Ulster Medical Society

JOINT MEETING WITH THE ULSTER
OBSTETRICAL & GYNAECOLOGICAL SOCIETY
19 November 2009
'*Hot Topics in Hyperprolactinaemia*'
Dr John S Bevan
Aberdeen University

Dr Noel Heasley:

I think we'll start, ladies and gentlemen. First of all, thank you for coming to this joint meeting of the Ulster Obstetrical & Gynaecological Society and the Ulster Medical Society. For those of you who don't know who I am, my name's Noel Heasley, and I have the great honour to be the president of the Ulster Obstetric Society this year.

This meeting has a track record of very prestigious speakers, and tonight's no exception. Our guest is Dr John Bevan, an endocrinologist. He's a renowned expert in his field, and he has also been a very good friend of Brew Atkinson for many years, so I thought that this would be a very opportune moment to ask Brew if he would introduce John to both the societies and his talk tonight, which is called, "Hot Topics in Endocrinology". Thank you very much, Brew.

Professor Brew Atkinson:

Thanks, Noel, and thanks everybody, on such an awful night, for coming out to support the joint meetings. When Dr John White, who's here, was talking to me about being president of the Ulster Medical Society, he pointed out that this was always one of the highlights of the year, to have a joint meeting, and we have a couple of joint meetings that go on during the year, and it's been, if I can just say, it's been a real pleasure to work with Noel and deciding on tonight, and what was going to happen, and with David Glen, who is secretary, and so that it is a great personal pleasure for me, and it's a great personal pleasure also to welcome John Bevan, and I'll come to that in a moment, but I can't resist telling you that our next meeting of the Ulster Medical Society, and I really do expect Noel to do the same for the O & G Society, our next meeting is in Derry, the Desmond Whyte Memorial Lecture, and that has got a very, another very distinguished speaker on Thursday 3rd December, in the Beech Hill Country House Hotel, and that's Sir John Tooke, who sadly will be a name that is very familiar to a lot of people, because, not for John's own problem, but John stepped in to write a report after the debacle of the MMC, and we're very fortunate, he's coming to talk about post-graduate education of doctors in the 21st century. We'd love a lot of people to go up, and it's very, very well supported by the GPs and by the medical staff in Altnagelvin. If you do make the journey, you'll get dinner and I'd love to see a very good turnout at that meeting, because it's very important, but back to tonight's business. I'm not quite sure how long John and I go back together, but we'd better not get into that tonight, but I think we hit it off from an endocrine point of view, from other points of view, a social point of view, a church point of view, over many years, and we've always enjoyed getting together at the British Endocrines and the American Endocrines, and I've watched John and he is a very organised man, and I'm sure that'll come across in his talk. He's had a very distinguished role in Aberdeen where he's a reader in the university, and a consultant endocrinologist and head of the department there in Aberdeen. He trained in Edinburgh, qualified in Edinburgh, spent six years in Oxford, has been very involved in drug management of hyperprolactinaemia, and many of you will know some of the reviews he's written, very involved with somatostatin analogues, in acromegaly, and very active in the Society for Endocrinology, and one of his interests there is, or I shouldn't say his interests, but he has really set up programmes that visit units and advise units to see what one unit can learn from another unit, and can take endocrinology forward, so he's very, very distinguished, and very distinguished in the Edinburgh Royal College as well, so it's a great pleasure, and we're very grateful to John for coming tonight to address this joint meeting, so I'm going to pass over to John now and I'm sure we're going to have a great talk.

Dr John Bevan:

Well, thank you very much, Brew, for an overly generous introduction. It really is genuinely a great delight to be with you this evening, and to have the honour of being asked to address both of these august societies here in Ulster. I feel back at home already. I've been fed very well before the lecture, which is probably not a good start, so if I do doze off a little, then perhaps someone can come out and give me a little bit of a nudge. It's good to look round the audience and see friends of a long time, David Hadden there, and Patrick Bell, and of course Brew himself. It's good also to see young trainees as well as the more senior members of the medical profession here in Belfast, and I hope that what I will do tonight will, there'll be some little nuggets for each of you at whatever stage of your training you're at, or whatever stage of your clinical career you're at.

As I come to you this evening, I bring greetings from a very similar society in Aberdeen. The Aberdeen Med-Chi Society is an almost identical sort of society to this. It was established actually in the late 1800s, in the late 1700s rather, by medical students who were rather fed up with the standard of teaching that the University of Aberdeen was offering, and they set up a rival society to improve the standard of continuing professional education and development for them. And this is a society which became a post-graduate medical society at much the same sort of time as the Belfast Medical Society also got its early origins in the early 1800s, so it's a great delight to be here, and

coming to lecture an august society, we should deal with a little bit of history. There's a lot of history in these sort of societies, and as we think about hyperprolactinaemia, it's good to realise that the hyperprolactinaemic syndrome was actually first described by good old Dr Hippocrates three or four centuries before the birth of Christ, and he, in one of his acclaimed aphorisms noted that a woman who had milk production, and who was not pregnant, was highly likely to have associated amenorrhoea. And of course, he didn't have the foggiest idea why that should be, and that remained undiscovered for a long period of time, and we have to fast-forward by many centuries until we get the well-known names of Frommel and Chiari, neurosurgeons in the mid-1800s, who again revived the interest in the lady after delivery who is not breastfeeding, yet continues to have amenorrhoea and galactorrhoea.

In fact, we have to go only about 50 years ago to begin to understand some of the endocrine mechanisms in patients with hyperprolactinaemia, and this paper here, published in the early 1950s, again looking at women with amenorrhoea and galactorrhoea, was able to identify in the very early hormone measurements, that this was a state of gonadotrophin down regulation, and oestrogen deficiency. As Brew and I were reminiscing over our dinner earlier this evening, really there has been very rapid advancement in the knowledge of prolactin in the last 30 or so years, starting with some pharmaceutical scientists exploring the medicinal applications of ergot alkaloids in the late 1960s, when a drug called bromocriptine became synthesised. At that time, prolactin was not identified as a hormone in its own right, and this became achieved in the early 1970s. It had been mixed up with growth hormone for a long time, growth hormone also having lactotrophic activity, and then shortly after the hormone was characterised, the first sensitive radioimmunoassays became available, including the one generated by Alan McNealy and colleagues at Bart's Hospital in London. And it was then that the two strands of research could be married together, and the first clinical studies took place of women with amenorrhoea and galactorrhoea, and mostly with microprolactinomas. In the late 1970s, the year that I graduated from medical school, perhaps it was significant that one of my professional interests was first described, the phenomenon of actual shrinkage of prolactinomas, and the opening of possibilities that these tumours could be treated with primary medical therapy, and without the need of the surgeon or the radiotherapist. Later on in the '80s, certainly as far as dopamine agonists are concerned, it became clear that only the true prolactin-secreting pituitary tumours shrank with bromocriptine treatment, and then in the last decade or two, we've had experience in the clinical use of much better tolerated long-acting dopamine agonists, and I'm sure cabergoline will be familiar to many of you in the room this evening.

