GENERAL MEDICAL COUNCIL

FITNESS TO PRACTISE PANEL (MISCONDUCT/PERFORMANCE)

On:
Friday, 6 July 2007

Held at:
St James's Buildings
79 Oxford Street
Manchester M1 6FQ

Case of:

GORDON ROBERT BRUCE SKINNER MB ChB 1965 Glasg SR
Registration No: 0726922
(Day Five)

Panel Members:
Mrs S Sturdy (Chairman)
Dr M Elliot
Mr W Payne
Mrs K Whitehill
Mr P Gribble (Legal Assessor)

MR A JENKINS, Counsel, instructed by RadcliffesLeBrasseur, Solicitors, appeared on behalf of the doctor, who was present.

MR T KARK, Counsel, instructed by Eversheds, Solicitors, appeared on behalf of the General Medical Council.

Transcript of the shorthand notes of Transcribe UK Ltd
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FITNESS TO PRACTISE

THE CHAIRMAN: Good morning everyone. This is the Fitness to Practise Panel hearing inquiring into the case against Dr Skinner. There may be some new members of the public so I shall go through the layout of the room again. I am Sandra Sturdy and I am chairing the Panel. On my right and left are Panel members and on my direct right is the Legal Assessor who advises the Panel on matters of law, and sometimes on my left or behind me is the Panel Secretary who does the administrative matters. On the right of the room is Mr Kark, who is counsel for the GMC, and on your left is Mr Jenkins, the legal team for defence for Dr Skinner.

If we can now proceed with the expert witness, Professor Weetman. Mr Jenkins.

ANTHONY WEETMAN, recalled

MR JENKINS: Madam, can I ask for these documents to be distributed? (*To the witness*) It is the *Pollock* paper. The *Stobhill* paper you referred to yesterday, Professor Weetman. (*Same handed*)

THE CHAIRMAN: This will be D6.

Cross-examined by MR JENKINS (cont)

MR JENKINS: This was the paper you suggested was the reputation of the *Skinner* document that we looked at yesterday, Professor Weetman. What I pointed out when cross-examining you yesterday was that the *Skinner* paper was calling for a larger study, more studies, on giving thyroxine (thyroid replacement therapy) to chemically euthyroid patients, or chemically normal patients, and this is the *Stobhill* study which I think is the study that you suggested was the one which refuted what Dr Skinner's paper was suggesting, namely that there were benefits, but let us look at this paper. It was published in the BMJ in October 2001. It is called *Thyroxine treatment in patients with symptoms of hypothyroidism but thyroid function tests within the reference range: randomised double blind placebo controlled crossover trial,* and Pollock is the lead author of the paper. The objective is listed as:

> "To determine whether thyroxine treatment is effective in patients with symptoms of hypothyroidism but with thyroid function tests within the reference range, and to investigate the effect of thyroxine treatment on psychological and physical wellbeing in healthy participants."

The design of the trial is a:

> "Randomised double blind placebo controlled crossover trial."

Setting, in an outpatient clinic in a general hospital.

The participants:

> "25 patients with symptoms of hypothyroidism who had thyroid function tests within the reference range, and 19 controls."

The methods were that that participants were given 100 micrograms of thyroxine or placebo to take once a day for 12 weeks.

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> "Washout period was six weeks. They were then given the other to take once a day for 12 weeks. All participants were assessed physiologically and psychologically at baseline and on completion of each phase."

The Panel will read the main outcome measures. The results are listed as:

> "22 patients and 19 healthy controls completed the study."

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It says:

> "At baseline, patients' scores on 9 out of 15 psychological measures were impaired when compared with controls. Patients showed a significantly greater response to placebo than controls in 3 out of 15 psychological measures."

I do not read the rest but encourage others to read it.

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The conclusions are recorded on that first page as:

> "Thyroxine was no more effective than placebo in improving cognitive function and psychological wellbeing in patients with symptoms of hypothyroidism but thyroid function tests within the reference range. Thyroxine did not improve cognitive function and psychological wellbeing in healthy participants."

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I do not want to spend much time on the detail of the study, but I anticipate you know it well?
A Yes.

Q If there is something that we need to look at as to the detail do point it out to us. We are going to look as well at the rapid responses (or some of them) that were lodged on the BMJ website after this article was published.

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Can I take you to the fourth page? It is page number 894, under the heading "discussion":

> "This is the first randomised double blind placebo controlled trial of thyroxine treatment in patients who have symptoms of hypothyroidism but are biochemically euthyroid.

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> ... Compliance was confirmed in both groups by the rise of free thyroxine and fall in thyroxine stimulating hormone whilst participants were taking thyroxine. The lack of significant increase in free triiodothyronine in patients taking thyroxine might reflect impairment of the peripheral conversion of thyroxine to triiodothyronine. Although this finding requires further investigation, anecdotal evidence suggests

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> that patients could benefit from thyroxine treatment alone."

