From Neurochemistry to Neuroscience
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You've had a career that has spanned the development of neurochemistry in Britain.
Most of the important names of the first wave are now dead-people like Richter, Blaschko, Feldberg. I wouldn't remotely compare myself with any of them or indeed with some members of the second wave but I suppose I am part of this second wave, I have been fortunate in being in an area of research that has become particularly lively as I have got nearer to retirement. When I started working on 5HT, it was often seen as a poor relation of the catecholamines but over the years the balance has shifted, largely because of the realisation that there were so many different 5HT receptors, with so many potential roles.

How did you come into the field
I wanted to do a degree in biochemistry but the biochemistry course at Leeds, where I lived was four years and the chemistry course was only three and a year at seventeen seemed to be an awfully long time so I did a chemistry degree but remained interested in biochemistry and did my PhD in it. Going into the Biochemistry Dept. and having to do animal surgery was quite a culture shock. There was then no requirement or opportunity to do preliminary training. It was "this is what you do, now get on with it". My PhD was officially on the vasoconstrictor effects of protein breakdown products. It derived from an idea of my supervisor that the hypertension of blackwater fever was due to proteolytic degradation products of haemoglobin. It didn't get very far largely because the degradation products we were working on did not have a reliable vasoconstrictor effect. This was around the time that serotonin had been identified as a vasoconstrictor substance in serum and shown to be 5-hydroxyindole ethylamine.

This was when
In 1948-9 by Rapport, Green and Page. Serotonin, being derived from an amino acid tryptophan, was, in a sense, a protein breakdown product, so there were a few lines on it in the introduction to my thesis. Subsequently, in 1953, 1 came to the Institute of Neurology, for an interview for a research fellowship with Dick Pratt who was a psychiatrist. He showed me the chemical structure of lysergic acid diethylamide and said "this causes hallucinations, how do you think it works?"- I'd never heard of LSD. It was shortly before hallucinogens were publicised by Aldous Huxley's The Doors of Perception on mescaline and long before LSD became a street drug. I said "its structure reminds of this new stuff in the blood called serotonin". Dick said, does serotonin exist in the brain"? and I replied "Not as far as I know". I did not know that a few months before, Twarog and Page had isolated it from brain. I also didn't know that a month or two later Gaddum et al would report that LSD blocked the effect of serotonin on smooth muscle. So these things came together and started me off on **my** interest in serotonin.

Were you offered the job?

I was offered the job on the strength of guessing the link between LSD and 5-HT. At that stage, speculations on the neurochemistry of mental disease tended to be based on analogies with sharply defined inborn errors of metabolism such as phenylketonuria. The idea was that major psychoses were due to the absence of a specific enzyme and hence a gross accumulation of some harmful substance. So I was "looking for the spot" in schizophrenia, the revolutionary technique then being paper chromatography. It was hoped that the substance would appear in chromatograms of schizophrenic urine. I found unusual spots but they turned out to be related to gut bacteria or a dietary peculiarity, like excessive tea drinking. Nevertheless, it was all quite exciting. Looking at the chromatograms fitted in with the romantic image of the scientist peering down the microscope and shouting, "Eureka". I guess I have always tended to get excited about the work I was involved in at any time. Then, because of the experience I gained of paper chromatography of indoles, I was given the opportunity of doing some of the early work on the elevated extracerebral 5-HT metabolism of carcinoid disease. I also became involved in work on amine metabolises in CSF of patients with neurological diseases such as Parkinson's Disease and Huntington's Chorea.

I was then working in the Department of Chemical Pathology under John Cumings, who eventually became the Professor of Chemical Pathology. One day he came into the lab and said "I have put you down for giving a lecture on the biochemistry of depression". I replied "I can't do it, I don't know anything about it" and he said "go away and find out". So I spent the next few weeks reading everything I could find about the biochemistry of depression, which at that time was not very much. I came up with the idea that depression was not a sharply defined metabolic disorder like phenylketonuria, but was due to **an** interaction between individual metabolism and responses to environmental stimuli and that secondary metabolic effects of the illness could exacerbate or stabilise the depressed state once it was established. The main key was overactivity of the hypothalamo-pituitary-adrenal axis in response to stress. The specific idea was that stress activated the HPA axis causing the induction of tryptophan oxygenase, (then called tryptophan pyrrolase) so that tryptophan was diverted away from 5HT synthesis - hence depression. There already was some evidence from Ashcroft and Sharman that depressive csf contained abnormally low concentration of 5HIAA, the 5-HT metabolite.

I thought this was very original when I published it in 1965. But there are very few really original concepts and around that time others were publishing rather similar thoughts. A few years later, Paul Bridges and I reported that a group of depressives showed abnormal diversion of a tryptophan load on the pyrrolase pathway. So we did get some evidence but a paper in the American Journal of Psychiatry disagreed. A problem in those days was that depression had not been as well defined as later and this increased the likelihood of disagreement in the literature.