So what are the hot topics that I'm going to just briefly unpack with you this evening? I'm going to look at a few diagnostic pitfalls, both clinical pitfalls, but also biochemical pitfalls. I'm going to spend quite a lot of my talk looking at some of the current treatment controversies in relation to dopamine agonist therapy, and then since this is a joint meeting with your friends in obstetrics and gynaecology, we'll just, for a brief moment, have a look at some aspects of prolactinoma and pregnancy at the end of the talk.

Before we can get into the diagnostic pitfalls, for those of you that are unfamiliar with some of the areas of prolactinology, then let's just have a look at a slide that I use in my medical student lectures. We've got general practitioners here this evening, so if a general practitioner sees a young woman coming in with amenorrhoea and galactorrhoea, and finds that she's got a raised prolactin level, then these are the sort of things that should go through his or her mind. The first thing to think about is pregnancy; the second thing to think about is a detailed drug history, looking for drugs that might be antagonising or reducing the effectiveness of hypothalamic dopamine, which physiologically inhibits prolactin; primary hypothyroidism can be easily excluded in primary care; and if a general practitioner has done all of that groundwork, it's very helpful to facilitate a referral to either gynaecology or endocrinology, because usually then you're going to be thinking about lesions within the pituitary, or more rarely in the hypothalamus, that need specialist investigation and management.

What are the symptoms of hyperprolactinaemia? —well, as we saw in that 1953 paper, there're symptoms of gonadotrophin down-regulation; so gonadotrophin down-regulation, with low oestrogen levels, producing secondary amenorrhoea, reduced libido and infertility in the female, and similar parallel type symptoms in the man. Galactorrhoea is very much more common in the woman that in the man, although it can happen in males as well, and if patients have a larger pituitary tumour producing prolactin, then they may have these characteristic pressure effects.

So here's a clinical pitfall number one: this is a young woman with headache, that was referred to the neurosurgical service in Aberdeen, and the story from St Elsewhere's was that she had this headache, she had rather irregular periods, and someone had found her prolactin to be twice the upper limit of normal, about 1,000 milliunits per litre. Here is the patient, and here is the scan that had been served up to the neurosurgeons. I don't know if any of you can make the diagnosis in this patient, but fortunately the house surgeon on the neurosurgical ward thought to check her thyroid function test, and this was a patient who in fact had been thought to be taking her thyroxine regularly, but was a rather poorly compliant patient with her thyroxine replacement over several years, and when we put her on thyroxine replacement, the patient has clearly transformed, the bio-

chemistry has transformed, and this thyrotroph hyperplasia within the pituitary disappears just through negative feedback and suppression of the TSH secretion. So hypothyroidism, something I've mentioned already, can be easily excluded in primary care.

The second clinical pitfall in a hyperprolactinaemic patient is to think about the drug history, and you might say to me, well that's not a pitfall if a patient is from the local psychiatric hospital, and is on anti-dopaminergic, anti-psychotic agents, or if there are a patient of the GI service and they're on regular anti-emetics, that's easy, but one has to take a very detailed drug history, and obviously drugs of abuse are not always the sort of thing that pop out immediately when you're taking a history, and nowadays it's important to remember that, I think a recent news item from London said that about 20% of people were buying medications over the internet. Patients are getting substances from all sorts of places at the moment, and one has to take an accurate drug history, looking for alternative remedies, herbal remedies, and as I say, other things that are being bought in over the internet. Drug-induced hyperprolactinaemia is really quite common.

The final pitfall to think about, I have labelled disconnection hyperprolactinaemia, and here's a clinical scenario for you—again a 30-year-old woman with again our familiar symptoms of period disturbance and galactorrhoea, who presents with a prolactin that would be in the typical microprolactinoma range, but when she has a scan, she's got a one to two centimetre swelling in the pituitary, not a microprolactinoma. She gets a trial of cabergoline, long-acting dopamine agonist, and she is highly delighted when she comes back to clinic, because her symptoms have gone, and her prolactin is undetectable. But the question is, what's the diagnosis?, and this sort of patient is often dismayed when you say that, well, the lesion hasn't shrunk on follow-up MRI scan and you need surgery to find out the true diagnosis and to debulk, decompress the pituitary lesion, and this patient turned out to have a non-functioning pituitary tumour that was compressing or preventing the delivery of hypothalamic dopamine to the normal pituitary, thus producing a slight elevation of prolactin. So slight elevations of prolactin that are genuine must be followed with pituitary imaging to see the size of the lesion.

Disconnection hyperprolactinaemia occurs in about 50% of patients with these bigger, non-prolactin-secreting lesions, although the level of prolactin is usually less than 2,000, and this is a fairly old study now from my Oxford days, showing here non-functioning pituitary tumours, half of whom have normal prolactins, half of whom have slightly elevated prolactins, usually less than 2,000, but sometimes disconnection hyperprolactinaemia can be in an overlap region with the lower secreting true prolactinomas. It's important to recognise that the serum prolactin in any patient is likely to fall substantially, whether the lump in the pituitary is an ordinary responsive prolactinoma; whether it's a prolactinoma which is not shrinking, or whether indeed it's another lump, like a non-functioning tumour or a craniopharyngioma that is not actively secreting prolactin. So just because you get a fall in prolactin on dopamine agonist therapy, doesn't necessarily prove that you're dealing with a true prolactinoma. Here's a more recent series looking at disconnection hyperprolactinaemia, this is some data from Oxford, again showing that most of the prolactins are in the less than 2,000 milliunits per litre range, four times the upper limit of normal, and similarly with non-pituitary adenomas, this is their series of craniopharyngiomas, similar levels of disconnection hyperprolactinaemia. Turning briefly to some biochemical pitfalls, so you've got a patient perhaps with menstrual disturbance, you've found that the prolactin is slightly elevated—can you believe the slightly elevated prolactin? Is it really telling you what you think it should be telling you?—and the reason for introducing this topic is to talk a little bit about macroprolactin. Now, macroprolactin, some of you may not have heard of it, it's a normally occurring, quite commonly occurring complex of prolactin and immunoglobulin, that is present in about 1% of the normal population, and if you're a biochemist working in the lab, then about 20% of your hyperprolactinaemia sera will have this high molecular weight aggregate form of prolactin.

