THE ENIGMA OF ISONIAZID
- MAX LURIE

(The conventional history of the antidepressants relegates everything that happened before Roland Kuhn and Nathan Kline to outer darkness; this applies particularly to early work on the anti-tubercular agents isoniazid and iproniazid. I accepted this for almost decade and only changed my mind when I went back to look at some of the primary sources. When one does so, it becomes clear that the work of Lurie and Salzer was an unrecognised breakthrough rather than simply an early fumbling. I was impressed enough to try and track down Max Lurie. My sister Miriam Healy, Herb Meltzer and George Simpson all came up with his phone number and address for me in the same week. I wrote and subsequently posted a draft of chapter 2 of The Antidepressant Era to him, which he commented on. We talked on the phone. He was reluctant to be interviewed. A year later he changed his mind.)

Can we start with your father, who was also a psychiatrist and I presume therefore one of the reasons you went into psychiatry?
My father was Louis A Lurie. He immigrated from Lithuania to the United States and to Cincinnati around 1900. He graduated from the University of Cincinnati. During his undergraduate work, he became interested in psychology and wound up teaching psychology at the University, while going to medical school at the same time. After completing his medical studies, he went into general practice which he continued until entering the Army Medical Corps during World War I. In the service, as I guess was the case throughout medicine at the time, psychology and psychiatry sounded very much the same to the average physician and so he was sent to Ann Arbor, Michigan for psychiatric training and then continued to practice psychiatry in the army. After being discharged, he trained further at the Boston Psychopathic Hospital for almost two years before returning to Cincinnati where he went directly into the practice of psychiatry. I believe there were only about five men practicing psychiatry in Cincinnati at that time. He became particularly interested in child psychiatry and in 1920 founded a residential treatment center for children known at first as the Psychopathic Institute and then as the Child Guidance Home, which later became the Childrens Psychiatric Center. He served as its Director until 1949 and thereafter as consultant to the Director.

That was pretty early? Who influenced him to go into this area?
Yes, it was early. I don't know who influenced him to go into this area. His primary interest seemed to be child psychiatry although he actively practiced general adult psychiatry. At the Child Guidance Home, he and a paediatrician, J Victor Greenebaum worked closely with the Jewish Hospital, the social agencies and with the public school - always seeking a possible physical basis for the child's abnormal behaviour. They did extensive work-ups on them, often keeping them in residence for many months. They attended a nearby school. While doing this, he did a tremendous amount of writing and research on all aspects of psychiatry and orthopsychiatry.

In later years, he became interested in whooping cough and what are now recognised as the encephalitides that can develop from that - the changes in personality that can occur. He was particularly interested in pancreatitis and the

development of depression in pancreatitis. His work was some of the first work to emphasise this connection. Yet another major area of interest was endocrinology. He began to study the children's endocrine development to explain their retardation or advancement, their physical growth or the lack of it. This led to research with pituitary hormones. Other areas of interest and research included pernicious anaemia, hypertension and the behaviour disorders generally. These were all parallel interests. There was always research going on in one area or another. At the same time, the child guidance work was expanded.

I came into the office with my father in 1948 and became involved in some of the research and some of the papers. Actually, the first one in which I was involved was back in 1943 and concerned the Determination of Bone Age in Children by studying X-rays of their epiphyses.

Well, now that we have moved on to you, why did you opt to go into psychiatry, was it because of your father?
We have to go back one step and ask why did I go into medicine. As far back as I can remember, it was a foregone conclusion. It was taken for granted by my immediate family, by my parents, by the relatives of the family that I would go into medicine. There was never any question about it. As I grew up and went through medicine, I was fascinated with seeing what he was doing in his practice. I got to know the other men who were active in psychiatry in the city and was accepted by them. It became what I wanted to do. I had no particular motive or goal, but I was very much interested in psychiatry.

The interest was intensified while working under the supervision of John Romano during my internship at the Cincinnati General Hospital, now the University Hospital. It became clinched while a resident at the Illinois Neuropsychiatric Institute in Chicago, Illinois. John Romano was eclectic but his successor, Murray Levine, was a dedicated psychoanalyst. Everyone in his department was encouraged to commute to Chicago, to the analytical institute there to be psychoanalysed. Drug research or anything pertaining to physical therapies was minimised. This, of course, became an important factor later if we consider why the isoniazid research didn't generate more impact locally. We were in a hotbed of psychoanalytical orientation.