What were the influences that led you to this - there had been early work by Harris on the Hypothalamo-Pituitary Axis, the HPA, and by Quastel and Richter looking at glucose and things like that.....

There had already been a number of papers on overactivity of the HPA axis in depression though some workers had discounted it as due to hospitalisation or secondary to the psychiatric symptoms and without causal significance.

But its one of those curious issues that has not been solved even 40 years later. The dexamethasone suppression test seemed at one point to settle things but it was a false promise. It didn't in the end clarify things.
I wouldn't put it as strongly as that but agree that what the primary HPA abnormality is remains unclear. Is there a single primary abnormality" There are many ways in which the HPA axis might be disturbed so that an abnormal sensitivity to stressful circumstances occurs. At that time, there were almost two separate communities in depression research - there were the HPA axis people and there were people like George Ashcroft in Edinburgh who suspected a defect in serotonin synthesis and that certainly made sense inasmuch as monoamine oxidase inhibitors, which were antidepressant, increased 5HT and reserpine which had the opposite effect decreased it. I was aware from the work of Knox and his colleagues that one effect of HPA overactivity was that tryptophan was metabolised more rapidly. This seemed to mesh together with the idea of a 5-HT defect in depression.

Then Richard Green came to do a PhD with me and I set him to see whether stress would decrease rat brain 5HT synthesis. During this period we published a fluorometric method for determining 5-HT and 5-FHAA in rat brain regions. We felt somewhat diffident about submitting it as it merely combined things that were already known. In the event, the method became the most cited paper from my lab. and was a standard method for about 20 years though it has now largely been replaced by HPLC. Our experiments on stressed rats were not progressing so we tried to cut the Gordian knot by giving rats cortisol instead and looking at 5HT metabolism. Levels did decrease. But even with our new method we could only measure total regional 5HT and 5HIAA. The ability to repeatedly monitor the bit of 5-HT that was out in the synaptic cleft was far in the future. Also, we didn't consider that increased HPA activity might have numerous effects as well as decreasing brain tryptophan and might hit 5-HT function at many points. But in those days we knew nothing about 5-HT receptors, for instance.

Looking back, it seems to me that most of the time, almost all scientists follow the current fashion. I can remember various stages of the 5HT story. First of all it was exciting to be able to measure 5HIAA, the metabolite, and then 5HT itself, and for years hardly anybody gave much thought to the importance of the availability of tryptophan for brain 5HT synthesis. Even though it was know that tryptophan hydroxylase the rate-limiting enzyme for it was normally not saturated with tryptophan, the whole question of its availability for the enzyme was largely ignored except by Eccieston, Ashcroft and Crawford who published on it in 1965, though we had in 1963 reported increased urinary 5-HIAA in rhesus monkeys on chronic high tryptophan intake but made little of it. For a long time what happened at postsynaptic 5-HT receptors evoked much less interest than the synthesis of the transmitter. Quastel visited the lab and said with great emphasis "the thing is Curzon, what's

happening at the receptor? What's happening at the receptor?" I was simply unable to discuss this question.

He must have been quite old then? Did he do much after he left **Cardiff and went to Canada?**
He was old but mentally very lively. Quastel's major work was in the early stages at Cambridge and Cardiff, where he preceded Richter. He was diverted away from brain chemistry for some years during the war when he was recruited by the Ministry of Agriculture and was largely responsible for the development of soil conditioners.

The tryptophan story seems to come around at regular intervals. I got involved early in my career measuring free and bound plasma tryptophan with a home-made apparatus of your designing for which I gave you no thanks at the time. It only cost a few pence to make and one of the interesting things even now is how frontier research can still be done with very simple bits of apparatus - a great deal of the high powered genes work for instance uses very simple technology. But anyway, there have been various reports of lowering of levels and then there is the tryptophan depletion drinks story. What does it all mean.
Very early on we did some work on plasma tryptophan in depression and found that it was low but the results were what I call significant but not significant. It was statistically significant but mean values were not so low that one could imagine it being a major causal influence in depression. Nevertheless, over the years the great majority of people who have reported on this have found statistically significantly lowered values.

Is this because they would not have reported it if they hadn't?
That's an argument that can be made against any positive finding. Initially there were some mixed findings and this kind of equivocal stage is often followed by a fizzling out of the whole story. But this hasn't happened and the balance of papers strongly indicates low levels, Is it due to increased HPA activity or to the fact that depressives tend to have poor appetites and therefore take in less tryptophan? Perhaps a combination of these factors.