Now, it's said that most patients that have this normally-occurring macroprolactin aggregate don't have symptoms of hyperprolactinaemia, but of course amenorrhoea or menstrual disturbance or impotence are very common symptoms, and if this abnormality is in 1% of the population, then occasionally you will have common symptoms and macroprolactin co-existing together. The laboratory in fact can screen for this quite easily by using polyethylene glycol treatment of serum, and then re-analysing the sample, and if there's lots of macroprolactin, it will be drawn down by the PEG, and therefore the subsequent prolactin level will be lower, that's measured. Something that's completely up-to-date in this month's Clinical Endocrinology, this is another study looking at the prevalence of macroprolactinaemia in the normal population. This is a large group of Japanese hospital workers from the low teens up to the early 70s, and in this population, about 4% of them had macroprolactin, without any endocrine disturbance, and 15 of these, had they just had a blood sample checked for prolactin, would have appeared to be hyperprolactinaemic. The key thing is that all 49 of these individuals had normal levels of monomeric prolactin after the PEG treatment of the serum.

Also fairly up-to-date, this is last month's Clinical Endocrinology, which started over this last year a series of clinical questions aiming to produce a series that is helpful to the practising endocrinologist, and we asked Joe McKenna, a good friend of ours in Dublin, to answer the question from his perspective,

should macroprolactin be measured in all hyperprolactinaemic sera, so that we are not tripped up by this. Now, I would recommend those that are interested to read his article, but to cut a long story short, he is a very strong advocate of our laboratories regularly screening all hyperprolactinaemic sera for macroprolactin, and in the latest NEQAS return, the quality control system that our biochemists operate, nearly all of the laboratories in the United Kingdom are indeed doing PEG evaluation of hyperprolactinaemic samples. And Joe, in the paper that he has put together, which is a very readable short article, makes the point that all prolactin assays will recognise this abnormal aggregate, but to differing degrees. So if you took this sample here containing macroprolactin, and you measured it in my assay in Aberdeen, it will give you answer of about 1,000, whereas if you measured it in the Glasgow Royal Infirmary assay, it will give you an answer of 3,000, so it's another reason for, as endocrinologists and gynaecologists, keeping in touch with your own biochemistry laboratory, and speaking to them about difficult situations, and situations where a high prolactin perhaps doesn't quite fit the clinical presentation.

Then here's something really close at home, and I'm grateful to Dr Wallace, I don't know if Dr Wallace is in the audience this evening, for sending me a copy of this nice poster that Brew and others from Belfast here presented at the BES earlier this year, and this was really a follow up of a series of just over 50 patients with macroprolactin, but they've written up in JC & M in 2001, and they've now had the opportunity to follow them down the line. Were there some of these patients who in fact had clinically important pituitary problems?—and the answer is, no there weren't, and none of them had developed clinically relevant symptoms, and in fact the mean prolactin level in this group had apparently fallen a little over the ten years of follow up, and so this group of authors from here in Belfast was able to give us all, in general endocrine practice, the reassurance that an extended review of patients, with macroprolactinaemia, was no longer necessary.

And then finally, in the laboratory set up, think about the hook effect. The hook effect has been described for a number of hormones present in high concentration, in human serum, but this is the situation where you have a big prolactinoma secreting lots of prolactin, and the prolactin saturates the capture antibody in the [omer?] assay, and the importance of this is that you may have a patient with a very big prolactinoma, eminently suitable for medical treatment, who ends up getting surgery because they have a low prolactin result in the assay, which is in the disconnection hyperprolactinaemia range. So another simple important practice point for all of you seeing new pituitary tumour patients, if you've got a patient with a large pituitary tumour and a slightly elevated prolactin, it's always worth getting the laboratory to do a serum dilution, just to make sure that this is a true level of prolactin that they've reported to you.

Now, I must say, I've been looking for the hook effect for a long time in my own centre, and have never seen a case in 20 years. This is one that was presented from one of the London hospitals in a BES a couple of years ago, a lady presenting with obviously a large tumour and pressure symptoms. Her pre-op prolactin was 3,500, and the caring doctors felt that this was likely to be disconnection hyperprolactinaemia, and she ended up with a craniotomy. They were then surprised when the post-operative prolactin was over 50,000. They then went back to the pre-op sample, and found that her pre-op prolactin was in fact over a million. So again, speak to your own biochemist and find out whether your assay for prolactin is at all susceptible to the hook effect, because clearly this patient might have been very nicely treated with medical therapy alone.

Moving on then to some treatment controversies in medical management of prolactinomas specifically. And really, over the last 20 or more years, we've perhaps become rather blasé about the very good medical responses of most patients with the commonest form of prolactinoma, the small microprolactinoma, that is seen commonly in gynaecology and endocrinology clinics. So these are small tumours, usually women in the reproductive years of life, and usually with relatively modest prolactin levels, and certainly with the modern dopamine agonist therapy with cabergoline, you would expect that probably nearer 90 than 70% of these patients have restoration of normal prolactin levels, normal fertility, and normal ovulatory cycles with medical therapy alone. Most of these tiny little lesions will shrink, and some of them disappear completely, and we'll return to that in just a moment or two, in terms of withdrawing medical therapy. So those are the commonest type of patients with prolactinoma, the lady with the microprolactinoma. Again, a little bit of history, and it's history, I guess, that's happened in my own lifetime, this is the first-ever prolactinoma patient I ever saw in Edinburgh in the late 1970s. This was an Edinburgh taxi driver who was driving around and a speck of dust blew in the window of his taxi, and he realised that he couldn't see out of one eye, and went to his doctor for help. Look how imaging has come on in the last 20 or 30 years, this is his CT scan at that time, which shows that he had a pituitary mass, with significant suprasellar extension. He was taken in as an emergency to the neurosurgical ward in Edinburgh, and even the neurosurgeons noticed that there was something a little bit odd-looking about this chap, clinically hypo-gonadal, with reduced secondary sexual characteristics. But the main reason for showing you this case is to illustrate the treatment that he had only 30 years ago. So here he was, we knew pre-operatively that he had a definite macroprolactinoma. He ended up having an emergency transfrontal craniotomy, with all of the morbidity associated with that. Predictably, he wasn't cured by his craniotomy. He then

