BARNEY CARROLL

Why did you go into medicine?
I went into medicine basically because it seemed like a good idea at the time. When I was graduating from high school I was thinking either medicine or law, even though no one in our family had been in medicine. My sister and I were the first in our family to graduate from University. So I sort of headed into medicine but it certainly wasn't because of family role models.

When got into medicine, how did you find it, did it seem like a congenial place to you or did it seem alien and strange?
The medical school curriculum in Australia was a 6-year program straight out of high school. So in 1958 I was a medical student at age 17. The very first year was a basic science year, so the only new thing was biology, zoology and botany, and they were ok. Medicine proper did not begin until the 2nd year. There we were introduced to some wonderful teachers and some fascinating material in the form of physiology and pharmacology and to a lesser extent biochemistry. Physiology really grabbed my interest. I thought it was the most wonderful subject, and I found myself reading Claude Bernard and thinking about physiology as a discipline rather than just something to get through on the way to a medical degree. I guess I've always thought of myself as a physiologist, whatever else I've done, and of course the endocrinology that I later transitioned into is really physiology. Nowadays I am exploring how to link neurophysiology with neurotransmitter theories of mood disorders.

For me medical school was a treat, and the 2nd and 3rd years went by very quickly. At the end of the 3rd year I decided to take a year out and do a research year. Nowadays they call it an intercalated BSc year, and it did give me a science degree. So I took my 4th year in the laboratory, in the Department of Pharmacology, working with Sam Gershon who had lectured us in the 2nd and 3rd year as a class in Psychopharmacology.

That year was structured so that we took advanced pharmacology classes and labs. We also had a lab project. Mine was to develop or to test antagonists to a drug that was thought to produce hallucinations. I'll come back to that in a little while. In addition to that we had some other course work that was more or less optional. I opted to take courses in psychology, statistics and Science German. That was a fun year, out of the pressure of the regular medical curriculum. We're talking 1961 now. An important influence that year was Keith Cairncross, who did some pioneering early work on the tricyclic antidepressants, which were very new drugs in 1961. Keith delighted in demonstrating through experiments on the cat nictitating membrane and on pithed rat blood pressure preparations that imipramine has a rapid action of potentiating the effects of norepinephrine. These experiments eventually led others to the recognition that tricyclic antidepressants block the uptake of norepinephrine by adrenergic nerve terminals, both in the periphery and in the brain.

During that year I was president of the Australian Medical Students Association, and in that capacity I travelled to an international conference of

medical student associations held in Jerusalem. En route home from Jerusalem I travelled extensively through South East Asia with the goal of setting up exchange programmes- which never actually came about, but the experience of seeing foreign countries for the first time was a real eye opener. I had no real idea of poverty until I encountered it in places like Calcutta and Bangkok.

One of my duties with AMSA was to chair a national conference in Melbourne, and we invited the two current Australian Nobel prize winners, John Eccles and Macfarlane Burnet to speak, which they very graciously did. After Eccles' talk I had to take care of him for the afternoon. We went to the art gallery and chatted and I told him about the project I was working on with the dogs in the pharmacology lab. He kindly offered to have me come to Canberra, where he headed up the physiology school, for a summer fellowship. I did that in fact but when I got to Canberra I had the feeling Eccles was unsure why he had asked me to come. He was running an internationally famous department, after all, with British and European postdoctoral fellows as well as Australians. Eccles was full time busy being Eccles.

He passed me along to David Curtis and Jeff Watkins, who had their own laboratory in his department. That actually was a very good thing because Curtis and Watkins at that time were establishing the neurotransmitter functions of the excitatory and inhibitory amino acids, glutamate and glycine. So I hung out with them, and learned to draw up multi barrel micro-pipettes for their experiments and absorbed neurophysiology by osmosis. And to this day I think like a neurophysiologist in addition whatever else I do.

But back to the project with Dr Gershon. This project was funded by the US military. It was the middle of the cold war in 1961. The US military were fearful that the Russians would get their hands on drugs that could cause hallucinations or other psychotic behaviour in the troops. So they launched a project to identify potential hallucinogens and then to develop antagonists, in the event they might be needed. We were working with a drug called JB-329, developed at Lakeside Laboratories in Chicago by John Biel. It was a glycopyrrolate anticholinergic drug and it did produce a psychotic state. I was given the job of administering this drug to dogs and then developing a rating scale of the dogs' JB-329 syndrome, so we could then chart the effect of antagonists.

We had a very lovely group of dogs, who by the way became conditioned to these experiments. I was struck that they appeared to actually like getting JB-329. They would trot into the lab and squat there and raise their paw ready for the injection into the forearm vein. In retrospect I would say the syndrome produced by JB-329, which was also called Ditran, was an anticholinergic delirium.

The antagonist we tested was a drug called THA, tetrahydro-amino acridine, which Frank Shaw, the pharmacology chairman in Melbourne, had developed some time earlier. The reason they were interested in a drug like THA was because there were cases of agricultural poisoning with organophosphorus

insecticides. These are irreversible inhibitors of acetyl cholinesterase. THA also is a cholinesterase inhibitor.

THA was used as a model drug to look at actions in the brain of inhibiting the enzyme because people were not really keen about using the more toxic compounds in the laboratory.

In all of the talk about the use of drugs like THA for Alzheimer's, does Frank Shaw get any credit these days?
No, I think Frank Shaw has been long forgotten. Mostly because he wasn't around to speak up for himself. During the year that I was in the pharmacology department at Melbourne, Frank Shaw took a leave of absence due to a nervous breakdown. He developed a paranoid psychotic state and that was really the end of his professional career. So I think in some introductory references you might see the name Shaw, but the application of the drug in Alzheimer's was a long delayed afterthought. And of course THA didn't make it as a general treatment for Alzheimer's because of its liver toxicity. It was then replaced by some of the other drugs.

At this point had Sam Gershon moved to the States?
He had been to the States briefly in the late 50s, then he came back to Australia for 3 or 4 years and that was when our paths crossed - in 1959 in my 2nd year of medical school. Shortly after I finished up with him at the end of 1961 he returned to the States full time and never came back.

The project I was on was funded by the US Army. At the end of my time with Sam I got a call one day in the lab to come up to his office. And when I got there, there was a US army colonel in the room with him and Sam said 'Give the officer a description of the project. What we have found and how much progress we have made'. So I did that and the guy later handed over another cheque for $50,000 to Sam to continue the work. That was a great deal of money in those days, but I wouldn't say all of Sam's work in Melbourne was funded from US sources. It was just that project, to my knowledge.