An important recent paper by Holsboer et al is relevant to the HPA/tryptophan story. They used a pepped up version of the dexamethasone test where it is given followed by CRF so that the increases in cortisol are magnified. Very high increases occurred in depression and first degree relatives of depressed subjects who were psychiatrically normal but with a strong familial component of affective illness had increases mid-way between the depressed and control groups. This might suggest that a tendency to high HPA activity does not confer depression per se but vulnerability to a critical further increase of activity in stressful circumstances and hence vulnerability to depression. Our rat experiments in which chronic corticosterone treatment caused decreased behavioural responsiveness of 5HT receptors could be relevant here.

Another important result as well as that from Holsboer was from Simon Young's lab at McGill where the tryptophan depletion procedure you mention was applied to ordinary normals and normal first-order relatives of depressives. Only the second group showed a lowering of mood, These findings taken together suggest that both that low 5HT function and high HPA activity are causally linked and confer a vulnerability to depression rather than that low 5HT equals depression. For most depressives, their moderately low tryptophan availability may not be causally very important but within the depressive population there may be a subgroup in which basal 5HT function is on the low side of normal so that moderate tryptophan deficits whether due to stress or low food intake could have pathological consequences. There is also the question of whether tryptophan is an antidepressant - In general it doesn't seem to be an effective antidepressant but some patients do apparently respond - perhaps they are the ones with a brain tryptophan deficit.

An interesting but arduous study might be to combine the Holsboer and Young experiments on a single group of subjects.

In terms of the 1950s, who were the key figures?
In the 1950s I was in my twenties and very much on the periphery and knew none of the key figures personally. I remember hearing Blaschko talking about monoamine oxidase in 1949, during my first year as a PhD student, at the First International Biochemical Congress at Cambridge, a meeting attended, as far as I can remember, by something like 200 people. A few years later Dick Pratt managed to get me into a small select meeting on biological psychiatry at the CIBA foundation. I remember thinking that I was the only person there who had never heard of. So when trying to answer your question, all of this has to be borne in mind. Many people who appeared prominent in the 50s did not turn out later to have been influential. Others were. For example, Axelrod, Brodie, Udenfriend et al at NIH, Blaschko, Feldberg, Gaddum, Richter, Vogt in Britain. But a decade is a long time in 20th century science history and many who are now already part of the history of neuroscience - what the Japanese would call "living human treasures" - had hardly got going then.

In the 1950s there seems to have been some feeling among the grandees of the field, Gaddtum and people like that the chemistry of the brain was **not likely to be very important, that chemical neurotransmission might happen in the periphery but not in the brain. Did this debate impinge on you at all?**
In those days I was not all that aware of the neurochemical implications of neurotransmission. In fact, It only gradually sank in to me that brain chemistry had essential differences from the chemistry of other organs. I remember very early on I gave a paper on brain 5-HT metabolism and during the discussion someone said "What about compartmentation?" I'm afraid I hadn't thought about receptors and I hadn't thought about compartmentation. My approach involved the unvoiced assumption that the brain was a kind of soup with active chemicals in it. I don't think the penny really dropped about compartmentation until the histochemical fluorescence method came out and one could actually see that neurotransmitters were in specific tracts. As for the multiplicity of central transmitters I remember in the

early days many of the neurologists here were sceptical about anything other than acetylcholine being a neurotransmitter.

That kind of thinking could still be picked up in the late 1970s.
Yes you are right. Criteria for a substance to be a neurotransmitter which had been defined largely through acetylcholine research had all to be obeyed and the gaps we had in our knowledge of other substances meant that they were referred to at best as a putative neurotransmitters. I certainly used the word "putative" in self-defence until quite late. A personal problem I had was that confidence when talking to Queen Square clinicians only came to me slowly. I began as a chemist - a Northern chemist in the fullest sense of the word in that while certain people at Oxford and Cambridge are rather pejoratively called Northern chemists, I was a Northern chemist who went to a local grammar school and did my degree in the North - at Leeds, my home town. When I came to Queen Square, I was the only post-doc- non-medical person here and surrounded by public school, ancient university products with that characteristically confident way of speaking. This was intensified by the fact that they were clinicians. After all, what the patient wants is the confident statement "you have X disease. I will treat you in the following way". So it took me a long time to stand up intellectually to them. Things have changed a lot over the years but there was an enormous gulf then between clinicians and non-clinicians.

Somewhere in the 1960s, the field of the biochemistry of the mood disorders began to take off. Why? Was it the work of Ashcroft and others?
The really critical stages were the opposite behavioural effects of reserpine which was known to deplete brain transmitters and of monoamine oxidase inhibitors which elevated them.

The reserpine story caused such controversy in the early days. Was depression due to low 5HT or due to low catecholamines" It now seems more likely that depression may be mediated by more than one neurochemical mechanism and that antidepressant drugs mostly increase the availability to receptors of 5HT or noradrenaline (or dopamine). I suspect that 10-20 years from now the standard antidepressants will be drugs acting on specific post-synaptic 5HT and catecholamine receptors instead of by pre-synaptic mechanisms, which is how most of the present ones act.