had external radiotherapy. He required bromocriptine, which he tolerated very poorly indeed, but of course it was the only dopamine agonist that was available at that time, and he has ended up with irreversible hypopituitarism. I've no idea whether he's still alive or not, but this illustrates the sort of scenario that patients with very big prolactinomas faced not that long ago within the clinical practice lifetime of many people in this room here; whereas nowadays, with big prolactinomas, we've perhaps also become a little bit blasé about the fact that most of them respond perfectly well to medical treatment alone without the need for surgery or radiotherapy, and the effects are really very fast. Prolactin will tumble within hours of the first tablet being given, the tumour begins to shrink within just a few days or weeks of treatment starting with a dopamine agonist, and as the tumour shrinks, if vision is impaired, then it begins to improve again remarkably quickly, and as the tumour shrinks, also there is decompression of the normal pituitary, and pituitary function may recover, if indeed it's been impaired by the prolactinoma. And the good news, from a clinical point of view, is that the vast majority of these patients show really good responses, and shrink by about half the tumour volume at least, and here's an illustrative case just in that little panel in the corner there, a big tumour to start with, and after two years of primary cabergoline therapy alone, very good tumour shrinkage and prolactin control. So you might think, well, what are the controversies that I'm going to be talking to you about? It sounds as though everything has been fairly well sorted out, but there are three areas that I just want to dip in on, one of which, the safety of dopaminergic therapy, is something that has become very topical and of relevance to us in gynaecology and endocrinology, namely the safety of treatment. So what to do when dopamine agonist therapy fails?—it will be an unusual situation, as I've told you before, but here are some data looking at the efficacy and tolerability of the three main dopamine agonists that we have available to us now in the UK—bromocriptine and then quinagolide and cabergoline that came online in the mid-1990s. If you look at the efficacy data in terms of normalisation of prolactin, normalisation/restoration of gonadal function, you can see that they're all pretty good, but the newer agents, and particularly cabergoline, is much more effective than the prototype drug, bromocriptine. It might surprise you to see these data, and if you ask your patients that you see in clinic, whether they've noticed any side-effects at all under dopamine agonist, then at least 50% of them will report some mild adverse effects. But the key thing, of course, is whether they prevent the patient taking the medication or not. For bromocriptine, there are at least 10% of patients who are just completely unable to take the drug, whereas cabergoline is very much better tolerated, with less than 3% having to stop treatment. In the clinic, when you've got a patient who appears to be failing on dopamine agonist therapy, in practice it's very difficult to tease apart compliance issues often related to poor tolerance of the drug, and true resistance to the dopaminergic agent, and it can be really truly impossible to tease those apart, but in patients who are, we believe, actually taking the drug, primary resistance to cabergoline probably occurs in about 10% of patients, and that figure is certainly higher for those taking the older drug, bromocriptine. Fortunately, when you have a patient whose prolactinoma is under very good control with a dopamine agonist, the emergence of later secondary dopaminergic resistance is a very rare phenomenon indeed. But how do you define dopaminergic resistance?—and the literature doesn't really help us very much in this. It's rather woolly, there are lots of different definitions. Some authors have chosen to look at simple clinical end points, in terms of restoration of gonadal function again. Some have added in a set reduction in prolactin, and in fact very few of the definitions of resistance also incorporate a measure of tumour shrinkage in the definition of dopamine resistance. But I think whatever definition you choose to use, it's vital that you talk about the type of dopamine agonist that you are using, and the dose and the duration of treatment, and I think it's a useful concept to think of resistance thresholds, and these are resistance thresholds that I would suggest for the three main dopamine agonists; in other words, we would expect the vast majority of patients on bromocriptine dose less than 15 mg a day, or a cabergoline dose of less than 3 mg per week, to be fully responsive, and if they're not, and they've received treatment for a decent length of time, then we can, I think, reasonably label these patients as resistant. This is an interesting paper that appeared in JC & M at the end of last year. It's a Japanese series, a decent number of patients, 150 prolactinoma patients, and about a third of them were macroprolactinomas, divided into three groups: 60 of them were *de novo* untreated patients; 64 had proved intolerant to bromocriptine or terguride, which was another dopamine agonist that they had available to them, and a small sub-group had been resistant to really quite decent doses of bromocriptine, and they were all started on cabergoline treatment, the modern long-acting dopamine agonist, and the Japanese workers really increased the dose at a pretty fierce rate, much fiercer probably than you or I have ever undertaken in a prolactinoma patient, but these were mainly patients that were seeking restoration of fertility so the investigators were setting quite a high store in the achievement of complete normo-prolactinaemia, so they increased the dose by half a milligram per week, at two to four weekly intervals. Several interesting outcomes from this study, but I think the most interesting outcome is that prolactin was normalised in every single one of these patients bar one, so the big series, many of whom had macroprolactinomas, and normal prolactin in all but one of them. Also, when you look at the doses of cabergoline that we used, it's surprising that only 14 out of the 150 were reported

as having side-effects, and I think even more surprising that none of the patients dropped out of this study, but perhaps that tells us more about Japanese physicians than the resilience of their patients to do as they're told when they're what we would be used to here.

But what dose of cabergoline was needed in that particular study?—and the left-hand panel here shows us that, in terms of the dose of cabergoline in milligrams per week, the vast majority of these patients were below the resistance threshold that I suggested on the earlier slide—89% were controlled by 3 milligrams or less of cabergoline per week. But look at some of the doses they used here—12 milligrams of cabergoline per week, and that would raise some safety concerns, as we'll discuss in just a moment. On the other side of the slide, you can see that another important practice point here is the intolerant group of patients, and their responses are even better than the previously untreated patients, and that reminds us that, if you have a patient that is intolerant to one dopamine agonist, it's always well worth trying the other two that you've got available to you. Here we've got the resistant group of patients, and they needed just over 5 milligrams of cabergoline per week, so quite a significant dose in comparison to what we are used to using in our standard prolactinoma patients. And in terms of the speed of prolactin normalisation, the untreated and intolerant group are mostly normalised within six months, whereas the resistant group as the dose was built up, taking rather longer to achieve normo-prolactinaemia, an interesting paper, and I'd commend it to you. It would be a good paper for your journal club, if the juniors are into journal clubs here in the local setting. So what are the options then, if you have a patient who's taking a dopamine agonist, and really does appear to have a degree of dopaminergic resistance? Well, I think the Japanese paper shows us that the dose increase often works, and in intolerant patients, a switch to another dopamine agonist is always worth trying. I've written down dosing supervision, and for some patients who perhaps have other additional medical and social and perhaps psychiatric needs, then with once-weekly cabergoline, this is a possibility, but most patients free-range don't take very kindly to having their medication supervised, and perhaps it's not generally applicable, but it might be worth thinking about in some special situations. Fortunately very few patients have tumours that continue to grow and are truly resistant in that sense, to dopamine agonist therapy. For those patients, we have to throw much more aggressive treatment into the situation, and some of them even need forms of chemotherapy for aggressive prolactinomas.