In Chicago it was an extremely interesting year under the aegis of Francis Gerty, Hugh Carmichael and Virginia Tarlow. Strangely, the Institute there was not as psychoanalytically oriented as the area here, even though we had seminars with Franz Alexander and other famous figures from the analytic group. In addition, there was much influence from the neurologists including L J Meduna and that kept things in balance. Medication and electric shock therapy was utilised. It was a neuropsychiatric institute that was symbolised by the shape of the building - two large towers which were connected only in the lobby and the cafeteria on the ground floor. The dichotomy was emphasised for a long time but there was great training there.

Unfortunately, being wartime, I couldn't get a deferment for a second year there, but it was possible to arrange for it with their close associates at the Psychopathic Institute in Iowa city, Iowa under Wilbur Miller, Jack Gottlieb and Paul Huston. They

were much less interested in the psychodynamic school and much more interested in the physical therapies, even though there had been some interest in these in Chicago. Both hospitals were interested in electric shock therapy. It fell to our lot as residents to give the treatments. We started very early on - 1944. Cerletti had first tried ECT in 1938. The equipment was primitive and difficult to work with. There were no medications with which to pretreat people. We had to develop techniques to keep the anxiety levels down, how to safely hold people, etc. When I got to Iowa they were doing a lot of shock therapy and insulin coma therapy. There was some psychotherapy but the system in the hospital was such that people were only there briefly so you didn't get a chance to get to know them. There was an interest in drug therapy starting up about that time - mainly using sedatives. I went into the service then I was lucky enough to be detailed to the psychiatric service. There were a variety of people from different schools there, but we again gave a lot of electroshock therapy. I was stationed in Germany after the War at the 317th station hospital in Wiesbaden.

By the time I came back here there had been improvement in electroshock therapy. Insulin therapy was also being used as were sedatives. My father, having grown up in general practice, used a lot of sedatives. He taught me how to use bromides and bromides mixed with hyoscine to smooth out the effect of the bromides. The bad taste was part of the therapy. Phenobarbital wasn't available at first - it was just beginning to come in. This was followed by Donnatal - a combination of hyoscine and barbiturate. That was useful but relatively minor compared to the introduction of Thorazine. However, these were all sedatives. There was very little in the way of treatment for depression other than electro-shock treatment and a modification of insulin coma treatment. We also gave sub-coma doses which had more of a tranquillising effect. It certainly wasn't very antidepressant. Hydrotherapy was another useful modality.

Now by this stage you must have met Harry Salzer. What's his background?
Harry Salzer had been practising here in Cincinnati for years. He was a good deal older than myself. He was Professor of Neurology, but he was moving over from neurology toward psychiatry. This is an important subject - the history of neurology. Neurology started out as an independent field. The knowledge base was, however, limited in scope. Harry was recognised for his expertise in neurology but, little by little, as there was less neurology and the psychiatric pastures were looking greener he began moving over into psychiatry. At about the same time, psychiatry began to engulf neurology and a lot of my training was in neurology. I started out with the anticonvulsants and working from that base we got interested in each other. There were relatively few neurologists, psychiatrists or neurosurgeons and we all functioned as one group to some extent. We affiliated as members of the Cincinnati Society of Neurology and Psychiatry.

Harry himself was an invalid. His health was failing when I came into the picture. When he was ill, I would cover for him. He was interested in electroshock therapy. I would give the treatments for him and the friendship grew from there. It became natural to work together.

He was a fairly rigid man. he was a very strong believer in electroshock therapy - the more the merrier. I could not always give treatments the way he would. He

would give multiple consecutive treatments. The net result was periods of intense confusion afterwards which to my mind were absolutely horrendous but that was what he was seeking. It was his theory that by producing all that confusion and memory loss you blotted out all the conflicts and problems that troubled the individual and then you could nurse them back to a better state.

A bit like what Ewen Cameron was doing several years later?
Yes. It may be that this is one of the ways in which electroshock works although, as the years went by, the trick became to minimise the confusion and the memory loss because we came to realise that some of the organic changes could be irreversible. In some cases, memory never did come back fully and that obviously was undesirable rather than desirable as was thought at first. That is where the spacing of treatments came in. When I was treating a manic patient for instance, I might treat him every day for two or three days and then move to every other day and then three times a week, twice a week, once a week, etc. My practice had been to taper off, especially with depressed patients - finally giving one every few weeks. This led to what we later called interval treatment which seemed to help with a lot of chronic or recurring depressions. By agreement we would treat them once every 4 to 6 weeks regardless of how well they were and that seemed to maintain them. Eventually it stopped with the advent of antidepressants. We were always on the lookout however for some other way to treat these patients, some equivalent to the way the sedatives seemed to treat the anxious patients. That's where isoniazid came into the picture.