Most of my interests have centred on 5HT as such rather than specifically on depression and I have gradually shifted from a purely chemical attitude to a more interdisciplinary approach.

What is a purely chemical attitude and what has the change been in your attitude - is it a move towards more systems based thinking?
I eventually decided to try to focus not so much on brain chemistry in isolation but on relationships between neurochemistry and behaviour. I then started to try to look at non-drug induced variations of transmitter metabolism and its correlation with behaviour but only limited progress was possible with the existing technology.

Monitoring techniques like in-vivo voltammetry or microdialysis were not yet available. Also, I knew nothing about animal behaviour in those days. What I have since learnt was largely thought by the people who came to work in my lab.

At that time it was my impression that too many drugs had come along that turned out to be less selective than first appeared and I felt cautious about using drugs as research tools which might turn out later not only to affect 5-HT function but also other things that had never been suspected initially. So I was resistant to novel pharmacological tools until made to realise their value by my collaborators.

At this stage I had a big interest in the effect of feeding on brain 5HT metabolism as brain 5HT synthesis requires tryptophan and as this was an essential amino acid it had to come from food. Charles Marsden had recently been studying tryptamine synthesis in my lab and there had recently been some work in Canada on tryptamine as a possible neuromodulator for 5HT. Colin Dourish then arrived in the lab. from Canada where h**e** had been working on behavioural effects of tryptamine. So I suggested to Colin that he should investigate the effects of injecting 5-HT into the brain with different amounts of tryptamine but he favoured using the new 5-HT_{1A}, agonist 8-OH-DPAT? This went against my reluctance to use new drugs but Colin Dourish and Peter Hutson tried it out on a few rats left over from another experiment. As soon as the rats were given 8-OH-DPAT they started to eat. Colin and Peter said "as we are interested in the effect of feeding on 5HT, why not combine this with the effect of 5-HTergic drugs on feeding?" It was one of those productive intellectual interactions. I had set the problem and they had made a creative jump from it. Peter Hutson who was a first class observer noted that the rats were eating more and in a very short time he and Colin had done a lot of experiments and Colin had produced a draft paper on the effects of $5HT_{1A}$ agonists on feeding. This started us off on effects of drugs acting at specific 5HT receptors on feeding.

In these studies, Guy Kennett found that activation of $5HT_{2c}$ receptors suppressed feeding - we were probably the first group to show a behavioural effect of activating these sites. I then went to a meeting in the USA at which I heard that a group at NIH were producing anxiety in humans by giving them the drug mCPP. As this was the substance we had been using to activate 5-HT_{2c} sites, I came back from the meeting and said "lets see if MCPP has an anxiogenic effect in rats and if this is due to 2C activation". That's how another strand of our 5HT work started.

Did the rats become anxious?
Insofar as one could tell. I tend to be cautious and write "anxiety-like" behaviour. They responded appropriately to established rat anxiety models like the elevated plus maze and the social interaction test. That arm of the work is being developed by Guy Kennett who is now at Smith Kline Beecham and involved in the study of a series of selective $5HT_{2c}$ antagonists as potential anxiolytic drugs. That's been quite pleasing - to have something that began in my lab being developed possible for clinical application. At the moment, it is not entirely clear whether they oppose anxiety via 5-

HT_{2C} or 5-HT_{2B} receptors. However, evidence that activation of 5-HT_{2C} sites suppresses feeding appears to be more conclusive.

Has the 5-HT and feeding story been finally sorted out yet?
Hardly, though we now know quite a lot about relationships between feeding 5-HT and appetite. Because of my early aim of avoiding drug experiments, much of our work started from a study in which Michael Joseph and Peter Knott were involved in which we tried to decrease brain tryptophan and hence 5-HT synthesis by a physiological mechanism i.e. by withdrawing food (and hence dietary supplies of tryptophan) for one day. To our surprise, brain tryptophan didn't decrease - it increased. Similarly, when Dick Wurtman and his colleagues at MIT gave rats a high carbohydrate, zero protein meal, brain tryptophan increased. George Sarna later confirmed this in my lab. These seemingly paradoxical findings are now readily explained. To my mind they imply that adequate supplies of tryptophan for 5-HT synthesis are normally effectively ensured in acute deficiency of dietary tryptophan. Wurtman's emphasis has been different - that is that the effect of feeding on 5-HT synthesis has physiologically important consequences for appetite. In my opinion, this idea is largely based on pharmacological/physiological borderland experiment involving very high carbohydrate or very high protein meals. They could well be relevant in extreme cases. For example, those rats that live in sugar cane plantations. However, almost all of our meals are more complex. Even the so-called carbohydrate snacks which are causally implicated in obesity are usually carbohydrate/fat snacks. However, it is an attractive idea that dietary effects on 5-HT could, in some subjects influence appetite whether in an appropriate or inappropriate direction. In the latter case, the result could be a disorder of appetite. Certainly, our work on 8-OH-DPAT and mCPP indicates that 5-HTergic drugs affect food intake. Indeed, dexfenfluramine, the principal clinically used appetite suppressant can release 5-HT though recent work both in Italy and in m**y** own lab. strongly suggests that a direct action on a 5-HT receptor is more likely to explain its effect on appetite.