The second controversy in terms of dopamine agonist treatment relates to safety. Just a brief comment first of all, about three situations that may occur in patients with big prolactinomas, who have actually responded very well to dopamine agonist therapy. These are all patients whose tumours have shrunk, but if you have a tumour that is inferiorly invasive, then as that tumour disappears, sometimes a channel for CSF leakage, an ascending infection can open up. If you have a tumour that is adherent to the optic chiasm, then as the tumour successfully shrinks, it may draw the optic chiasm down and cause visual failure as the tumour shrinks into the pituitary fossa, and finally, if you have internal changes within the prolactinoma following medical therapy, particularly cystic changes, this may predispose some of these patients to secondary haemorrhage and pituitary apoplexy, and I think these three phenomena, perhaps you've seen them in your own local practice, but as a generalisation, I think are relatively under-recognised, and once a tumour starts to shrink, we tend to put our feet up and think that's the job done and dusted, but there can be these situations that occur, even after successful treatment.

The big, hot potato at the moment in the prolactin dopamine agonist field is the safety of these drugs, many of which are ergot derivatives, in relation to cardiac valve fibrosis, and whether this is relevant to the tiny doses, relatively, that we use in endocrinology and gynaecology. And many of you may be aware that all of this came about from the neurology literature, looking at Parkinsonian patients treated with pergolide and also cabergoline, and showing that quite a percentage of them have restrictive valvulopathy that develops during treatment. But of course, it will be immediately obvious to this audience that the Parkinsonian population is rather different to the endocrine population. A typical daily dose for a Parkinsonian patient translates to perhaps 20 or 30 times the dose that we use in endocrinology and gynaecology. They may have different susceptibilities, and certainly a patient with Parkinson's disease will build up a cumulative, a large cumulative dose of cabergoline much more quickly than our endocrine patients, although I would say in passing that we still don't know whether the valve toxicity is related to cumulative dose, or whether it's related to drug levels that are actually achieved in patients on higher doses. The valvulopathy effect is a serotonergic 2B receptor agonist activity. Pergolide has in fact been withdrawn by the FDA, and is not, I think, generally used anywhere in the UK, certainly not in an endocrine setting, any more, but of the drugs that we have available to us, cabergoline has most activity at this receptor, followed by bromocriptine, and then quinagolide, of course, is a non-ergot derivative, so you would not expect quinagolide to have any of these effects, if they prove to be relevant, in an endocrine setting.

All of this got quite exciting at the end of last year, when I received this email from a GP in the back of beyond on my patch, right up in Wick, in the north of Scotland, so I suddenly got this email out of the blue, amongst all the hundreds that we get every day, saying this chap's under your care, he's on cabergoline. As you know, Dr Bevan, there are now echocar-

diographic requirements to survey these patients and I don't have access to echo, what are you going to do about it?—and this was a surprise to me, and it was a surprise to me even more, and to us in the endocrine community, when we discovered that all our friends and colleagues in primary care had received this drug alert from the MHRA in relation to cabergoline and bromocriptine, but the MHRA had not thought it sensible to send it to endocrinologists, and to people that were actually prescribing cabergoline, and so a number of potentially embarrassing situations cropped up in those early weeks, but this is quite a concerning wording in this drug safety alert. "Ergot-derived dopamine agonists, risk of fibrotic reaction in chronic endocrine uses." It sounds as though it's been proved, it sounds as though it's definite, and something that we should change our practice urgently about, and certainly those that wrote this warning would have us do quite a lot of things now. They want us to do an echocardiogram before we start anyone on a dopamine agonist, and in patients on cabergoline, they want us to repeat echocardiography at really quite startlingly low intervals, and I don't know what the waiting time for echocardiography is here in Belfast, but it would certainly cause quite a lot of stress in the system in my local centre. I doubt whether there is anyone in any endocrine or gynae setting in the whole of the United Kingdom that is following this to the absolute letter, certainly not until further data become available to reassure us or otherwise, and talking about data, it was quite interesting that, in the same month that that alert came out, this review article appeared in the European Journal of Endocrinology, summarising the evidence that was actually in the published literature at the time. It's a complicated slide, but I'll just briefly extract the relevant bits.

Here we've got eight papers on patients with Parkinson's disease. The cumulative dose is large, up to eight grams, seven or eight grams in some patients, and significantly more valvulopathy in the treated patients with Parkinson's on high-dose cabergoline. Here however, already in the literature, there were six papers from endocrine centres, often controlled studies of patients on endocrine doses of cabergoline for prolactinoma, a much lower cumulative dose, as you would expect from our usual requirements; three of these papers, no significant difference between endocrine patients and controls; two of them non-significant differences, and really only one paper, the paper from Naples, showing that apparently there was significantly more moderate TR [tricuspid regurgitation?] in endocrine patients given cabergoline. This paper is interesting in the sense that the prevalence of valvular abnormalities in their normal controls was very much higher than in any of the other studies, so I still have a personal question mark as to whether that is a true finding. This caused quite a lot of excitement at the end of last year across the Atlantic. The reason for that is that they don't have quinagolide in North America, so their only choices for hyperprolactinaemia are between cabergoline and bromocriptine, and Mark Mollich, in fact, writing a leader in JC & M, commenting on the Japanese article that I shared with you earlier, pulled together some of this and really wrote what I think is a very sensible editorial, and it really summarises pretty much my current practice at present, and I'd be interested to hear how it compares to what you're doing here in Ulster.

So he took the controlled studies of prolactinoma patients treated with low-dose cabergoline, and he reckoned that there was an 11% prevalence of valvular abnormalities in the treated group, compared to 8% of controls, not actually statistically significant, and when he added in the uncontrolled published data, the prevalence of these abnormalities in the endocrine treated group was exactly the same as in the control group. This is what he currently does, and what he currently advocates that people might care to follow. In patients on standard doses of cabergoline, he reassures the patient, because a lot of our patients know about this from their internet trawling and reading packet inserts, etcetera, these days, so the thing has to be discussed, but they can be reassured, I believe, in the light of the evidence that is currently published in the literature. He does an echocardiogram only if the patient expresses concern, or if he's concerned about other possible cardiac features in these patients on low-dose cabergoline. For those on higher-dose cabergoline, he accepts that at the current state of evidence, we do have to do some level of echocardiographic surveillance, but perhaps not at the intensity that the MHRA is recommending we should be doing in the UK. The UK Society for Endocrinology has been active in this area, to help its members, hopefully, and in fact they were well ahead of the game, they had a position statement in 2007, which was updated in February of this year. The ticks here indicate the bits that haven't really changed between the two statements, so I'm sure everyone here will be relieved that dopamine agonists are still recommended as first line for prolactinoma. We should, of course, in line with standard good practice, use the lowest-effective dose, and we should try stopping it every now and then, and we'll say a little bit about that in just a moment. The way in which the two statements differ is that, in the 2007 statement, it was said that screening echocardiograms should be used for patients on higher doses—not very helpful, because higher doses wasn't specified at this particular level of cabergoline. But then in the latest position statement, I think the people at the Society really felt that it was very difficult, from a medico-legal point of view, to go against what had been said, and so the guidelines are pointed out to us as practitioners, and I guess each of us is deciding how we are interpreting these guidelines in our local clinical practice. Everyone is agreed that more data is necessary to try and retain this extremely effective and generally very safe drug in en-