How did you come up with the idea of trying isoniazid?
I was reading an article on tuberculosis by Robitzek and colleagues. I cannot in all honesty say why I was reading it. But what caught my eye was that these authors were complaining that a significant problem with treating tuberculosis with isoniazid was that unlike other treatments which were usually uncomfortable or even depressing, their patients were getting euphoric. That's where the idea came to my head - "Hey, is this something that could specifically treat depression?". I talked to Harry about it and we decided to try using it. You must bear in mind that in those days the boundaries of many of the psychiatric syndromes were very fuzzy. They still are today, but it was worse then. In retrospect, many of the so-called hebephrenics would more properly be called schizoaffective, depressed type now. We both had patients in hospital and we started working with them and with office patients using isoniazid. There was one individual who clearly responded to parenteral isoniazid who hadn't responded to the oral dose, but apart from that one patient, I can't particularly remember a difference between the two modes of delivery.

Looking back at our original paper in 1953, there is something else in there that seems very topical today. We've been hearing a great deal in recent months about withdrawal effects from antidepressants, especially the SSRIs. The thinking now is you should taper them off and not stop abruptly. Now in our study we had this in mind. We tapered people very slowly. We just didn't know if there would be a problem.

Do any of the early cases stand out in your mind? Did any early responses persuade you both to continue with this line of investigation?

Yes, the early responses influenced us, but even looking back over the case histories in the paper I still cannot specifically recall any of the patients. What I do remember is the intense thrill of seeing a number of these people getting better. Not necessarily getting well, but getting significantly better. That was extremely gratifying. We were seeing faster results than we had seen with anything else. We were seeing results from a treatment that was so much easier to administer than sub-coma insulin or electroshock therapy. It was always worrisome to me if they hadn't responded to 6, 8, 10 or 12 treatments or even if they had, when you saw some of them relapse. You must bear in mind here the manner in which the treatment was given in those days. It was totally different to today. At first there were no sedatives and there were no muscle relaxants. We traded on their retrograde amnesia. The individual could remember being brought into the room and being placed on the table. Some could remember the electrodes being put on their head, but nobody ever remembered more than that. It was a big step when Anectine was introduced and after that the use of anesthesia. These agents had their own difficulties because a muscle relaxant could effect their breathing and that could be very frightening. It was very hard on those of us giving the treatment. It was a cold callous treatment so when an antidepressant came along and you could give a pill by mouth, it was more gratifying.

When you had the first series together you gave a talk at the American Medical Association in 1953. How did the audience respond? Was there anybody there who thought the treatment of depression might be of any interest?
There was, in retrospect, an interested group from the Section on Nervous and Mental Diseases. They weren't beating down the doors, but there were psychiatrists there whom I knew from the Central Neuropsychiatric Association. One man from the audience cut me down during the question and answer period. He said this is all very interesting but "I hope the authors will treat as many people as possible as quickly as possible before the effect wears off".

That's a standard way to put down new developments - Nolan Lewis used it a lot. But apart from that, were there any arguments put up as to why you weren't really seeing what you claimed you were seeing?
No. The main point I think was that he just wasn't convinced that it would work en masse. There was scepticism everywhere. We received a better reception outside Cincinnati. For example, the psychiatrists at Ohio State University were much more interested.

Did any other groups use it?
Not groups, but some other psychiatrists locally did indeed use it and obtained comparable effects. Why it faded out was, I think, owing to the relative potency of isoniazid compared to iproniazid and imipramine when they came along.

As compared to the potency of the action of these drugs or the potency of the sales action of the companies or the figures who were pushing these other therapies - Kline, after all, was very flamboyant and well placed to bring iproniazid to public attention.
Yes, your point is well taken. It was important then, as now, for a drug house to really push it. Probably the problem was that there wasn't big money to be made for Eli Lilly in isoniazid.

Can you remember who you approached in the company?
I cannot recall, but I did maintain a relationship with the company and later did some work for them on Aventyl.

Did the fact that isoniazid was produced by Lilly and Roche and Squibb make any difference and perhaps the fact that, at least for the first series of patients, you got the supplies of the drug from both Lilly and Squibb?
That certainly lent credence to the possibility that they did not anticipate any potentially substantial profits from isoniazid. These companies are highly competitive and very profit oriented.