You said that your approach was initially chemical but became more integrated. This seems to be the paradigm of the emergence of neuroscience - people working in disparate areas who at some point in the 1980s became neuroscientists.
I guess it was in the 1980s or thereabouts that I started thinking of myself as aneuroscientist though it was my impression that many people got there about ten years before.

Other than the Institute run by Francis Schmidt, I am only aware of neuroscience concept appearing with any regularity at some point in the mid-1980s.
This is a somewhat etymological issue. The first people calling themselves neuroscientists were mostly not so much neurotransmitter centred neurochemists/neuropharmacologists like me but neurophysiologist and neuroanatomists. But these classifications are becoming less important.

Why? Science normally seems to proceed by breaking things tip but for some strange reason in the neurosciences we seem in one sense to be putting things back together again.
Well, subjects as previously taught in universities were based on the convenience for teaching purposes of having for example one set of lecturers text books, degrees etc. for physics and another for chemistry and so on. But the problems nature sets us are not easily solved by means of these tidy academic subjects in isolation.

When were you aware that the field seemed to be developing into a neuroscience field?
My own development in that direction began about 20 years ago soon after I got my first MRC program grant. I decided to try to study behaviour as well as brain chemistry so I asked the MRC for a supplementary grant to buy an activity meter. They went to the trouble of sending a very distinguished behavioural scientist with an FRS to see whether it was Justifiable to give a neurochemist £1,000 for a piece of behavioural equipment. I by no means convinced him. In fact he tore me apart! Not too difficult because I knew almost nothing about behaviour at that time. Finally, he said "What will happen if I say you shouldn't have this £1,000?" I replied that I would continue doing neurochemistry and not try to relate it to behaviour and that this would be a pity. In the end we got the activity meter. I soon realised its limitations but it did get us started on trying to assess behaviour though I didn't get heavily involved until we started to work on serotonergic drugs and feeding. Although much of the stimulus for my research has come from thinking about human psychiatric Illness, most of it has not been on human material. The psychiatry department here was small with few patients and they often tended to be complicated cases who were not good subjects for research. Round about the 1970s there was a report on medical education advising that teaching neurology and psychiatry in London should be on one site. But the Maudsley people didn't want to join with Queen Square and the Queen Square people didn't want to join with the Maudsley. My research would have probably had a larger clinical component if the integration had taken place.

Moving to the organisational framework in which you have worked, what were the societies in which you were involved in the 50s for instance?
A lot of my early papers were in the Biochemical Journal. These were on something I haven't mentioned, the enzyme kinetics of plasma caeruloplasmin, the copper protein deficient in Wilson's disease, which was a big interest of John Cumings the head of the Chem. Path. Dept. of which I was then a member. This was very enjoyable and intellectually stimulating and formed much of any research apprenticeship but it was not neurochemistry. Then I began to do work that was published in journals with "neuro-" or "psycho" - or "pharmaco" in their titles. Quite a lot went to the Journal of Neurochemistry because that was an appropriate place for our work on feeding and brain 5HT synthesis. More recently much of the work on effects of drugs on 5HT function was published in the British and the European Journals of Pharmacology. Some of the early papers (with Richard Green for instance) also went to the British Journal of Pharmacology.

I am probably trying to avoid answering your question because apart from editorial work, my time on the MRC Neuroscience Board and occasionally helping to organise a session at a meeting my involvement with organisational aspects of neuroscience has not been great. I do not look on myself as a good committee man. Different scientists divide their time up in different ways, which is probably a good thing. To misquote the Bible: "In the scientific kingdom there are many mansions". I must say though that I had not appreciated how much effort some other scientists have put into the service of the profession until I became the historian/archivist of the International Society for Neurochemistry (ISN) and started to go through its archives.

Were you involved in the Brain Research Society?
I went to some meetings in the early years when it was a rather small informal society. Nowadays, most meetings that are of interest to me have a big pharmacological component and I also go to most ISN meetings partly because being the historian of the Society I try to organise sessions with a historical component. But I find that more and more papers given at purely neurochemical meetings are outside my area of interest and knowledge, whereas psychopharmacology meetings are becoming of more interest to me.