docrine and gynae practice. I would just emphasise, there's still no report at all in the literature of any single patient who's developed clinically significant valvulopathy following treatment with cabergoline. There is another big study about to start in the UK, and it's a study that is largely funded by the Clinical Endocrinology Trust. It's not a controlled study, but we hope to get a lot of patients into it, and we'll be able to do a cross-sectional evaluation of their echocardiographic features in relation to their ergot dopamine agonist exposure, and I know Belfast is one of the centres that is being recruited into this study, so perhaps many of you will be involved in identifying patients, to try and build up the safety data, database and reassurance for cabergoline.

The final area of controversy, just to explore very briefly, is to ask the question, after you've successfully treated a prolactinoma with medical therapy, do you ever cure the patient?—so do they go into remission after long-term treatment, and we'll think a little bit about the small tumours and the larger tumours. Many of you in your practice, I guess, will be in the habit of stopping treatment every two to three years in a patient with a microprolactinoma. If that's what you do, then your practice is well supported by a number of studies in the literature, and here's one of them, just to illustrate the point, a study from Cardiff, showing about 100 patients, mostly treated with decent lengths of therapy with cabergoline, and the patients had their treatment stopped. Within one year, two-thirds of them relapsed, but more importantly, after two years, a third of these patients with small microprolactinomas, either visible or not on MRI scanning, remain in remission, clinically and biochemically. But what about a patient like this? This is a patient of mine, presenting originally with an invasive prolactinoma, and prolactin of 50,000; responds exquisitely well to low-dose cabergoline. Here he is almost ten years out, with virtually no tumour to be seen, and normal prolactin, and taking only one tablet of cabergoline per week. This patient in fact looked up the internet, and said, I think there's some data out there that suggests I could probably stop treatment now—can I stop treatment? He did, and he relapsed, but then that's another story.

What data are in the literature? I think until fairly recently, most of us felt that patients with macroprolactinomas were pretty much on dopamine agonist therapy for the long term, for life, and part of the reason for that is one of these early withdrawal studies. This is quite an ancient study now, 25 years old, a small group of patients treated mainly with the only drug that was available at that time, bromocriptine, and with treatment stopped and followed up with CT scanning, and you can see from the panel there that most of these patients have recurrent hyperprolactinaemia, even though their tumours didn't re-expand in the short term on CT follow up alone, and people generally felt, well this is good evidence that macroprolactinomas need more prolonged treatment. But the redoubtable Dr Colao in Naples also has been active in this area too, and this is a series of data that she published first in the New England Journal in 2005, and then updated the series in Clinical Endocrinology in 2007. And it's important to understand the structure of this study, to appreciate the results properly. A good number of patients, most of whom were in the gynaecological size, the small microprolactinomas, but a reasonable subset who had macroprolactinomas as well. They'd been on cabergoline alone, and they'd had a decent length of treatment, and she then chose, within her whole population of prolactinoma patients, this subset that she felt were eligible for withdrawal from cabergoline, and that's an important point, so these were patients who, having reduced their dose of cabergoline to just one tablet a week, still had a normal prolactin level, had either no tumour on MRI scan, or at least 50% shrinkage, and who were going to be around for a decent period of follow up. So again just think perhaps of some of the patients in your clinics with larger prolactinomas, and ask yourself how many of them are on just one tablet a week with completely normal prolactins, and virtually no tumour on scan—certainly not a large proportion, I would suggest. Any rate, these are the results of the Colao study, and what these show is, the two top bars show the patients with either microprolactinomas or normal scans; long follow up after withdrawal of cabergoline, and about 70% of them remaining in remission, much more favourable than some of the other studies had shown, but remember she was very highly selective on the patients that she withdrew therapy from. Even with the macroprolactinomas, and this was the aspect that surprised many endocrinologists around the world, she found that 40% of the macroprolactinoma cohort remained in remission after long term cabergoline withdrawal.

She then went and tried to look at individual predictors of those patients that went into remission, and she looked particularly at a very low prolactin of less than 160 milliunits per litre, or a very small tumour remnant of less than three millimetres in diameter, and if she had patients that satisfied both those criteria, this is in the whole group, then about 80% of them have long-standing remission. By contrast, if you have patients with neither of those two criteria, and this will include a number of the macroprolactinoma patients, then the long-term remission rate is very low indeed. So these are interesting data, and I think encourage us to at least think about dopamine agonist withdrawal, even in patients with larger prolactinomas. One final paper, and this is a paper that appeared in the last issue of JC & M, and this is, if you like, dopamine agonist withdrawal in the real world. So this is a small single clinic, a small group of patients with prolactinomas, about a quarter of whom had macroprolactinomas, and the investigators here simply looked at the Pituitary Society criteria for trying patients off treatment, namely normalisation of prolactin and any degree of tumour shrinkage after a

reasonable course of cabergoline. And as the graph shows and the estimated figures show, 63%, two-thirds of these patients, in this mixed group, sustained a recurrence after 18 months of cabergoline follow up. As you might predict, but again useful in terms of clinical practice, the larger the tumour remnant, the more likely it is that your patient is going to relapse again, but note that just under half of the macroprolactinomas were still in remission, although the overall follow up is relatively short in this study, again encouraging us to think about the possibility of withdrawing treatment in patients, even those who have just had medical therapy alone for their prolactinoma.

Finally, just for the obstetricians, and also the endocrinologists, to think a little bit about the situation of pregnancy in patients with prolactinomas, and of course, all of this concern is really based on a historical literature, where patients often receive gonadotrophin induction of ovulation, and didn't really have prolonged dopamine agonist therapy before pregnancy occurred, and in some of those patients, particularly with larger prolactinomas, the high oestrogen levels of pregnancy induced tumour enlargement.

