metabolites that led to the development of schizophrenia – the "trans-methylation hypothesis" of schizophrenia (Osmond and Smythies 1952).

PMA had mild, brief psychedelic effects and was also found to have strong pressor effects in some subjects (Shulgin and Shulgin 1991).

I was skeptical about Smythies proposal, since the clinical effects of amphetamine were rather different from those of psychedelic agents. More pertinent for scientific purposes, however, was the fact that we had saved the urine of our subjects in our studies of experimentally induced amphetamine psychosis. I reported Smythies proposal to Drs. Gershon, Friedhoff and Jack Schweitzer, the analytical chemist in Dr. Friedhoff's lab. They felt sure they could identify PMA if it was present in urine and were eager to run the analyses. This was done and no PMA was found in the urine of any subject (Angrist, Schweitzer, Friedhoff and Gershon 1970).

I was busily patting myself on the back when Dr. Friedhoff interrupted my self-congratulations with the thought, "what if PMA is a very labile, rapidly metabolized molecule?" We, therefore, administered PMA to normal subjects. Doses given ranged from 10 mg/subject to 1 mg/kg. PMA was detected in the urine of all subjects, including those who received the lowest dose (Schweizer, Friedhoff, Angrist and Gershon 1971). The one high dose subject (myself) had

a brief but alarming pressor effect (BP 240/130), from which I learned some lessons about recklessness that have not been forgotten.

2. The Comparative Psychotomimetic Effect of Stereoisomers of Amphetamine

Amphetamine was known to increase synaptic levels of both norepinephrine (NE) and dopamine (DA) but the specific relationship to amphetamine-induced behavior remained somewhat uncertain. In 1970, Snyder et al reported that the d and l isomers of amphetamine had brain area specific magnitudes of effects on (DA) vs. (NE). For example, d-amphetamine was ten times as potent as the l-isomer in inhibiting the uptake of NE in synaptosomes from cortical areas but only one or two times as potent as the l-form in inhibiting the uptake of dopamine from striatum. Behavioral correlates showed a ten to one potency for d- vs. l-amphetamine in causing locomotor stimulation but only a 1-2 potency for inducing stereotyped behavior. These findings, taken together, indicated primarily noradrenergic mediation of increased locomotor behavior and dopaminergic mediation of stereotyped behavior, respectively (Snyder, Taylor, Coyle and Meyerhoff 1970).

We then did a study in which three subjects took cumulative high doses of d- and l-amphetamine on separate occasions. Each had his own characteristic response to both isomers! The first subject received cumulative doses of 510 mg of d- and 640 mg l-amphetamine. During both studies, he became progressively more irrelevant and diffuse in his thinking and developed mild ideas of reference to the effect that the TV was directed particularly to him, as well as dose-related flattening of affect. Some of his productions are noted in part one of this report (see the quotation on the “balance of nature” from the last patient in that report).

Subject #2 developed the same type of thinking disorder characterized by irrelevance, tangentiality and diffuseness of thought as well as progressive flattening of affect and olfactory hallucinations on both isomers (270 mg d-amphetamine, 415 mg of the l-isomer).

The third subject received the same dose of each isomer (475 mg) and developed a paranoid psychosis each time.

The doses of d- and l-amphetamine required to produce these effects were on the order of between 1 and 2/1 (d vs. l), suggesting a role for dopaminergic events in the development of psychosis (Angrist, Shopsin and Gershon 1971).

3. Catecholamine Metabolites in Cerebrospinal Fluid After Amphetamine Administration

In these studies, four subjects were observed on the research unit drug free prior to lumbar puncture. They then received cumulative doses of 400 – 525 mg racemic amphetamine prior to a second lumbar puncture. One of the four subjects developed a paranoid psychosis that precluded his cooperation with the second LP until 16.5 hours after the last dose. Cerebrospinal fluid (CSF) was analyzed for 3-methoxy-4-hydroxyphenylglycol (MHPG) and homovanillic acid (HVA). No changes were seen in either metabolite and inspection of levels revealed no trend toward consistent change in either (Angrist, Shopsin, Gershon and Wilk 1972).