Given Sam and Melbourne, I have to ask you about lithium and Cade. Did you get to meet John Cade at this point in time or did the issue of lithium and its use come up in any way?
Sure. John Cade had introduced lithium back in 1949. Throughout the 1950s it was widely used in Melbourne so that by the time I came along in the late '50s it was yesterday's news. We assumed that everybody knew about lithium. When Sam lectured to the class he discussed lithium in the treatment of mania and described the work that Cade had done. And then subsequently in my clinical years I had Cade for one of my psychiatry teachers. And also his son, David Cade, was in my medical school class and I knew him quite well. In fact on occasion we would go around to the Cade household, which was located on the grounds of Royal Park Hospital in Melbourne.

Cade was a very admired and beloved individual. He was a very Edwardian character, smoked like a chimney, in fact I'm sure he developed vascular disease related to his smoking. A somewhat rigid Edwardian personality but

very kindly as long as things were going the way he thought they should be going. He examined me on my long case for the DPM and that was a very agreeable experience. So he was not the kind of teacher who would abuse students or residents. He did have a quirk for going off on ideas that, lets say, other people would not have pursued. He published a paper at the time in the Medical Journal of Australia on his theory of schizophrenia, which was that he thought schizophrenia was related to the consumption of stone fruits, particularly peaches. His main evidence for that was that the highest epidemiological incidence of schizophrenia in the State of Victoria was in the orchard district. Now that's a bit of a leap scientifically.

And the path that he followed in discovering lithium was similarly fraught with knight's move thinking. But he's published his own account of that and I don't need to recapitulate it here, except to give him credit that when he stumbled upon his finding that lithium urate quietened down guinea pigs, he had the good judgement to ask 'is it the lithium or is it the urate?' His original hypothesis was that it would be the urate and of course it wasn't. So I think it's fair to say that after his original clinical study, John really never made a substantive contribution to the lithium story. He did some work looking at lithium and magnesium. I think he started some of the work on intracellular lithium levels, but it never added up to very much, and had it not been for Mogens Schou, lithium probably would have taken much longer to get out into world wide use.

As you came towards the end of the training did you have any sense that you were going to go into the mental health field?
I thought I would probably end up in clinical pharmacology. I wasn't thinking about a career in psychiatry as such. I remember having a discussion with Sam Gershon as I was winding up with him and facing the prospect of 3 more years of medical school and then internship and so forth. I told Sam that it was such an exciting time in psychopharmacology that I wasn't sure I wanted to go back and finish medical school. And he said 'well why not?' I said 'well I'm afraid that by the time I get back into the research arena all the important discoveries will have made and there'll be nothing left to do'. Sam just laughed and patted me on the head and said 'don't worry about that, there'll be plenty to do.'

I took his advice and went back to medicine and regular clinical training. During that time we had our psychiatry instruction. Part of that was Saturday mornings with Dr Cade at Royal Park. The medical school class would assemble in the auditorium at the hospital, which was a state mental hospital. Dr Cade would be up on stage with a couple of nurse assistants. He conducted classes like I understand Kraepelin used to conduct his teaching sessions. He would snap his fingers and from stage left the schizophrenic patient would be walked in and sat down in a chair. Dr Cade would put the patient through his paces, send him off stage right, talk about the case then snap fingers again and the nurse attendant would bring in a manic patient. Cade would put the manic patient through his paces in front of the audience, and that was how the instruction went along. They were both entertaining and instructive sessions and it's clear that Cade was a very astute clinician.

Why then psychiatry?
I graduated medical school at the end of 1964. I went on a conveyor belt into an internship at Royal Melbourne Hospital. I had the usual experiences there - a turn in internal medicine, a turn in surgery, a turn in geriatrics and a turn in the emergency room. At the end of that year, more or less on a conveyor belt again, I rolled over into a 2nd year house officer's job and there some things began to crystallize. I had four rotations in that year,1966. One was in the academic department of medicine with Austin Doyle and the renal hypertension unit. There I saw for the first time real clinical investigators.

There was another rotation to endocrinology with Skip Martin, who became a very close friend and a role model. In addition to the regular clinical aspects of the work, Skip set me to work on a research project - looking at the data on hypothalamic pituitary function tests. The reason for his interest in these tests was because at that time patients with diabetic retinopathy were being treating by pituitary irradiation. The idea was to knock out the pituitary gland, and so knock out the production of growth hormone which, it was thought, would slow down the proliferation of abnormal blood vessels in the retina. Skip himself was a diabetes specialist. So I began looking at these so called HPA function tests. They had done quite a lot of work with these patients using procedures like hypoglycaemia to stimulate ACTH and then cortisol release and growth hormone, or pyrogen administration - giving intravenous injections of a lipopolysaccharide bacterial pyrogen - causing a mild fever and looking again at the ACTH-cortisol response, and giving lysine vasopressin which also released ACTH and cortisol. Those were the main ones.

I put together the data and we published a very nice report on these tests essentially delineating the normal range of response and the values found in people with pituitary irradiation. In the course of doing that work, the light bulb went on in my head – here in principle was a way of getting at brain function through neuroendocrine testing. In principle, this approach could be applied in people who were receiving the new psychotropic drugs that were the subject of intense interest at the time, particularly the antidepressant drugs. Remember, the monoamine theory of depression had been proposed by Biff Bunney, John Davis, and Joe Schildkraut just in the previous year, 1965.

When I finished up with Skip Martin my next rotation was to psychiatry with Brian Davies, who was the new Chair of Psychiatry. He had arrived from the Maudsley Hospital in 1964. So I took this neuroendocrine idea to Brian and said you know I think there's a way, not just in animals, but in patients to test out these monoamine systems and the effects of antidepressant drugs. Brian was already quite familiar with some of the early work on cortisol and mood states – he was good friends for example with Jim Gibbons who had published a very nice study with Paul McHugh a few years earlier. So Brian resonated to this idea. For the remainder of my 3 months with him there was no time to begin doing anything but we talked about it and I more or less made the decision at that point to switch out of a track leading to clinical pharmacology and into psychiatry, because I knew that in order to study these

drugs I would need access to the patients, and so I would need to have some basic psychiatric qualifications.

At the end of that year, Brian offered me a newly created position in the Department of Psychiatry as Clinical Supervisor. So in 1967, which would have been my 3rd postgraduate year, I began work in the department as a junior faculty person cum resident at the same time. In my role as Clinical Supervisor, I just had to keep track of the teaching schedules for medical students, and the rest of the time I was free to round with Brian on his ward, and to see patients in his outpatient clinic. That was where I first got the experience of an outpatient lithium clinic and a setting to do the kinds of HPA function studies that we had discussed.