When Thorazine appeared and had the impact it did, I know Eli Lilly, among other companies, went back to their shelves to see what they might have there that had a psychotropic effect.
True, but don't forget reserpine. This played a part, too, in stimulating them to look for other new compounds. It was an interesting decade. The psychoactive drugs were just burgeoning in psychiatry compared with what we'd had before. Thorazine, reserpine and imipramine were the three that I think had the biggest push. And the same thing was happening in the rest of medicine. A lot of conditions were being delineated that hadn't been sorted out before. Drugs were coming out hand over fist. You might say it was part of an information explosion in medicine. These things made isoniazid small peanuts.

But in 1952, the fact remains there was nothing else. We had no comparative antidepressant drug we could use as a baseline standard against which to compare isoniazid. You can argue about the criteria we used. Nobody gave much thought as to whether the subjects should all be hospitalised patients because hospitalised patients are more severely ill or should they all be outpatients because they're milder. Should you exclude anyone who has had more than one episode and treat only first episodes. I touched on all of these points in the paper.

Well, you reported results that are the results you would expect from any antidepressant now - two/thirds of people responding and taking tow to three weeks to respond. The papers are a lot more persuasive than the early reports produced by Kuhn or particularly by Kline. The first patient Kuhn reports on responded after only 5 or 6 days, while Kline's patient samples seem to have been an unholy mess and it's very difficult to get an idea now from his papers as to what actually was going on. Were there any other forums you took the results to?
The next one was a follow up study presented to the Ohio Psychiatric Association in 1954. As the name implies, this was a branch of the American Psychiatric Association. There were psychiatrists from all over the state with varied backgrounds and training including psychodynamically oriented therapists, psychotherapists who incorporated the physical therapies as well as psychoactive drugs in their armamentaria as well as psychoanalysts. The paper was well received. How many more tried it after that, I don't know. The paper was delivered in 1954 but it was a while before it appeared in print - in 1955 - and, by that time, we were entering into the Thorazine era. Attention was dramatically drawn away from the antidepressants toward the tranquillisers. "Let's give Thorazine or reserpine" is

what you heard - “this is going to cure depression.” Thorazine was brought out with great fanfare and the business people could see big money in it. The detail men began to come around promoting it.

Probably the two biggest things that acted against isoniazid was the fact that we were working in a hotbed of psychoanalytic therapy and the university department here, which might have otherwise supported us, didn’t help promote it and the lack of push from the drug houses along with their interest in chlorpromazine instead. We were just a little bit ahead of our time, not in terms of what we thought we were doing, but in terms of what we found. As I look back at the methods we were using, in many ways they were more organised than the early protocol that was being used, for instance by Smith Kline & French when they were developing Parnate. Ten of us went up to Philadelphia in 1959 to talk about our experiences with Parnate and I don’t think that there was as much organised protocol in that series of studies as we had in our two articles.

You say Thorazine came on stream and the companies went after schizophrenia because they could see big bucks coming from the fact that there were a lot of visible patients around with schizophrenia, but did any of the lack of interest in an antidepressant stem from the fact that people didn’t think there was that much depression around the place?
Part of the issue was the fuzzy borders and overlap between agitated depression and anxious depression. The thinking was that if Thorazine is this good a drug, maybe we can use it in anxious depressions as well - give it in a graded dose. This is what permeated the scene and it took some of the impetus away from developing antidepressants as such.

I’m sure you’re right but another problem, which may have been more a European one because there was much less office practice in Europe, was that the drug companies over there, when they thought about depression, thought about melancholic depression and there’s not much of that. Besides which ECT was already a pretty good treatment for it. They didn’t see the anxious depressions as depression, they saw anxiety and said well we’ve got anxiolytics for that. Did you have that over here?
In those years, depression was not their primary thrust or interest.

Did you at any point go to Eli Lilly and say look you’ve got a treatment for depression?
I’m sure they were shown the results of our research and had copies of our papers, but we didn’t go to them in any aggressive way. Nor did we ask them if they had any similar drugs in their pipelines which we might study in depressed patients. We talked up isoniazid wherever we could and obviously continued to use it.

Till when?
Until imipramine came along. Iproniazid concerned us. I didn’t know just what bothered us, but something about it made us hesitant. Then Tofranil came along and that was great.

Why did you switch? Was it more potent?

Yes, it seemed to be. But then, too, you must go with the flow. The referring doctors had heard about Tofranil, whereas they hadn't heard much about isoniazid. It's the same reason why we use any new drug. We tend to try out and use the latest medications that the pharmaceutical companies bring to us.