When did you get interested in the history of neuroscience
It didn't come from an interest in the history of science as such. In fact when I was younger, I was rather scornful about scientists getting interested in the history of their subject as they got older. In my case it started from a more general interest in history during which I became particularly attracted to the approach of the French Annales group of historians who were to apply numerical methods to economic and social history - people like Braudel, Le Roy Ladurie, and Duby. I felt that if there is one area of history to which numerical methods might be applied it was the history of science. I also became interested in numerical applications of the citation index. About twelve years ago I wrote to Brian Ansell, then the secretary of the ISN, putting forward my thoughts about these things. He handed on my letter to Henry McIlwain who was the ISN historian. I was invited to give a historical paper at the next meeting of the society. Eventually, Henry proposed that I should succeed him as the historian.

My work on the history of the subject has shifted over the years. The first historical paper I did was essentially non-quantitative. It was about one particular incident, the identification of the structure of tryptophan by the great Frederick Gowland Hopkins. Then I did an analysis of the history of the development of research on reserpine and chlorpromazine using a quantitative approach based on citations. The time courses of their citations turned out to follow very different patterns. Reserpine had what you might call a normal pattern-after one or two key papers the citation rate increased rapidly and then slowly came down again. But in the case of chlorpromazine, the initial discoveries were followed by many years with very few citations and then suddenly the citations zoom up. This raised questions about the different patterns. The answer probably taken us back to the point I made earlier which was that neurochemists were initially not very interested in receptors even though they were aware of their existence. Thus, reserpine, which acted presynaptically was easily

understandable but a drug which acted on a post-synaptic site didn't spark off much scientific interest until many years later, even though clinically it was extensively used. The next history paper I did was completely quantitative. It was an analysis of the history of neurochemistry as revealed by changing contents of the Journal of Neurochemistry over thirty years. I guess the idea for it came from one of the Annales approaches. What they called "the history of the long duration". That is, the revelation of trends only apparent from
analysis of Iong spans of time.

How do you read the interest in history in the field. It always seems less to me than it should be particularly for psychiatry which lives by its ability to take history.
There certainly have been psychiatrists who were distinguished historians of their subject. For example, Richard Hunter who with Ida MacAiplne, did the study on which Alan Bennett's play "The madness of George III" was based. Hugh Freeman, a recent chief editor of the British Journal of Psychiatry has published important work. But, in general, historical knowledge among psychiatrists seems not very apparent. Recently the Lancet published an - in my opinion - magisterial article on Freud which led to a large correspondence that exhibited powerful preconceptions but little historical knowledge. One might have though that there would have been letters from serious students of the history of psychiatry.

When I came here in 1952 1 knew essentially nothing about psychiatry and was surprised to find that many psychiatrists were largely dismissive of psychoanalysis. This was when educated laymen mostly saw psychoanalysis as having scientific validity. This attitude is now fading away though one still gets involved in dinner table discussions in which people insist that analytical methods are highly successful and also have a kind of higher authority than the methods of biological psychiatry. Ideas take a Iong time to die!

It is a pity that scientists tend to get interested in the history of their subject only as they approach retirement. I would be pleased if a neurochemist who was still in the thick of active research but with an interest in the history of the subject would take on the job of ISN historian from me in a few years. I don't want it just to be a hobby for retired scientists.

What can be done to change that?
Perhaps if there was more of a historical component in the way the subject was taught more on the development of ideas - then more younger scientists would became interested. But I am not too hopeful, one doesn't expect many explorers to be interested in the history of exploration.

The field has grown old enough for people to reinvest your ideas about tryptophan and cortisol and be unaware that this was all there 30 years before, are you aware of this?

Yes, I am though I don't know about it having been all there! I am afraid that once papers and reviews especially don't quote the early literature it becomes buried and more deeply so when early papers are not accessible by electronic methods. Long ago when the literature was much smaller, scientists would often browse in the early journals. I read somewhere about organic chemists browsing through all the back numbers of Leibig's Annalen as part of their education. This kind of thing would be out of the question now.

Nothing that happened before 1966 exists anymore.
That's true, things are reinvested every 15 to 20 years although often they are re-invented in a rather more sophisticated way aren't they? There are two images of progress in science, the linear ideal and the more realistic circular or rather the upwardly helical one.

You've mentioned Charles Marsden, Guy Kennett, Colin Dourish, Richard Green, many who've gone on to make substantial names for themselves, is there anyone else?
I have been very fortunate in the people who came to my lab. I started with a degree in chemistry and most of what I've learned about biological science has been from colleagues who were trained in different subjects. Richard Green, my second PhD student's findings on the idea that HPA activity influenced 5HT metabolism produced some high-profile papers so that the lab became more prominent and other good workers were attracted to it including Peter Hutson, Michael Joseph, Simon Young, Mark Tricklebank as well as those you have mentioned. They are now leading figures and it is gratifying that, on the whole, they have remained in research and in the field of adjacent fields.