During 1967 I began running these HPA function tests in patients. The original hypothesis was that we would probably find normal HPA function in depressed patients, and that the drugs would modify the results in a manner consistent with the basic pharmacology of the neuroendocrine system. This approach is what we and others later termed the 'neuroendocrine window strategy' for studying psychiatric drugs or limbic system disorders.

My job was to conduct the protocols on the ward – that is to give insulin tolerance tests, to give the pyrogen tests, to give the lysine vasopressin tests and to give the overnight dexamethasone suppression tests. I also rated the depression severity concurrent with the testing – indeed I quickly committed the Hamilton depression scale to memory. So I ran those neuroendocrine tests, I drew the blood samples, and then I was also the person who had to learn the laboratory assays for cortisol, and run those assays myself. In the course of doing that I recognised a pattern – patients with what we then called endogenous depression had extremely abnormal DST results in the form of failure to suppress plasma cortisol. In those days we were using a 2mg dosage of dexamethasone so these were patients with a severe form of DST nonsuppression. Moreover, at that early stage we were only sampling at 8 o'clock in the morning. We were not going out later in the day. That was something I introduced only after I got to Philadelphia. So it is very clear now that we had discovered or stumbled upon a striking neuroendocrine abnormality at baseline, before treatment, in these depressives. Also, pretty early on we saw that this abnormality did not show up in patients with what at that time were called neurotic or reactive depressions.

It was the patients who would now be called melancholics. Now I've got to say that these were severely ill patients. They were inpatients. There were very few inpatient beds in the city at that time. They were extremely ill and many of them were treated electively with ECT. So that gives you some idea of the original population that we studied. Once we had made that observation, the research took a 90 degree turn. Instead of focusing on what the drugs do, my focus shifted to what the hell is going on with these patients that their neuroendocrine function appears to be so abnormal. I de-emphasised the pharmacological mechanism and focused more on the pathophysiology of the abnormal DST.

How did Brian or others receive the data?
Both Brian and Skip, who were my research supervisors, were very struck by the data. We looked around for potential confounds that might have been leading us astray. We were aware quite early on that barbiturate drugs would accelerate the hepatic metabolism of dexamethasone, as would certain other drugs like phenytoin and carbamazepine - so if you had an accelerated drug metabolism you would have low blood levels of dexamethasone and you might have apparent nonsuppression. I discussed that issue in my PhD dissertation written in 1971 and by then we ruled out that DST nonsuppression was an artefact of barbiturate administration.

Basically I just brought the data back and Brian and I sat down and looked at it and said hm that's Mr Jones, yes. Hm that's Mrs Smith, yes alright. Later we began getting some post treatment repeats and for the most part they were normalising. Then we had a story and by late 1967 we had enough data to send our first manuscript off for review. It went to The Lancet, who turned it down. We turned right around and sent it to British Medical Journal which did publish it in 1968 and it has become one of the citation classics in psychiatry.

This was pretty good, for a person new to the field, entering on a wave as it were.
Even the journal Nature ran a commentary on our report, but we did not realize at the time what influence it would have – we were just doing our thing. The attention this work got didn't become apparent to me until I got to the States a few years later. Maybe that's a blessing of being more or less isolated down in Australia. We just went ahead and did our thing and I rounded out the work with a number of other publications. I never had the impression that I was some kind of whizz kid - not the way Bob Sapolsky was regarded, for instance, who rode a media wave with his work on stress and the hippocampus. There was never any of that 'ballyhoo' around our work.

How did you make the move from Melbourne to the States?
Well I completed all my formal training in Melbourne. In 1969 I took the DPM exam. Then in 1970 The Royal Australian and New Zealand College of Psychiatrists was established. And, as usually happens, I was grandfathered into college membership by virtue of already having a DPM. There was a pro forma examination, but basically anybody who had a DPM when the college was formed was automatically a founding member of the college. In 1969 I enrolled for a PhD in the Faculty of Medicine on the topic of neuroendrocrine function in depression and submitted my thesis dissertation in mid 1971.

Meanwhile, in 1970 I had gotten a travelling fellowship from the Endocrine Society of Australia, which gave me the funds to travel to the APA meeting in San Francisco in 1970, and after that to visit half a dozen clinical research units in the US and Britain. In the course of that trip I made contact with Bob Rubin in Los Angeles, whom I already knew, with John Davis in Bethesda, with Joe Mendels in Philadelphia, with Ron Fieve at the lithium clinic at Columbia in New York, and with Ed Sachar at that time at Montefiore Hospital in New York. I went also to Britain and visited the Maudsley, Newcastle and Alec Coppen in Surrey. In all of those places I was essentially looking for a

place to go for a research fellowship, and that ended up being Joe Mendels' unit. He was the first who made an overture and so that's how I came to go Philadelphia in 1971.

How did Joe's program look to you then?
It looked like a very good deal from the outside. He had a dedicated clinical research unit in a VA hospital with about 10 beds across the hall from the chaotic general inpatient psychiatric service, which at that time was flooded with discharges from the Vietnam war. The Mendels unit kept a low profile and was very selective in the patients it accepted. It had good laboratories attached, and a large staff. So I fitted in quite well there and I had a very good time.

Except I pretty soon discovered that the Mendels unit really didn't have enough patients. So I began looking elsewhere for clinical collaboration. I ended up joining William Dyson, known as Dutch Dyson, in his lithium clinic across the street at HUP – the Hospital of the University of Pennsylvania. Dutch was a former surgeon turned psychiatrist who thought the only thing that stood on solid ground in psychiatry was the use of lithium - a pretty typical surgeon mentality. Also with Joe Mendels' encouragement I went to southern New Jersey to a private hospital called the Carrier Clinic just outside Princeton. We enrolled some patients there in some studies and as a result you'll see the name Arthur Sugerman on a few of my papers. Arthur was the liaison person at the clinic, where we did some of the work on urinary cortisol for example.

As a research fellow, the experience in Joe Mendels' unit taught me a lot about the logistics of running a clinical research program. Joe was very generous with his time and advice. Even the limitations of the unit in Philadelphia were instructive for me. And I took those lessons with me when I went to Michigan.

The original plan was to have 2 years in Philadelphia and then return to Australia. I had decided that I didn't want to go back to Melbourne, but Lesley Kiloh in Sydney had discussed with me coming back as Director of a programme affiliated with his department at the University of New South Wales. It was called the Neuropsychiatric Research Institute. Up until that time that facility was basically a small programme within Callan Park Hospital in Sydney where some neurosurgeons were doing a few things more or less along the lines of Robert Heath in Tulane. But there was not really any well organised programme.