There's a good point here in that we have switched en masse to SSRIs even though some evidence now points to the fact that the older drugs were more potent and in my experience at least one of the SSRI companies knew this even as they brought the compounds out, so I'm sure a lot of our impressions have to do with the marketing that gets done. Can I chase you a bit further on the other people who were using isoniazid. In your list of references for the 1955 paper you've got William Turner listed under personal communication. Did he ever publish that?
Not that I'm aware of. I think he must have known Harry and presumably the communication was to him.

The interesting thing is that he came from New York. Now the relevance of this is when Nate Kline came to do his work on iproniazid he doesn't refer to any of this and you might have thought that if someone else was doing this sort of work in the New York area, Kline should have known about it.
Your point is well taken, but I've tried to remember and I can't come up with anything.

Were you aware of the French use of isoniazid, not in terms of being influenced by them because they weren't doing it any earlier than you but their findings confirm your own. Kline held a meeting in '58 to celebrate Marsilid and Jean Delay was there saying that he was very excited at the developments with iproniazid but he would like to point out that he and Buisson had got similar results in 52/53 with isoniazid.
No, I was unaware of that interesting and important fact. I must own up to a lack of sophistication.

I don't think that it's anything to do with a lack of sophistication. For some reason the isoniazid story didn't take off. You've alluded to a few possible reasons but Delay was one of the most famous names in world psychiatry at the time and even in his hands isoniazid didn't make it.
There are other interesting aspects to this story. Today you often find that if patients respond to one drug but then discontinue it, they may not respond as well if they later relapse and the drug is restarted or else you may have to use a higher dose. In our studies, we reported some people who stopped isoniazid because they felt they were doing very well but they later relapsed. They responded again, however, to the same dose and just as well the second time around.

My first reaction to that is that it was probably because you were dealing with a treatment naive group but they weren't were they - your paper makes it clear that many of then had been tried on a range of other things and a third of them had had ECT before.
Yes, many of our subjects had a fairly severe depression and many of them were experiencing recurrent depressions. Another thing in retrospect, not only was isoniazid having an antidepressant action, but it was having it without any of the

horrendous side effect profile we've come to expect from other antidepressants and even from some of the newer ones. It had very few side effects. One man in the 85 patients we gave it to had to stop because of what we described as a thyroid-like effect - in other words, a stimulant-like effect. One patient developed a rash. Some of our patients developed a hyperreflexia, but this didn't require them to stop treatment. The side effects in general were mild and they were reversible. In particular, the drug wasn't plagued by the horrendous side effects seen in the monoamine oxidase inhibitor group. At first there was some question as to whether isoniazid was an MAOI, but it's not.

What does that do to the whole theory about how the antidepressants work. Do you know anything about the biochemistry that might indicate how it works?
It proves that here is something else for the neurobiologists to figure out - it's beyond my capacity. All this biochemistry has surfaced well after I finished medical school. I had no training along those lines. I try to keep up with the literature, but it's not enough to really be able to answer your question.

Well I pose the question from an Emperor-has-no-clothes perspective. I think most of the biochemistry is biomythology really that is good marketing copy rather than good science. But if isoniazid had registered maybe we wouldn't have had fluoxetine for instance because all these drugs in some sense came out of the idea that MAOIs increase brain amines and depression is about having low amines. Isoniazid must do something else completely and arguably there is something else completely that all of the other antidepressants do that we've been neglecting all these years which we mightn't have done if more people had paid heed to isoniazid.
Would we have been better off or worse off?

Who knows. How did you or Harry Salzer feel when people like Nate Kline then went on to be recognised as the discoverers of the antidepressants?
It's hard to say how I felt. Disappointed, of course. Truthfully, it was sometime before I fully appreciated the real import for the future of the concept of antidepressant medications.

Those were exciting years - then and subsequently. I have always found myself more interested in the psychopharmacological approach to the treatment of mental illness than purely in the psychodynamic. My interest in psychopharmacology continued and I continued to do research studies on subsequent antidepressant agents.

Before we leave isoniazid, just one more thing. You say you were actually trying to find an antidepressant rather than just a pill to improve sleep in people who were depressed. You were clear on that even though no one else had ever found one - something that would work fairly directly on mood rather than indirectly.
That's right. What we were seeking was something that would work on the mood which we saw as the core of the depression. By definition, such a substance was an antidepressant.