One idea I've always had is that psychopharmacology is not the kind of science that proceeds by the hypothec-deductive method that is so beloved of places like Oxford, Cambridge and the Maudsley. It seems to me that the technology leads us. A new drug throws tip observations that theory has to accommodate to rather than the other way around.
Medawar has written a paper on this called "The Scientific Paper is a Fraud" which says that science doesn't proceed in the way we were taught at school - hypothesis, experiment and then deduction. Certainly, in psychopharmacology, a great deal has come from accidental observations. Also, intuition and day dreams play a part - the famous example is Kekule's vision of the snake biting its tail from which he derived the structure of benzene. My own ideas often come when my mind is drifting - for example in the morning while shaving. As for technology leading us. this has been true in the past - the availability of paper chromatography in the late 1940s permitted advances that would otherwise have been impossible, Sanger's determination of the structure of insulin for example. But I wonder whether technology is starting to offer an embarrassment of riches. I remember Krebs saying about 20 years ago that we will one day be able to measure anything in everything so that the problem will be to decide what is most worth measuring. But this does not discount the influence on neuropharmacology in recent years of the development of techniques like HPLC

which have enabled us to monitor transmitter concentrations in the extracellular spaces of the brain.

But to come back to ACh, its a good case in point in that form being the pre-eminent neurotransmitter because we haven't had the methods to detect it the way we have had for the catecholamine or serotonin its withered on the vine, it hasn't found a niche even though clearly many of the drugs we use affect it even more than they do the other neurotransmitters.
Well yes. Merton Sandler has often said the reason there is so much research on catecholamines and 5HT is because they have been more measurable than other transmitters and unlike, for example glutamate, they occur only in neurones and not elsewhere in the brain.

So in a sense we're still fiddling at the margins, we're playing around with the easy problems
I wouldn't quite say that! We are looking at a landscape. Parts of it are obscured by clouds, - our ignorance, our preconceptions, unspoken assumptions. Parts of it are too far away. But there is no reason to assume that the parts we know about are less important than those we don't know about. Nevertheless, if you ask me "will we ever completely understand the brain", then I really have no idea. Is the brain complicated in the way that lets say a one inch to the mile map of the British Isles is complicated? That is, while there Is no great difficult principle involved, its just damned complicated, there are a lot of roads and rivers and hills and footpaths and while any part of it is easily understandable, no one person can take in the whole map. Or is the brain something that we can learn things about but the overall understanding of it is simply beyond the capacity of the human brain? Some philosophers have said that as we are ourselves part of nature, there is no intrinsic reason why our minds should be constructed in such a way that we are capable of understanding all of the concepts on which nature is based. There's a cartoon by Gary Larson, showing dog scientists in their laboratory. One of the dogs is describing a diagram of a doorknob to students. Another is dissecting, a doorknob. A third is looking at a doorknob down a microscope. The caption says "The dog scientists know that if they could only solve the doorknob problem it would benefit dogs all over the world". They are obviously not going to solve the doorknob problem. There may be more subtle doorknob problems that even human minds are simply not up to.

This is not a negative point of view. There is still much that we know or can learn about the brain. For example, that a drug has a particular influence on mood and that this is mediated by a particular neurochemical change. But if I try to think how can a chemical change alter mood, consciousness or awareness then I'm up against a blank wall. Dennett wrote a book called "Consciousness Explained" but others have called it "Consciousness Ignored" or "Consciousness not Explained" and I tend to agree with them.

But isn't the interesting thing how with very selective probes like LSD or Ketamine in very small doses you can radically alter self-awareness.

Small doses but lots of molecules! That a chemical substance could alter mood had a great impact. Many people found it repellent. They would say "do you mean that the brain is just so much chemistry?" I don't find it too difficult that actions of transmitters at receptors can, for example, influence movement by neuromuscular links. How they can affect mood, consciousness or awareness is beyond me.

The next ISN session with a historical component that I hope to organise (with Susan Greenfield) is called "The Neuroscience of Consciousness: Past, Present and Future". A great interest in consciousness has developed in recent years. Philosophers used to say that it can't be defined and that if it can't be defined it can't be studied. But now many of them are trying to study it as are any number of basic scientists from different disciplines, such as Francis Crick and Roger Penrose. There is also the hard data we are learning from PET scanning and so forth about what parts of the brain are activated by different kinds of thinking.

Coming back to the LSD story. When I first came to Queen Square to work with Dick Pratt in 1953, part of our project was for him to give psychiatric patients mescaline or LSD and record their mood changes while I would look for associated changes in urinary indolic and phenolic substances.