About half way through my time in Philadelphia, Kiloh gave me a signal that the funding for the programme we had discussed was looking shaky. And later he confirmed that there had been change in government in New South Wales, with a change of priorities, so there wouldn't be any unit for me to go back to. That was the point at which I began looking seriously at possibilities in the US. I had offers from John Davis in Chicago, from the University of Michigan and also to stay at Penn. Adding it all up, I thought Michigan had the best prospects. So that's where we went in mid '73.

Had you met George Curtis who also moved to Ann Arbor at this point?
I met George in my first year in Philadelphia. George then was a faculty member at the Eastern Pennsylvania Psychiatric Institute, same place that Charlie Shagass used to work - they were affiliated with Temple University. But George would come across to meet with Joe Mendels from time to time and so he and I got to know each other during my first year at Penn. George then moved to Michigan and he had a lot to do with my recruitment in '73 to Michigan as well. But the main people who brought me there were the Chairman, Albert Silverman, and the director of the Mental Health Research Institute, Gardner Quarton.

The big drawing card to Michigan was the presence of the Mental Health Research Institute, along with the support that the Department of Psychiatry was providing. It took both components to get a research program together. George and I received appointments as Research Scientists in MHRI, as well as faculty appointments in the department of psychiatry. We were the first clinical investigators accepted to the institute. Many of the established Research Scientists within MHRI didn't believe there was such a thing as clinical research, and some were openly offended that we were admitted to their precious basic science domain.

The Department gave us a 26 bed inpatient service. George Curtis and I ran that unit. We each had two residents, and he took half of the ward and I took the other half of the ward. Our very first job was to turn the ward into a contemporary clinical service. We're talking 1973. The dominant force in American psychiatry at that time was psychoanalysis. The inpatient service that we took over billed itself as an adult inpatient psychoanalytic service, where they claimed major character reconstruction was performed. The average length of stay for these adult patients was 18 months, which is astounding by today's standards. It was all paid for by indemnity insurance and by the State subsidy to the psychiatric programme.

The very first thing we had to do was discharge a lot of long stay patients, who really had no business being there, and educate the nursing staff to a more contemporary mode of management. So we were very pleased when we got the average length of stay down to 6 or 7 weeks. Now, even 6 or 7 weeks by today's standard is unthinkable, certainly in the US. I don't know about over where you are. I think the only country where such long stays occur anymore may be some units in Germany.

A good number of the nurses could not accept this change in philosophy. There was some early friction, and we advised some of them that frankly they would be better off going to work some place else, because their expectations were not going to be met by the program we were developing. But once we got past that initial period of readjustment things began to work much better, and the nursing staff began to acknowledge to us that the patients were obtaining better outcomes.

After a year or two George decided that he wanted to focus on outpatient anxiety disorders, and at that point I persuaded Albert Silverman to reduce the number of beds from 26 to 13 and to essentially carve out half of the space for clinical research support staff. By this time we had NIH funding coming on line so we had the funds to support a cadre of research staff. I'd say from '76 onwards the program really hummed.

We had both an outpatient and an inpatient component on the one floor. We had a number of junior faculty working with me. Michael Feinberg headed up the outpatient research clinic, and John Greden oversaw the 13 inpatient beds. We had a number of fellows that the Department helped us to bring in, people like Ari Albala, Meir Steiner, Roger Haskett, Ziad Kronfol, Norman James from Australia, Leon Grunhaus, Elizabeth Young. We had a number of residents who graduated the program and wanted to work with us as well. Richard Katz joined us as a postdoctoral fellow in behavioural neuroscience from Larry Stein's lab. Barbara Turner came, too, as a postdoc from Bruce McEwen's lab. Richard and Barbara attracted very talented undergraduate research students like Kevin Roth and Laura Liebler. Another key development was our recruitment of Jim Ritchie as laboratory director. Jim was a genius at collaborating effectively with clinicians, and at establishing new laboratory methods. Meir Steiner undertook a PhD in neuroscience, studying behaviour across the oestrus cycle in rodents. I set up a research clinic for Meir and Roger to study menstrual cycle related mood change. Roger Haskett set up a collaboration with the Endocrinology service to study patients with Cushing disease. Norman James worked with the Department of Genetics. Ziad Kronfol collaborated with the department of medicine on immune markers in depression. Peter Smouse, a statistician in the Department of Genetics worked with us on the validation of the Carroll Depression Scale. Elva Poznanski from the children's psychiatric service worked with me on the DST in depressed children and also on the Children's Depression Rating Scale, that is now a standard research instrument. Bernie Agranoff and I recruited Stanley Watson and Huda Akil to join the department and MHRI in 1979, and Elizabeth Young worked with them on several endocrine projects. Thanasis Zis joined us from NIMH and began working on HPA axis interactions with morphine and naloxone, which turned out to be abnormal in depression. So the whole clinical research machinery kicked into high gear in those years between '76 and 1981. We were publishing steadily along the way.

In 1980 I took a 6 months sabbatical. I didn't go anywhere. I locked the door and refused to speak to anybody for 6 months but I stayed in Ann Arbor because that's where all my research files were. In that 6 month period I completed the writing of 16 manuscripts for publication, one of which was our major paper on standardisation of the DST that was published in January of 1981. It was a very productive period, and by the time that paper came out along with an accompanying review in 1982, I really felt that I had probably contributed my major work to the field.

Having observed Joe Mendels' exit from the academic research arena, I began even that early to think now what do I want to do going forward from

here? Do I want to be a squatter sitting on resources but not making very good use of them or do I want to move into some other role and leave the resources to some younger person coming along just as I had myself? Right around that time Al Silverman was exiting the chair at Michigan and more or less by default I found myself in the role of acting Chair of the Department. This was in 1982. So that gave me a taste for administration, and I began to get calls from other places about whether I was interested in being a chairman here or there. Psychologically I was at that point ready to separate from the clinical research resources that I controlled.

I finished up accepting a Chairman's position at Duke, and in that capacity basically set about running interference for and fostering the careers of junior faculty, which was a very rewarding role for the most part. I kept a research grant but I basically handed over the running of the grant to a very capable young person called Ranga Krishnan. Ranga essentially had the benefit of my NIH grant to get him up on his academic legs, and he eventually ended up as Chairman at Duke, which I was very pleased to see. So that was my psychological progress.