But did the word antidepressant actually exist in 1952. The stimulants as you said earlier were being used to treat depression but they weren't called antidepressants and Nate Kline a few years later was calling iproniazid a psychic energiser rather than an antidepressant. Even Tofranil was called a thymoleptic for a while rather than an antidepressant - so was there such a word before your 53 paper where much more clearly than anyone else at the time you called isoniazid an antidepressant. Where did you get the term from?
We called it an antidepressant because we wanted something that would work specifically against depression - therefore it would be an anti-depressant. Isoniazid seemed to fill that requirement. I don't think popularly it was known as, or looked upon, as an antidepressant but we were calling it that as opposed to an anti-anxiety agent.

Let me push you further on this. Did you actually coin the term? I think you may have because I'm not sure there is an earlier use in the literature.
That's for someone other than me to determine. I don't think we were looking to make up a word or term. On the other hand, I don't remember anyone else using it. It wasn't like naming a baby - we didn't go through a phase of debating what should we call this agent, but this effect was definitely what we were seeking. Therefore, we referred to isoniazid as an antidepressant.

Before we turned the tape on, you said that the group in Ohio State University in Columbus got you involved in the early trials on Parnate - tranylcypromine - can you tell me anything about that work?
The Psychiatric Department at Ohio State University was quite interested in psychopharmacological research and treatment. Because of my work on isoniazid, I was approached at a Central Neuropsychiatric meeting in Columbus, Ohio in regard to an antidepressant drug, SKF 385, which was being studied. They asked whether I knew anything about it and when I said no, they asked me whether I would be interested in working on it. I was. The prospect was exciting. I became involved in the study and began to use it. I worked with Smith Kline & French and went to a meeting in Philadelphia in 1959 when they were reviewing the results. There were 12 of us in attendance. That's when I got to know Frank Ayd. I already knew Howard Fabing from Cincinnati who was also there. Everybody at the round table presented their impressions of the drug. They weren't prepared papers as such. Each of us gave a summary of what we were doing, our observations and experiences. What strikes me going back now and rereading the proceedings of the meeting was the seeming looseness of the research project. The parameters of the project were not rigidly defined - what group of patients should be treated, whether they should be hospitalised or office-based or even the dosage of the drug that should be used. The dosage given was quite variable. At that point, on one was comparing SKF 385 to imipramine or to any other drug - imipramine hadn't yet been accepted as a baseline or comparative treatment agent.

What was the feeling in the company about the compound at that time?
They were excited about it despite the fact that there were indications that it had more side effects. The nasty one, of course, was the very severe, devastating headaches which turned out to be hypertensive crises. I had a man - an attorney, no less! - on it and he developed one of these headaches. We brought him through it. He knew it was a research drug. The bottom line was that the drug was very helpful

to him and he continued to use it. At this early meeting, some of us had seen the problem of headaches and some of us hadn't. Dr Roebuck had encountered the problem of headaches in two subjects. We had talked about the problem before the meeting and in his presentation, he expressed it as relating to a heavy meal - that was the conclusion we had come to at that time. We had pinned it down to food and we thought it had to do with a heavy meal. The advice that went out from that meeting was to avoid excessively large meals. Although it was just a hunch, it was a good start.

Did you meet Alfred Burger the discoverer of the drug at this meeting?
No. That would have been a thrill.

What impression did Frank Ayd make on you?
He came across as a brilliant researcher. He was very positive in his approach to things. If he had an idea, he tried to follow through on it. He was a very determined person and very successful. He did a tremendous amount of research. I later sent several patients to him for consultation and he delivered a lecture to the psychiatric group here in Cincinnati.

Fritz Freyhan was also there. He was one of the really big names in the early days. How did he come over?
He, too, was an impressive researcher. However, I didn't have an opportunity to get to know him.

You have told me before that people like you who were working in private office practice got forced out of clinical trial work because of insurance problems. Can you tell me about what happened?
That was a hurtful turn of events. When the thalidomide scare occurred, the insurance companies became frightened and began to alter their rules and coverage. We were quietly told to be careful what we got involved with because though they presumably would cover you if you gave a drug to someone and got into trouble, thereafter you might find it very difficult and expensive to get further insurance coverage. I went both to Smith Kline & French and to Eli Lilly - I was working on Aventyl at the time. I said to them look the way it stands now is if I give your product to a patient and some irreversible side effect happens, I'll get covered for that case but from then on I'm persona non grata. It was a frightening situation.