What is the current situation in the era of modern dopamine agonist therapy? Microprolactinomas, the risk is extremely low indeed, and in fact I cannot think of a single microprolactinoma patient in my practice that's got into trouble with significant tumour enlargement during pregnancy in almost 20 years. So my usual practice in patients with microprolactinoma is to stop the dopamine agonist as soon as the pregnancy is confirmed, to encourage the patient to let us know if she has an unusual headache, or any concerns about her vision during pregnancy, but I don't see them every month during pregnancy, I don't do routine visual field checks, and I certainly don't measure prolactin, because prolactin rises to almost 10,000 milliunits per litre during a normal pregnancy, even in someone without a prolactinoma, and if these patients can't breastfeed their babies, I don't know who can, and they can certainly be encouraged to go on and breastfeed their children.

Macroprolactinomas, the situation is slightly different, and one cannot be too cavalier, and each patient has to be thought about on an individual basis. Even so, the overall risk is much less than the 50% risk quoted in the older literature. It's probably well below 20%, and in fact if you look at subsets of patients that have had several months of dopamine agonist therapy prior to conception, the risk is probably well under 10%. What do I do?—well, if the tumour has shrunk in the preparation for a future pregnancy, to within the fossa, then I still stop the dopamine agonist.

I would follow these patients up more closely during pregnancy, and I would probably do a couple of formal visual fields just to cover my own back if nothing else, as the pregnancy proceeds. If there's persistent suprasellar tumour at the time the woman falls pregnant or wants to fall pregnant, that is a more difficult situation. In times gone past, these patients have been operated on or even irradiated prior to attempt at conception, but I think the modern approach is to continue the dopamine agonist throughout the pregnancy. Now, do you use bromocriptine, which has the longest track record of safety?—but also has the highest chance of making a woman vomit during pregnancy?—or do you use cabergoline? There's now increasing reassurance that cabergoline too can be used in reasonable doses throughout pregnancy. Back to the redoubtable Dr Colao for my second-last slide, and she has just reported on a European-wide multicentre cabergoline surveillance programme, which now looks at 380 pregnancies exposed to cabergoline, and I'm not an obstetrician or a gynaecologist, but the paper reports that the spontaneous miscarriage rate, the type and the frequency of foetal malformations and maternal health, is really not distinguishable from the general population.

And if you look at the sort of doses of cabergoline that the babies are being exposed to, they're as you would expect for a microprolactinoma population, mostly less than one milligram per week, and if you look at the duration of exposure, then you'll see that most of these patients are withdrawn within four to six to eight weeks of pregnancy being initiated, although of course cabergoline is a very long-acting drug, and will persist for many weeks after it has been withdrawn, and even in this study here, 14% of the patients were treated really for a large proportion of the pregnancy, again without any adverse impact on the overall results. So, over dinner these evening, Brew and I were just musing to say that, here we are in 2009, and what an amazing amount of progress has occurred in the prolactin and medical treatment field over the last 30 years. I hope I've illustrated to you this evening that there's still plenty of work for the younger generation to do, to confirm the safety of medical therapy and to look at the subsets of patients for whom medical therapy alone is truly curative for patients with prolactinoma. So I'm going to hand over now to the next generation, this is my young grandson wearing a bib that I brought home from the American Endocrine Society, which I think is rather good, and I hope he might take up the baton for the future. Thank you very much indeed.

Dr Heasley:

Thank you very much, John. I'm sure you wouldn't mind perhaps fielding a few question?

Dr Bevan:

Not at all.

Dr Heasley:

Could I maybe begin by asking, I had a patient recently who, the GP had inadvertently been prescribing ten times the dose of cabergoline that she was

meant to be on. Is there any concern, this had probably been over maybe a year, a year-and-a-half, she felt dreadful, absolutely dreadful. Is there any concern regarding her cardiac valves, in that time?

Dr Bevan:

I wouldn't have thought so. I too have had patients inadvertently who have mistakenly taken the tablet on a daily basis for several weeks, and have also often had the usual GI side-effects that you will get from a dopamine agonist in that sort of dose. I don't think we have any data to say whether she is at particular risk or not. You say she's had treatment for a year or a year-and-a-half?

Dr Heasley:

She had it for a year, and then we reduced it again whenever we found the mistake.

Dr Bevan:

But even at that sort of dose, she probably had what, half a milligram of cabergoline every day for that period of time?

Dr Heasley:

Yeah, five milligrams a week.

Dr Bevan:

So by Japanese criteria, she was on quite a low dose of cabergoline!—so probably fine, I would say.

Dr Heasley:

Would anyone like to ask some questions?—Robin?

Robin:

Yes, thanks John, an excellent talk, very clear. Could I ask you, in obstetric and gynaecological practice, as time has gone on, clinical signs are of less, seem to be of less and less importance. You mentioned that you undertake visual field to cover yourself. Do you advocate visual fields of clinical examination in these patients at all, or are you laying a situation where technology is what is required here, to assess the severity of the problem?

Dr Bevan:

I feel mortally wounded!—no, no, we still do clinical confrontation when we see our patients in the clinic, but I mean, in other areas of pituitary tumour practice, one is only too aware of the insensitivity of the waggling finger compared to formally plotted visual fields.

So I think in pregnancy, particularly if the pituitary tumour remnant is only just confined to the fossa, there's a small suprasellar extension, I think it probably is good practice to chart formal visual fields, but what would you do, Brew, in that situation?—in a patient who's still got a reasonably chunky remnant, as she falls pregnant?

Professor Atkinson:

Well, I wouldn't be dealing with that particular situation, but I think with every pituitary clinic, we would be measuring corrected visual acuity, I think it's the greatly forgotten thing in pituitary disease, and I think that is very easy to do. It's like having an Ulster Medical Society programme and getting the patient to do that with their specs on, and then we would do the fields of vision by confrontation, and I think if you've got a normal waggling finger, and a normal visual acuity, you're pretty [?], but it certainly should be done.

Dr John Craig:

As a neurologist who still loves clinical signs, we also use a lot of dopamine agonists [not?] from ergot, and we've essentially stopped using the ergot-derived dopamine agonists, because we've got so much choice. You didn't mention pramipexole or [?] or [?]. Do they not work?

Dr Bevan:

Well, I don't know the answer to that, and I don't know why we're not exploring in endocrinology some of these other possibilities, but they've not, I'm not aware of any published, decent published series, of these newer second-generation dopamine agonists in an endocrine setting. Brew?

Professor Atkinson:

We used, the first one John, say the first one again?

Dr Craig:

Pramipexole.

Professor Atkinson:

Yeah, we've used it a couple of times, when our backs have been to the wall although I haven't used it routinely enough to really know what's happening. I think it's a good point.