Then in 1990 I left the Chair at Duke and I went back to a very agreeable role which was Senior Teaching Clinician. I took over what I called a foxhole away from managed care in the form of the Geropsychiatry Institute at John Umstead Hospital, a state hospital about 20 miles from Durham. I had set it up for the Duke psychiatry residents to rotate at JUH, and we also set up a Geriatric Psychiatric Fellowship there. I arrived there in 1991 with no particular credentials as a geriatrician but a lot experience in general psychiatry, and I fitted right in. I took over as director of a centre grant in geriatric depression that was originally run by Dan Blazer. Plus I had 2 RO1 research grants of my own as well. I had a set up out there at John Umstead that allowed me to pretty much do whatever I wanted to do and I had no managed care constraints to worry about. It was a very happy and productive 7 years out there until Sylvia and I decided to move to California 10 years ago. During those years at JUH I served as mentor for several junior faculty members and fellows. I should mention especially Fred Cassidy, working on bipolar disorders; Eileen Ahearn working on fundamental assessments of mood disorders; and Paul Kim from Seoul, with whom I am still collaborating on pharmacogenetic projects.

Barney when did the DST begin to have a wider impact? When does the world begin to sit up and notice?
I'd date it to 1976 when we had two major publications back to back in Archives of General Psychiatry describing the graded abnormalities of the test results in parallel with clinical change. The 2nd of that pair of papers was an initial look at possible diagnostic uses of the test. That's when the DST really came to prominence. I would say from 1977 through 1980 I was in high demand as a speaker at various conferences because of that work. The 1981 dataset was still being accumulated so I was not out talking about that but about the implications of the 1976 papers. And those two papers really had a high impact on the field. Each of them has been cited over 500 times.

How much do you suppose the success of the DST in a sense made DSM III credible? Because it must have looked like you were really carving an illness out here that was as real an illness as anything in the rest of main stream medicine.

Except that the DSM III paid no attention to it. There was a lot of tension between us and Spitzer and Klerman around how mood disorders should be approached in the wake of the DST. We were pointing clearly back to the rightness of the Newcastle approach, and Klerman and Spitzer didn't want to hear anything about that. So they proceeded in DSM III to take the field all the way back to Aubrey Lewis in effect, who said that there's only one type of depression and its either mild or severe. They jettisoned the hard won, fine grained distinctions between clinical depressive subtypes that were now being validated by biology. They didn't want to hear about it. So I don't see that the DST did anything at all to bolster DSM. DSM was a train running on its own track and there was no way we were going to influence that.

I'm sure that the DST is at odds with DSM but the success of the DST preceded DSM, and I'm just wondering if the fact that biological psychiatry seemed to be bearing fruit helped pave the way for the more general kind of acceptance of the DSM.
Not really. Having lived through that era in the US right in the centre of it, I never got that impression at all. You have to remember that the Washington University group were agnostic about causes and so were Spitzer and Klerman.

There was a meeting around 1982 held by the NIMH looking at the DST, where as I understand it you found yourself lined up against people like Bob Spitzer?
Indeed I was, yes. They came at it much the way Ross Baldessarini later came at it - namely with an attitude of requiring an impossible standard. They were looking for absolute sensitivity and absolute specificity. If a biological procedure was not close to perfect in those regards, they thought it was not worth pursuing.

My main exchange at that meeting with Spitzer was to metaphorically grab him by the scruff of the neck and say 'look here you are blithely accepting this and that symptom as having diagnostic weight for let's say major depression and you know very well that the sensitivity and specificity of each of those symptoms is far worse than for this biologic marker. But you don't see the logical inconsistency of the position that you are taking.' His response to that was 'its very important to remain agnostic and it would be a big mistake for DSM III to endorse a biological marker because that would be taken as endorsing a biological etiology and we don't know that.' That was the kind of position that we were up against.

Can we date and place the meeting?
This was held in Bethesda Maryland July 20-21, 1982. The meeting was chaired by Robert Hirschfeld, and Stephen Koslow was the co-chair because this was an NIMH sponsored meeting. I would say those who were more

inclined to agree with me were Walter Brown, Irl Extein, David Kupfer, Peter Loosen, Jim Maas and Steven Targum. And then there were others like Thomas Insel, who is now the director of NIMH, Don Klein, Herb Meltzer, Spitzer and Peter Stokes who were looking at it the other way. Actually a lot of those people were on the fence and I think what nobody was really prepared for was the onslaught from Spitzer.

And the reason for this onslaught?
I think he was defending the conceptual structure of the DSM which had only come out two years earlier. One of the ironies is that when DSM III came out people piously talked about it as a series of hypotheses, but once it was out it rapidly became orthodoxy, and challenges to DSM were definitely not welcomed.

In terms of the place that a biological marker might have in this new scheme of things within the operational criteria framework a book called Beyond Normality had a big influence on you.
Yes - the authors of this book were Galen and Gambino. It was published in 1975. I remember getting the book and opening it in my office one Saturday in Ann Arbor and being transfixed, reading the entire book in one sitting because it finally gave me the conceptual tools to think about our DST data. It was basically a standard clinical biochemistry exposition of laboratory testing from the perspective of sensitivity, specificity, predictive value both negative and positive, and the interactions of these with disease prevalence. These were the major insights. For me in '76 it was an eye opening book. I had been intuitively working up to these constructs myself and now suddenly here it was laid out for me. My contribution subsequently was to introduce American psychiatry to those lessons, to those constructs. All those terms that I've just mentioned have entered every day language and I was the main portal through which they entered the world of psychiatry.

In terms of a philosophy how would you characterise the philosophy that you find in that book?
It's essentially a frequentist philosophy, it's not Bayesian. The only place where it begins to get Bayesian is where they discuss the interaction with disease prevalence or base rate, and they give a very lovely example, which is the case of phenylketonuria and screening of newborns for PKU.

It turns out that the sensitivity for the PKU test is quite high - over 90% and the specificity is remarkably good as well, somewhere around 98%. Practically speaking, that is as good as you're ever going to get in the world of laboratory medicine. However in clinical practice it turns out that the majority of reported positive results are false positive, and the reason for that is because the base rate of disease is only 1 in 10,000. So, even though the PKU test picks up most true cases with only a 2% false positive rate, the overall number of false positive cases ends up swamping the number of true positive cases.

This has led to a great deal of soul searching about community screening policies for newborns - with the very appropriate question 'Are were doing more harm than good by screening and then treating?' I think the answer is a

screen is a screen, and then if you get a positive screen you need a confirmatory test rather than just proceed to treatment on the basis of the screen.

With the DST, we had a different but related set of issues. It was introduced as a confirmatory test for melancholia but it came to be used in many places as a screening test – something I always cautioned against. When the DST is given to everybody, a good many false positives will be encountered. Clinical judgement and Bayesian context then are needed for interpretation of the results. For instance, generally it doesn't really matter that the DST is abnormal in 25% of cases of Alzheimer disease. Who cares, when the patient in front of you is a 30 year old person with a depressive episode? This was the point that Baldessarini and Spitzer completely failed to grasp.