I wanted to continue doing research work so I asked the companies to provide liability insurance coverage, point out that if the drug is successful, I do not get a nickel but if it's successful you make a fortune, so why don't they insure me? Apparently a lot of people were saying that to them, but they refused to supply liability insurance coverage. Some people were later able to organise themselves into research groups and get coverage that way - through hospitals, etc. I couldn't see how to get it and where I had two youngsters at the time, I couldn't afford to take the chance. The financial risks were too great. I could have been wiped out so I backed off.

How many people were forced out of clinical trials because of this?
I think that a majority of the individual investigators were forced out by this change. For individuals who were studying drugs in private practice, the whole liability factor

became too frightening. Malpractice rates went up astronomically high. Individual drug research was one of the risks that were specifically frowned upon. I dropped out of the Aventyl research in the middle of it. It didn't make sense for me to continue.

When you stopped doing clinical trial work in the 60s what sort of research did you get into after that?
I became involved with our esophagus center studying associated psychiatric problems and personality traits demonstrated by some of the patients with dysphagia. This included a group of subjects who required esophageal reconstruction surgery. We elicited some striking and not readily explainable findings, especially in those subjects with a background of functional dysphagia. A number of them revealed some dare devil, aggressive personalities, habits and hobbies - such as hang-gliding. One man comes to mind. He used to watch railroad crossings and when he saw a train coming, he would time himself and race it to the crossing. For a variety of reasons, we did not pursue these observations with a formal study.

Other interests have included involvement in forensic psychiatric work and especially in psychiatric problems stemming from industrial accidents. As the various new psychopharmacological drugs such as the SSRIs and anti-psychotic agents have been introduced, I have eagerly tried working with them in my private practice. In recent years, I have become more involved in geriatric psychiatry and the treatment of individuals in their late 80s and 90s. This has included the use of the newer psychoactive drugs, including the atypical antipsychotic drugs, but using individually titrated and significantly reduced dosages. Overall, their response has been quite gratifying. however, I am not involved in any formal research study at this time.

I notice on your wall a plaque saying that you were the president of the Central Neuropsychiatric Association in 1980/81. This has come up in the conversation before - what was this group?
The Central Neuropsychiatric Association was founded in 1922 as a unique association of neurologists, neurosurgeons and psychiatrists selected for membership by invitation. The purpose was to promote interest in their related fields. Membership was limited to physicians who had already reached a position of prominence or who demonstrated some success and promise in their respective speciality. A further purpose was to promote the acquaintance and relationship of the members with each other. This philosophy soon expanded to include the spouses and to foster a relationship amongst them. As the members moved, the territorial boundaries gradually spread from the original central states to include the entire United States.

At first, all of the presentations were given by the members themselves, describing their current studies and research, and with part of the program devoted to each of the specialties. In more recent years, outside speakers were brought in and the papers were directed towards a central theme. I was elected to membership in 1954 after attending the required two annual meetings to become known. Since then, I have presented several papers to the organisation and have been on the Executive council for almost 20 years. I was President from 1981 to 1982.

References:

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Ad Sitsen, Professor of Clinical Pharmacology in the Medical Faculty at Utrecht University and Head of Clinical Projects - Depression in N.V. Organon was asked to comment on this interview and also to answer a number of questions.

First of all let me say how interesting the interview with Max Lurie was. I also enjoyed reading his papers on the antidepressant effects of isoniazid. The discovery of psychotropic drugs - and for that matter many other drugs - was and usually still is a serendipitous process as evidenced by the way chlorpromazine, imipramine, lithium and iproniazid were discovered. It is important to note that astute clinical observation of patients treated with experimental drugs played a major role in these discoveries. The antidepressant action of isoniazid is just such an astute observation that until now has escaped the attention of historians. Fortunately and rightfully this almost unknown action of isoniazid has now been brought to the surface again. Why was it buried for so long? Lurie himself gives some ideas in his interview. At the time isoniazid was marketed by several pharmaceutical companies and there was probably insufficient commercial push further to pursue its use as an antidepressant. In addition, iproniazid came along and a great deal of attention and scientific interest went on this new compound.

With the benefit of hindsight can the antidepressant action of isoniazid be explained with today's psychopharmacological knowledge?