However, it was likely that absolute levels of neurotransmitter metabolites did not reflect turnover. Inferences about turnover, however, could be made if egress of transmitter metabolites from CSF was blocked with probenecid (Goodwin, Post, Dunner and Gordon 1973). We, therefore, studied a fifth subject under 3 conditions: (1) drug free, (2) after probenecid alone (100mg/kg over 18 hours) and (3) after both amphetamine 250 mg over 21 hours and probenecid 100 mg/kg over the 18 hours before the lumbar puncture was performed. MHPG did not change over the experiment. However, HVA increased from less than 20 ng/ml drug free, to 120 ng/ml on probenecid alone and to 200 ng/ml after both probenecid and amphetamine 250 mg, suggesting that the amphetamine had indeed increased dopamine turnover (Angrist, Wilk and Gershon 1974).

4. Antagonism of Amphetamine-Induced Effects by Haloperidol

This study was done in eight subjects, who either entered the hospital with acute psychotic symptoms after taking amphetamine or were administered moderate doses of the drug on the research ward. The latter group was not psychotic, but did show clear hyperarousal and over-activation. Each subject was interviewed and his psychiatric pathology rated on the Brief Psychiatric Rating Scale (BPRS). A single injection of haloperidol 5 mg was then given and psychopathology rated 45 minutes to one hour past injection.

The antagonism of amphetamine effects was clinically quite striking. Hyperarousal and activation cleared nearly completely, any psychotic symptoms cleared completely, or nearly so, in almost every case. Even in this small group, two BPRS items, “suspiciousness” and “excitement,” decreased to a degree that was statistically significant (Angrist, Lee and Gershon 1974).

The effects of haloperidol may not be entirely selective for the D2 receptor but the affinity at that site is substantially greater than for other biological targets. Thus, the robustness of the clinical effects, particularly after the comparatively low single dose of 5 mg/subject, suggests rather strongly that the effects seen were due to the D2 receptor blockade.

I gratefully acknowledge that the suggestion to do this project was made by Dr. Randrup, when I visited his lab.

References:

Angrist B, Lee HA, Gershon S. The antagonism of amphetamine-induced symptomatology by a neuroleptic. Am J Psychiat 1974;131:817-9.

Angrist B, Schweitzer J, Friedhoff AJ, Gershon S. Investigation of p-methoxy-amphetamine excretion in amphetamine induced psychosis. Nature 1970;225:651-2.

Angrist B, Shopsin B, Gershon S. The comparative psychotomimetic effects of stereoisomers of amphetamine. Nature 1971;234:152-5.

Angrist B, Shopsin B, Gershon S, Wilk S. Metabolites of monoamines in urine and cerebrospinal fluid after large dose amphetamine administration. Psychopharmacologia 1972;26:1-9.

Angrist B, Wilk S, Gershon S. The effect of probenecid and large dose amphetamine administration on cerebrospinal fluid homovanillic acid. Biol Psychiat 1974;8:113-4.

Goodwin FK, Post RM, Dunner DL, Gordon EK. Cerebrospinal fluid amine metabolites in affective illness: the probenecid technique. Am J Psychiat 1973;130:73-9.

Osmond H, Smythies JR. Schizophrenia: A new approach. J Ment Sci 1952;98:309-15.

Randrup A, Munkvad I. Stereotyped activities produced by amphetamine in several animal species and man. Psychopharmacologia 1967;11:300-10.

Randrup A, Munkvad I. Biochemical, anatomical and psychological investigations of stereotyped behavior induced by amphetamine. In: Costa E, Garattini S, editors. Amphetamine and Related Compounds. New York: Raven Press; 1970, pp. 695-712.

Schweitzer J, Friedhoff AJ, Angrist B, Gershon S. Excretion of p-methoxy-amphetamine administered to humans. Nature 1971; 229:133-4.

Shulgin A, Shulgin A. PIHKAL. A Chemical Love Story. Berkeley: Transform Press; 1991, pp. 707-9.

Snyder SH, Taylor KM Coyle JR, Meyerhoff JL. The role of brain dopamine in behavioral regulation and the actions of psychotropic drugs. Am J Psychiat 1970;127:199-207.

April 7, 2016

October 24, 2019