You call people like Ross Baldessarini the purists. Do you have anything further to say about that?
I became very frustrated with Ross because his approach to the issue was not flexible. It was purely scholastic in an area that called for Bayesian thinking. Plus Ross, like Spitzer and others, had a tendency to what I call catastrophise on behalf of the field 'oh my god what would happen it some GP somewhere treated a patient for depression just on the basis of the DST.' There was a good deal of talk of that nature circulating - what I call worst case scenarios. Another form of this tendency was catastrophizing 'Oh my god, the sensitivity of the test is only about 50% so in the field the true diagnosis of melancholia will be denied to many patients because of a negative DST result.' The irony is that the management of depression in the community could scarcely have been worse than it already was. And I didn't see that the DST was going to cause any material worsening of that situation.

If the DST had come into more main stream use, what do you suppose would have happened to drugs like Prozac, which while they can be extremely useful drugs clinically they don't treat people who are DST non-suppressors, they just don't work for this group of patients?
It's pretty easy to infer what would have happened, they would have been less widely used. I think one of the scandals of modern psychopharmacology is that the new generation of antidepressant drugs has been approved while any biological leads that might limit their market were studiously ignored. Back in the 1980s and 1990s I said to a few companies, and I know other people did as well, that they should run DST or sleep EEGs for REM latency and density and look at how the results of treatment matched up to the biomarkers. The corporations did not want to hear that because they had the marketing people at their elbows telling them that this would potentially cause a modification of the FDA labelling and a consequent restriction of the market.

They were much happier to spend extra millions of dollars on ever increasing sized clinical trials with a decreasing discriminatory value or signal-to-noise ratio to finally get their approval, than they were to look at these biomarkers, because they knew that at the end of the rainbow was a pot of gold worth billions. An extra $10 million to run a trial that required 400 patients instead of 150 didn't bother them a bit, knowing what their ultimate financial objective

was. Had they taken the other approach, they could have run a smaller, more efficient and more definitive trial. Frankly they would have done something to improve the management of depression in the community because right now patients who are DST positive, for example, get these drugs and they don't improve, as you say. That is why current drug treatment algorithms for depression as so disappointing, as the STAR*D project has taught us. The myth of efficacy of the SSRI drugs has been exploded.

What were the forces that lead to the DST's eclipse?
I think there were a few contributing factors. One was the stuff from Baldessarini which came out around '85 I believe. The doomsday talk that I mentioned – 'it is not perfect, therefore it will be misused and therefore we shouldn't touch it'. That was the emotional message conveyed.

The second reason for its demise was the growing realisation that plasma dexamethasone levels really do matter in terms of obtaining a valid test. We had looked at that and published on that back in 1980 before the main study was released because we wanted to be sure about it. In retrospect we simply had too small a sample to see the signal, but in larger samples its very clear, and we have confirmed it in our own reports, that there is in effect a blood level window. If the dexamethasone level is too high – above the window – then everybody is a suppressor and if the level is too low then you get a lot of false positives. However within the optimal blood level window the test performs as we described. Once it became clear that the average hospital community laboratory would need to add plasma dexamethasone assays as well as plasma cortisol then I think people said 'ah this is too much to worry about'.

What about the role of the pharmaceutical companies who perceived the test as perhaps potentially restricting their market?
They had nothing to do with the research program that led to the test. They were interested observers, and any conversations that I had with them were as a consultant. But there was never any public position taken by pharmaceutical corporations, they just voted with their cheque books by not allowing investigators to incorporate it in large scale clinical trials. I can't really point to any one company or any one person and say that's the reason. It was just that they were observing from the outside and they saw no reason to buy in.

Barney when did the DST begin to be called the DST?
Probably around the late '70s. Up until then I insisted that we call it the dexamethasone suppression test, precisely because I did not want it to become a catchy shorthand expression. But eventually the forces to contract 'dexamethasone suppression test' to 'DST' prevailed, and that's the way the field took to describing it. It was already called the DST in endocrinology. Psychiatry didn't invent the term DST. As you know, the DST was invented in the first place by endocrinologists, not by psychiatrists. That's why Skip Martin had me look at it back as early as 1967, because it was already used as a diagnostic test or screening test for Cushing's disease. There were several versions of the test in regular use within endocrinology - there was the

multiple low dose, the multiple high dose and, shortly before I began, there was a paper on single dose overnight DST, and that was the protocol that Skip Martin suggested I pick up.

Why did the DST succeed when later tests like the CRF test didn't really have any impact?
I think because it was so focussed. If you look at the dex/CRF test there's a certain lack of focus about that body of work. To begin with there are several variant forms of the test. Some use human CRF, some use ovine CRF, and you get very different looking endocrine responses to those two substances. The ovine CRF has a much longer action. Second the dex/CRF test became domesticated too quickly, without being checked out as to the standardisation of test parameters, for dosage, for ovine versus human peptide, and for frequency of samplings. With the dex/CRF test you have two end points - one is ACTH and the other is cortisol, and often in the literature it almost appears as though people will choose one or the other depending which one works best to suit their pre-existing hypothesis. There is actually a good deal of inconsistency between the ACTH responses and the cortisol responses. So, as I have summed it up when reviewing some of these papers for various journals, the question is what does the dex/CRF test test? And does the dex/CRF test using ACTH as the dependent variable test the same thing as the dex/CRF test using cortisol as the dependent variable. The field remains confused about all of that. As a result, one sees a lot of glossing over these difficulties in published reports, and one sees the adoption of terms that don't really explain anything – terms like HPA axis dysregulation.

In addition roll in the issue of plasma dexamethasone levels, which are almost never controlled for, and you've got, sadly, dozens of studies reflecting enormous manpower and resources that don't add up to very much at all. I think the lack of focus was probably the major problem with the dex/CRF test. When it became clear that it was frequently abnormal in some anxiety disorders, then suddenly we saw a subtle shift in nomenclature to where the theorising was framed as HPA axis dysregulation in anxiety/depression spectrum conditions.

Another reason why the dex/CRF test hasn't caught on, although it could have remained as a research tool, it's a lot more difficult to perform and a lot more expensive of laboratory resources than a straight DST. It isn't clear that you are getting all that much more diagnostically in return.

The DST gave rise to a hectic period when a range of neuroendocrine tests came on stream. Trailing in its wake there were the TRH tests and the clonidine induced growth hormone tests. How did all of these look to you? Did they ever measure up to the DST?
Not really. Arthur Prange and Peter Loosen at Chapel Hill had a lot of TRH test data. Until our publications they had never figured out a way to analyse and present those data in terms of laboratory testing - meaning they'd never read Galen and Gambino. When they saw our 1981 DST paper, they quickly put together a report published in American Journal of Psychiatry, probably in

1982, I believe, more or less staking out what best case could be made for the TRH test. But the TRH test didn't get replicated consistently enough.