Zeller in 1983 recounts that "when the two antitubercular drugs iproniazid (Marsilid, Hoffmann-LaRoche) and isoniazid became available in 1952 they were immediately accepted as promising tools for our investigations [on MAO]. Isoniazid, as expected, exhibited DAO [diamine oxidase]-inhibitory action while at the same concentration it was without noticeable effects on MAO. In contrast, iproniazid turned out to be a much stronger MAO-inhibitor than ever seen before". Nevertheless, isolated cases of the 'cheese reaction' and other interactions have been published and Robinson et al in 1968 described that at therapeutic doses isoniazid inhibits plasma monoamine oxidase. Thus it seems that isoniazid, at clinical doses used for the treatment of tuberculosis, possesses at least some monoamine oxidase inhibiting properties. This may be particularly relevant in patients who are slow acetylators. Like moclobemide, isoniazid inhibits mainly monoamine oxidase-A, which may explain the rare occurrence of the cheese reaction. To what extent this property explains its

antidepressant action right now is unclear but merits further investigation. It is conceivable that isoniazid is a kind of moclobemide 'avant la lettre'.

Another interesting pharmacological property is its inhibition of glutamic acid decarboxylase, which reduces the brain concentration of GABA and may result in seizures. It does this by inhibiting the enzyme pyridoxyl kinase which catalyses the formation of pyridoxyl-5-phosphate which is a cofactor for glutamic acid decarboxylase. In pharmacological experiments, isoniazid is used as a convulsive agent and convulsions are a side effect in man, in particular in patients with seizure disorders. Overdoses with isoniazid may also result in seizures for which pyridoxine is the antidote. It shares this epileptogenic property with most if not all currently available antidepressants but relating this to its antidepressant action is difficult.

For completeness sake, it is worth mentioning that the mechanism of its antibacterial action is not well understood either. Effects on lipids, nucleic acid synthesis and glycolysis have all been proposed. An inhibitory action on the synthesis of mycolic acids would explain the high degree of selectivity of its antimicrobial activity because mycolic acids are important constituents of the mycobacterial cell wall.

Would an earlier appreciation of isoniazid's antidepressant effects have changed the course of antidepressant drug development?

Who knows but it is interesting to speculate. Isoniazid inhibits DAO particularly for which histamine is an important substrate. Histamine is an important neurotransmitter in the brain with an effect on sleep patterns and pursuing the mechanism of action of isoniazid may have shed light on the role of histamine in various psychopharmacological processes earlier. In addition to a role in sleep, H-3 heteroreceptors found on central catecholamine, indoleamine and acetylcholine nerve endings could inhibit or increase the release of these neurotransmitters. Polyamines are another important substrate for DAO and these are currently vigorously being investigated. Affective disorders are associated with maladaptive responses to stressfull life events. Based on the observation that rapid but transient changes in brain polyamine metabolism are a characteristic response to stressfull stimuli, it has been hypothesised that a maladaptive polyamine-stress-response system is involved in the pathophysiology of the affective disorders. Because of their involvement in the functional states of a variety of receptors and their multiple role in cellular metabolism, it has been suggested that the polyamines deserve special attention, although at present the evidence in favour of their specific involvement in neuropsychiatric disorders is scarce. Would other antidepressants have been discovered by focussing on histamine and polyamines further? It is a possibility I would not exclude.

Another aspect that should not be neglected is isoniazid's inhibition of GABA biosynthesis. GABA is the major inhibitory neurotransmitter in the brain and gabaergic neurones are widespread through the brain. The hypothesis that GABA might be involved in the aetiology of mood disorders emerged following clinical observations that valproic acid was effective in the treatment of bipolar mood disorders. This increases brain GABA and GABA also interacts with other amine systems. GABA function is also related to anxiety and facilitating GABA neurotransmission is associated with a reduction of anxiety in animal models. The

benzodiazepines in part exert their anxiolytic action this way. Interestingly, Salzer and Lurie already noted the anxiolytic effects of isoniazid.

In addition, carbamazepine, another anticonvulsant, is thought to act in limbic structures through an interaction with GABA-B receptors and this has psychotropic effects and is used in mania. Vigabatrin, another anticonvulsant with GABA-agonist properties has recently been reported to induce psychoses and affective disorders. But in view of the still somewhat unclear 'mood-stabilising' effects of GABAergic compounds, I doubt whether investigations on the involvement of GABA in affective disorders would have provided insights that would have altered antidepressant drug development.

In summary, I had no idea that this compound had such a complex pharmacology. It is a pity that the early opportunity for research on psychopharmacological aspects of isoniazid and on the development of antidepressant drugs that was provided by the early clinical observations of Lurie and Salzer were not followed up.

A list of 18 references supporting the points made here can be obtained on request from Ad Sitsen.