Dr Bevan:

I mean, I guess some of the concerns are that these are often women in their reproductive years, that you're using these drugs on, and I don't know what the, probably no-one knows the pregnancy safety profile of these drugs. The safety profile for bromocriptine is reasonably good now, by dint of how long it's been around. Cabergoline is sort of reasonable, but it's not on big numbers of patients, but you're not the first person to have asked me that actually, from a neurology perspective, when I've given a talk like this, and I keep meaning to do something about it, but I never have. I'm not aware of any published stuff on it.

Audience member:

Within the different specificity to the serotonin receptor, are you using quinagolide at all?

Dr Bevan:

Well, we haven't swung over to quinagolide wholesale. I mean, some centres in the UK have absolutely stopped using cabergoline, which seems to me to be a rather extreme reaction, given the published data that are out there at the moment. I think we should, before we leap with enthusiasm to quinagolide, we should recognise that the published literature on it is still actually really quite limited. It became available at roughly the same time as cabergoline, and because cabergoline was so long-acting and so superbly tolerated, that it's a relatively understudied drug.

The other slight caution that I would have, and I wouldn't want to overstate it, but there were a number of small series of patients treated with quinagolide who had quite marked psychiatric side-effects with quinagolide, by which I mean psychotic reactions, hypomania, compulsive gambling. And there were a number of actually quite high-profile medico-legal cases in relation to that, so that concerns me a little bit. As I said in the talk, I think we still don't really know whether the drug level that you achieve in serum in a patient on our doses of cabergoline even gets on the dose response curve for this adverse reaction, we don't know that. A lot of our patients are on low-dose cabergoline for a relatively short period of time, some can come off treatment. So that's a rather long-winded answer to saying no, I haven't swung wholesale to it. I think it's a useful drug to have around, and I've certainly seen patients who have been able to tolerate quinagolide, mostly who haven't been able to tolerate bromocriptine. Sometimes it works, cabergoline to quinagolide, so it's worth having in the armamentarium, but I haven't swung over to it wholesale.

The makers of quinagolide, of course you probably have noticed have been writing to all of us, saying don't forget this non-ergot-derived dopamine agonist that's available.

Professor David Hadden:

I have always thought that endocrinologists have been too reticent, that really bromocriptine in particular was a real cure for tumours, and that it should be said so. People say, well, you can't cure cancers, you can't cure them—here is one that can be cured, and has been cured by the endocrinologist, and it should be perhaps more widely known. We're a little bit too reticent. But the problem that still exists, I remember one patient, and perhaps Brew or someone will know what has happened to her, where it was really too effective, because this was a lady with a great big enormous, giant prolactinoma, and when it shrank, which it did, as you say, enormously and very rapidly, she developed CSF rhinorrhoea, she had water dripping down her nose, and the more we treated it, the worse the rhinorrhoea got, so we had to actually stop treating her in order to let the thing get a bit bigger to cork it up again!

Dr Bevan:

That can be a real nightmare when that happens, because the surgeons, of course, want to try and fix this with a permanent seal, but it's a bit like, if you're patching a hole in your yacht, do you put the patch on the outside or the inside?—well actually, you have to get on the inside to seal it up properly, so often these patients who've had very successful treatment with a dopamine agonist end up having a craniotomy to seal it from the inside, at least the few that I've dealt with have ended up that way, and it's not always possible to walk the tightrope and relax on the dose and let it just re-expand a bit so that the cork goes back in the bottle again.

Often times in that situation, you've still got some smaller tracks. It's not so much the CSF coming down, it's obviously the risk of ascending meningitis and infection.

Dr Patrick Bell:

John, have you any advice for us on the indications for measuring prolactin in the first place? I suppose this question may more directed towards primary care, but do you get many instances where you think, my goodness me, I wonder how that thing was measured at all?—might it have been better, etcetera?

Dr Bevan:

Yeah, I mean, I could give you a long list of clear indications for measuring prolactin, but I mean, to develop what you're saying, I think we are looking after a population of folk that are increasingly looking at rather dubious sources of information on the internet, and will turn up in general practice, and maybe people from general practice here would like to comment, saying, I'm just not right, my periods are not as clockwork regular as they used to be, I need a hormonal screen.

And a hormonal screen usually, in our neck of the woods, involved thyroid function tests, maybe a testosterone if there's any vague sniff of PCOS, and a prolactin level. And of course they're the very patients, 1% of those patients, or 2% of those patients, are going to have macroprolactin, and if you're unaware of that, then they can be down the road and on cabergoline before you know where you are.

So you've got to think very carefully about the signature symptoms that have led to the test being requested in the first place.

Professor Atkinson:

That's very interesting, because I've talked often with our endocrine lab, which we get a great service from, and asking them why they really do a menopause profile, which is LH/FSH, oestradiol, and prolactin, and they say that, just the request that they get in, they'd be frightened not to do all of them. We've missed cases of hyperprolactinaemia, and yet actually get some incidental findings of hyperprolactin as a result of offering that service.

Dr Bevan:

Does the lab here automatically do a PEG screen, on any positive test?

Professor Atkinson:

Yes, well the Belfast one does, I don't know about the others. So you can't win really, trying to stop it.

Dr Heasley:

Well John, thank you very much indeed for a wonderful and beautifully illustrated lecture.

There is tea and coffee, I think, being served, so you're very welcome to stay, and thank you all for coming, especially as Brew said, through all the rain and the bad weather, and he gave me a very good idea, just to advertise our next meeting, which I'd forgotten about. Our next meeting of the Ulster Obstetrics Society is 5th February. It'll be in Coleraine, and we have some very good speakers coming, including Professor Lesley Regan, who is a world expert on recurrent miscarriage, and she's agreed to come and speak to us, so we should have a good meeting, so that'll be 5th February.

Professor Atkinson:

Can I just say, not to take over the meeting, but we really need, I say this every meeting, we really need the young people to join the Society. The Society is not guys my age, but all of you guys, and it's just such a thrill to see so many young gynaecologists, obstetricians, endocrinologists, general physicians, but please join the Society. Of course, if you're in the Ulster O & G you should also be in the Ulster Medical Society. Anyone who practises medicine in Northern Ireland should be a member of the Ulster Medical Society, it should be a *sine qua non*, so please don't go without signing your name, you'll get a little bit of a sheet of paper, sign your name, and your email, and we'll join you up and we'll get the [?]. Sorry, back to you.

Dr Heasley:

He really is a good salesman, isn't he? Well, I think that concludes the evening. Thank you all for coming and having such a good turnout, and once again, thank you, John, and I think we should show our appreciation in the usual way.