As far as the growth hormone tests are concerned I made a strategy decision very early in my career to stay away from growth hormone because I thought there was just too much variability in growth hormone responses and too much unpredictability in baseline growth hormone levels. As I look back I think that was a good decision. I'm familiar with things like clonidine stimulation and GHRH stimulation but they're very difficult to interpret as to mechanism.

Did the failure of these different neuroendocrine tests to be of clinical use feed back to the willingness of people leave the DST behind?
I don't think very much. I think the DST floated on its own bottom. Had one of the others proven to be useful, people would have been thrilled. But I think despite that the DST basically like I say floated on its own bottom.

Early on in the course of things there was a few people who were working in broadly the same cortisol area, people like Ed Sachar. Did the fact that Ed died early have any impact on how things went?
Not really. If we go back to the '60s it's very clear that the DST was what's often referred to as a multicentric discovery, meaning several different groups in complete ignorance of each other were working on it at the same time. The very first people to play around with dexamethasone in depression was a group of Canadians – Joe McClure and Robert Cleghorn.

They looked very briefly at dexamethasone as a possible treatment of depression. The only publication is a bit of a mention in a discussion in a book chapter - something most people would never have seen. And then Peter Stokes at Cornell in New York was working at it and by 1966 he had some early data but he was very slow to publish. His data didn't really hit the street until '68 or '69 in an NIMH publication. Simultaneously around '67, Will Carpenter and Jan Fawcett at NIMH were working on DST and they adopted the multidose low dose and high dose DST protocol. Peter Stokes did some of that but he also began to do the overnight DST protocol that we used. And then at the same time in '67 in London Mike Besser was looking at DST.

All of us were unaware that the other groups were on the same track. So it was definitely a multicentric discovery. Essentially the finding from each group was depressed patients have trouble suppressing with dexamethasone. Sachar was at work in the same era but he was looking at cortisol secretion rates and patterns of daily cortisol release with multiple samples across 24 hours. He made some important discoveries, one of which was that cortisol spiking continues during sleep in depressed patients whereas you don't see that in normal subjects.

Sachar was a psychoanalyst, and it was this discovery that finally convinced him that you couldn't explain all of the cortisol data in terms of breakdown of ego defences against anxiety, because if you saw cortisol hypersecretion when the patients were asleep then something else was going on. But it took Ed a long time to get around to that perspective.

Then, right around 1976 when our two big early DST papers appeared, Ed moved from Montefiore to Columbia as Chairman, and he became obviously distracted by administrative duties, and he took his eye off the ball as far as cortisol studies went. He had some very capable junior collaborators – Uriel Halbreich, Swami Nathan, Gerhard Langer, Greg Asnis, and of course Kim Puig-Antich who studied depressed children – but I got the impression that they were more or less left to their own devices. Ed himself for some reason got side tracked onto studies of prolactin responses to neuroleptic drugs, which I always thought was a pretty uninteresting topic scientifically. But he was still on that track at the time that he had his stroke which occurred I guess in late 1980. He then developed a post stroke depression and he committed suicide a few years later.

If the DST was a multicentric discovery, how come you've been so linked to it? Was there any particular reason why your name is the one that really comes out on top of the pack?
I think because I stayed very focussed. Will Carpenter and Jan Fawcett did it as a project under Biff Bunney at NIMH, but they eventually moved on out of the program. They were not all that well educated about endocrinology to know where to go with it. And, we're talking around 1970 now, I think they didn't understand the potential importance of it. Besser in London looked at it a little bit but he was a card carrying endocrinologist, he didn't know much about depression. Apparently he didn't form any ongoing psychiatric collaboration to extend his early observations. Peter Stokes carried it forward with, I think, a pretty good focus, but somehow he just didn't have the personality to get it out there, and also, like I say, up until our '81 paper nobody had the conceptual tools to look at it as a diagnostic or screening tool. Nobody had the language, the clinical test terminology to discuss it intelligently in that way.

This was still the era of frequentist statistics, and paper after paper in the main psychiatric journals showed group differences on variable A and variable B but no real attention to the distributions and to the marginals, and the significance of the zone of non-overlap or to the magnitude of that zone. That is how you can calculate sensitivity and all the other measures.

It would be helpful if you could explain that in as concrete a way as you can?
Well in frequentist statistics you look for two population means and standard deviations and you look for differences between the two populations as signified by, say, a t-test. It's possible for two populations to be significantly different statistically by t-test, depending on the population sample size, but to not differ by very much in salience. If you have 10,000 men whose mean height is 5ft 10 and another 10,000 men whose mean height is 5ft 11, then statistically that's a highly significant difference. But the overlap between those two means is going to be huge, so that it would only be on the very tails of the distribution that you can make any conditional probability statements. When working with clinical variables, be they behavioural variables or

laboratory variables, what many people in the ‘70s neglected to do was to examine the distributions and in particular the overlap of the distributions.

A common saying among statisticians is that before you do any formal testing you need to eyeball the data, and the best way to inspect the data is with a scatter graph. That will immediately tell you how much overlap and how much separation there is between the distributions for the two populations. Things like laboratory tests become useful when that zone of non-overlap begins to enlarge, and that’s also the same principle that is used in setting the cut off point or criterion value for separating normal from abnormal on a test. In the process of doing that, you go through the obligatory trade off between sensitivity and specificity.

The lower you set the criterion or cut off level, the more cases you will detect so you improve sensitivity but you pay a price for that, and the price is loss of specificity. The higher you set the criterion value the fewer cases will be captured but with greater specificity. And these are the considerations that enter into choosing a cut off level. That choice is going to be determined by a number of external factors, chief of which is the cost of a false positive or false negative. Do we err on the side of inclusiveness or do we err on the side of exclusiveness? These were the issues that people like Spitzer and Baldessarini were unable to deal with.

At any point during your work on DST did the issue of chronobiology come up?
Sure. It came up in our very first paper in 1968. If you look at that paper you will see that we made some reference to Dorothy Krieger who had been looking at chronobiology and had shown for example that if you give drugs that effect neurotransmitters at certain times of the day you will block the circadian rise of cortisol the following morning. So in our very first publication we allowed that maybe a chronobiological factor was at work. We conducted some supplementary tests where we administered dexamethasone not only at midnight but also at 9pm, three hours earlier, against the possibility that the results were signalling a chronobiologic abnormality rather than a feedback abnormality. We looked at chronobiology in another sense in our 1976 publications, by showing that escape from dexamethasone suppression became more prominent towards the end of the post-dexamethasone day.