There are great problems giving anything like that these days.
Yes, a lot of early work on effects of psychotropic drugs on normal humans was financed by the US military in ethically dubious ways for ethically dubious purposes.

I'm sure that's influenced attitudes since. There's a certain lingering suspicion as to why anyone would want to do this kind of thing. But in contrast almost when you began the idea of taking biochemical approach to these intimate areas of human functioning that would have seemed to many people in the street almost Satanic yet now we're in the era of the designer drug and Prozac is a topic of coffee table conversation and people are quite unfazed by all of this. What's happened?
Perhaps the coffee table conversations you have are at a more knowledgeable level than some of those I have. If one says "a chemical can affect how we feel about ourselves", people still often say "oh but what about the soul?" Or if one speaks about brain mechanisms, they say "do you mean its just a mechanism"? They often don't have the concept or the vocabulary to realise that whatever's going on up there is occurring through a mechanism of some kind or other. They tend to think of mechanisms in terms of clockwork toys from Woolworths. I suffer a great deal from the things that educated non-scientists say about the brain. You must have had this one "can you really learn anything about the human brain from work on animals?" Well not everything but quite a lot!

But the change in culture is actually quite striking isn't it?
Yes I agree that the advent of drugs like Prozac is shifting attitudes. But there is a lot of suspicion about drugs that affect the brain - some of it justified of course, but there is also a tendency to lump all drugs that affect the brain together with cocaine and

heroin. There is a tendency also to see effects of drugs on mood etc as diminishing our self-hood or self esteem which is strange because, after all, the effects of alcohol or a good meal on mood have been known for thousands of years. However, in our society, substances perceived as drugs that affect behaviour and mood are looked on with suspicion though other societies may be more accepting.

Not in the same way.
I suppose it depends on the preconceptions of the particular society. If one believes the Gods have given us the gift of the mescal cactus or the hallucinogenic mushroom through which we can experience a reality that is normally hidden then ones attitude is going to be different but, on the whole, Western religions haven't involved the use of chemical substances. Being unpleasant to yourself in various ways perhaps to attempt to attain union with the divine or punish yourself for your sins but not interventions with chemical substances. Alcohol in particular in the form of wine, is used but not to produce intoxication.

Who have been the important people in the field? Who have been the potential Nobel laureates?
Arvid Carlsson was one, when you consider his involvement in the recognition of the behavioural importance of brain dopamine. It would have been reasonable for him and Hornykiewicz to have got a joint Nobel Prize. Snyder also for his pioneering, work in receptorology. But a problem nowadays with the Nobel Prize is that it is getting more and more difficult to ascribe major findings to individuals. Even Newton said "I have stood on the shoulders of giants". Scientific papers around the turn of the century had one or two authors, three was very rare. Now the number of names on biological science papers is going up all the time. The one author paper is essentially unknown, the two is rare, the average in neurochemistry is somewhere between three and four so its very hard to say who is "the" person anymore. Indeed, not only is the average numbers of authors/paper rising but also the number of laboratories, even countries per paper. I have heard someone say "he got the Nobel Prize and it was a <u>good</u> Nobel Prize" meaning that it was unusual in that one individual was definitely responsible for the important finding. The age of the lone worker looking down the microscope has largely faded away and labs are getting to be more like small factories. Perhaps the big prizes should be awarded to laboratories rather than individuals.

What about Brodie, should he have got one? Did you know him?
I went to meetings that he was present at and we might have said a few words to each other but I wouldn't say I knew him personally. A Nobel would have been completely appropriate for Brodie but there's only a limited number of Nobels and only a fraction of the scientists who might reasonably have got one do get one. Consider the enormous increase in the number of working scientists since the Prizes began.

But its rare that there isn't some pedigree to ideas

Well, it depends what you mean by "pedigree". In the case of Carlsson and Hornykiewicz, there was a well defined idea that dopamine was a transmitter, not merely a noradrenaline precursor and that it was deficient in Parkinson's disease, that its precursor dopa had therapeutic effect and that there was a very satisfactory link up with the classical neuropathology of the disease. These certainly were tremendously influential findings and altered neurologists attitudes. I remember in my early years at Queen Square, a distinguished neurologist saying that pharmacology had little to offer the neurologist. There was a meeting here at which I said "Homykiewicz in Vienna finds that Parkinson's disease is due to a defect in dopamine". A great eminence stood up and said through clenched teeth "if Dr. Curzon had ever seen a Parkinsonian brain, he would know that this disease is nothing to do with chemistry". Indeed, I hadn't seen a Parkinsonian brain and I felt too crushed to say that chemistry has something to do with everything that goes on in the brain. Anyway, years later, Hornykiewicz came to give a lecture at Queen Square and I had the pleasure of using the story when I introduced him.

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