So very early on, people were paying attention to chronobiology. All of us early on agreed that the differences in baseline plasma cortisol between depressed and control subjects were maximal at night rather than in the morning and daytime hours. You will see this consistently in our early publications, and in Besser’s and in Sachar’s, that if you look at 8am blood samples depressed and control subjects look very close together, at 4pm they are separating and at midnight they are much more widely separated. That’s what I take you to mean by chronobiology.

Now the DST has probably seemed like distant history for most people until recently when Max Fink has raised the profile of melancholia once again.

Yes, I remember saying to Stuart Checkley on a visit to London in I guess ’81, ‘82 that I had set the DST floating on the waters and it would do whatever it was going to do but that the field would determine that, not me. I never had any particular goal to “make the DST succeed.” I believe that science is a social process, and the satisfaction for me was to demonstrate what we did, and if other people didn’t want to use it, well that’s up to them. I’m not about to make it a crusade.

Max now, though, has looked at it in relation to his thinking about melancholia and is beginning to promote a revival of the DST. And I have helped Max with information about recent developments and so on. What it will take for the DST to come back is for somebody to do a pragmatic study of useful clinical information provided by the test.

There are a number of kinds of prognostic information already out there in terms of preliminary signals. First is the drug v. placebo response rate difference. DST positive patients have a very low rate of response to placebo and a good rate of response to antidepressant drugs of the tricyclic class. Whereas DST negative patients have a high rate of response to placebo and they don’t do much better at all with tricyclic antidepressants. Now what’s needed are some further large scale pragmatic studies along that line.

A second type of prognostic information concerns course of illness – such as rates of switch from unipolar to bipolar. The existing data are that the relative risk is around 8. If you are a unipolar depressive with a positive DST your relative risk of switching to bipolar is about 8 over the next 5-10 years. Now that is a huge effect. The person who identified it is Bill Coryell in Iowa with their follow up data, and it has been amazingly neglected.

Another type of prognostic information is suicide risk. We published some early data, and there have been later publications, associating risk of completed suicide with abnormal DST in depression. Again the relative risk is about 8. When you go back and look at things like elevated cholesterol for myocardial infarction or stroke, relative risk doesn’t get anywhere near 8.

The third kind of prognostic information has to do with risk of relapse and rehospitalisation and overall cost in terms of health care system resources. Here again the relative risk is about 8 when you compared DST positive to DST negative depressed patients.

These are the kinds of large scale pragmatic studies that are needed, along with incorporation of the DST into clinical drug trials of established and new antidepressant drugs. All of these are meaningful clinical outcomes, and what’s astonishing is that the field has not pursued them. What is going on? It’s not as though the field has a lot other hot leads. It’s a neglect syndrome or what Roy Poses calls the anechoic effect. These leads appear in the literature but nobody picks up on them. One reason is that the pharmaceutical companies have no interest in the study of biomarkers. A second reason is that within NIMH under a succession of directors neuroendocrine research became less valued than imaging studies and genomic studies.

When you outline the story like that the thing I think of is the Barry Marshall story and helicobacter and how it was a close run thing that the discovery of the helicobacter actually made it into main stream medicine. The companies producing the H2 blockers weren't interested and weren't actually supportive.
I think what is a real shame, though, is that we gave the field a very promising lead and they failed to run with it. Hypercritical but influential voices like Spitzer and Baldessarini have much to answer for. When I used to speak to community medical groups, primary care physicians and psychiatrists would tell me 'Dr. Carroll, thank you for developing the DST – let me tell you about a patient who was put on the right track because of this test.'

Part of the problem is that psychiatric diagnosis in Spitzer's DSM-III was cast as a metaphysical exercise rather than a clinical exercise. As a consequence, the notion of uncertainty gets short shrift; so does the notion of arriving at a diagnosis in stages. Much of that problem can be traced to the heavy hand of managed care and reimbursement practices. I know of instances where psychiatrists were upbraided by insurance monitors for not arriving at a diagnosis of an inpatient admission on day 1 and for not starting an antidepressant on day 1. We never had that indignity in the 1960s and 1970s. Never forget that Gerald Klerman, the administrative architect of DSM-III, was very conscious of insurance pressures on the profession, because the Freudian model had been discredited and nothing was in place as an alternative.

Once the clinical frame of reference is discarded, then the door is opened to bad science such as epidemiologic surveys based on counting symptoms without any reliable indicator of caseness. Likewise, recruitment of patients to antidepressant drug trials is compromised. That in turn opens the door to disease mongering and drug marketing. Even Spitzer has belatedly come around to agree with Wakefield and Horwitz on that point.

To return to the issue of laboratory testing, the hypercritical view in the 1980s was that candidate laboratory markers were held to a standard that did not apply to other diagnostic criteria such as clinical signs and symptoms. I have already commented on the inconsistency of this position. The alternative path would have been to mine the promising biomarkers for the incremental help they can give in the process of diagnostic assessment – leaving aside their importance for prognostic information of high clinical utility, as I discussed earlier. In general medicine, "imperfect" laboratory tests have been shown to have real utility in the diagnostic assessment process when they are used as part of a clinical exercise. For instance, diagnostic imaging procedures with specificity between 68% and 77%, when used as conditional strategies, perform better than clinical diagnosis of acute abdominal pain (Lameris et al 2009). Studies of depression biomarkers similar to this example are needed. Once again, one of the blind spots in the field's evaluation of biomarkers is the weak performance – sensitivity, specificity and stability – of clinical diagnoses of mood disorders.

Does the DST need to be improved? No doubt. But that is no different from the history of other biomarkers like the glucose tolerance test in general medicine. To this day there are debates about whether the 25 gm or 50 gm glucose load GTT is preferable, or whether the fasting blood glucose conveys equivalent information, or whether an insulin tolerance test has superior performance for the diagnosis of diabetes mellitus. In general medicine these normal scientific debates are decided on the basis of evidence rather than metaphysics.

In terms of the predictive value of a switch from unipolar to bipolar disorder of course you mean a switch from melancholia to Kraepelin's manic depressive illness, which of course is quite different in a sense to what passes for bipolar disorder these days. How much do the DST data support Kraepelin's version of the illness do you suppose?
I think they are completely consistent with Kraepelin. I've always thought that. You find abnormalities in bipolar I depression as well as in unipolar melancholic and you find a particularly high frequency in mixed bipolar.

Reference:

Lameris W et al. Imaging strategies for detection of urgent conditions in patients with acute abdominal pain: diagnostic accuracy study. British Medical Journal 2009;339:b2431 doi 10:1136/bmj.b2431