A Mr Jenkins, I am not sure how you want to proceed but you have invited me to respond.

Q I have indeed. Of course.
A I think that statement, there is one that I would have concern about in that it is well-known that if you treat somebody with a replacement dose of thyroxine, namely 100 micrograms of thyroxine, as in this study, you would not expect a rise in serum free T3

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for the very reasons that we discussed yesterday. It is only if you get to the doses we have seen in some of the patients in the discussion, namely doses of 200/225 micrograms of T4, that you would expect to see a rise in T3.

Q The suggestion I make is that one should have concerns about this paper generally, not just in that regard. That there are flaws in the study.
A As, indeed, you will be aware I have drawn attention to.

Q The suggestion you were making yesterday was that this was the best research on the question of giving thyroxine to patients who had signs and symptoms of hypothyroidism but were chemically within the reference range.
A I think what I said was it is the only study that we have. I did not say it was completely flawless. You then asked me if I felt that further research in the area was indicated. I said that I felt that if funding was available there are other areas that I would put funding into first and I went on to say that if one could show definitively that there was no benefit of treatment in sub-clinical hypothyroidism then that would add weight to this study, because, clearly, if there is no benefit to treatment in patients whose TSH is elevated a little then one would not expect it in those whose TSH is entirely normal.

Q Let ---
A No, please let me finish, Mr Jenkins. I know these are technical matters and you may not have understood my response properly, but I do want to amplify because I was very careful in my response to you yesterday and I did not say that research in this area should be stopped full stop. What I said was that research into sub-clinical hypothyroidism is still needed. That is where I would put funding and resources and effort if I was directing this and that that would help in dissecting this further, if it needs to be dissected.

Q Sub-clinical hypothyroidism is patients who have no signs and symptoms but whose chemistry is abnormal. Outside the reference range.
A No, sub-clinical hypothyroidism is a biochemical definition again, which is an elevated TSH and a normal free T4.

Q But sub-clinical means there are no clinical indications?
A That is the controversy that we discussed yesterday and I do not shy away from.

Q What you have suggested is that there should be further research into patients where the biochemistry is outside the normal range.
A Exactly, as I have drawn attention to in my report.

Q What I am dealing with here is whether there is any reliable research into patients whose chemistry is within the ”normal range” but who have signs and symptoms.
A I have been clear in my report and what I said yesterday. There is only one reliable prospective double blind placebo controlled trial. Like all initial or first or single studies in any area, it cannot be regarded as definitive. I did not say yesterday it was definitive. What I have said is it is the best evidence that we have and the evidence is that there is no benefit.

Q We will come on to what this study may actually show and the criticisms that have been made of it, but you would agree, I am sure, that an absence of evidence for something is not evidence of absence?
A Yes, but that is not the same as saying that one should then proceed as if this

A evidence, such as it is, does not exist and depart from existing guidelines.

Q Let us keep going with the article and, again, if there is a point where you feel you have to make a comment you should do so. I have dealt with the biochemical results passage. I will read the next one:

> "Psychological testing showed that patients differed from the controls at baseline."

B Patients are those with symptoms. Controls are those without symptoms. Yes? (*No verbal response*) Just to make it clear.

> "Cognitively, they scored worse on immediate and delayed verbal recall and had slower motor movements. They also perceived themselves to have poorer general health, more fatigue, increased problems with routine tasks and activities related to work, and higher levels of anxiety and depression. These findings may be
C consistent with a depressive illness, although no formal assessment was performed.

> Controls showed no significant changes in psychological measurements after treatment with either thyroxine or placebo. This suggests that, contrary to widespread belief, thyroxine does not have a non-specific effect on wellbeing. In the participants who received placebo first, patients showed a small but significant
D improvement in general health, physical wellbeing, and anxiety and depression after placebo when compared with baseline. Thyroxine treatment, however, had no greater effect than placebo in this group of patients. This contrasts with previous studies in biochemically hypothyroid patients, where thyroxine treatment was associated with psychological improvement.

> ... The small number of participants in this preliminary study means that, although
E there was no significant difference between placebo and thyroxine in 13 of the 14 well validated psychological tests, the power of the study may not have been sufficient to eliminate definitively a possible biological effect of thyroxine. If this was the case we would have expected to see a trend in favour of thyroxine over placebo in the test results, especially as a recent open intervention study of thyroxine (mean dose 125 micrograms daily), reported self-assessed improvements in energy and poor memory in 80% of 139 participants",

F - that is Dr Skinner's paper.

> "Our study showed no discernable trend.
>
> Conclusion
> We can find no support for the hypothesis that people with symptoms of
G hypothyroidism but thyroid function tests within the reference range benefit from treatment with 100 microgram thyroxine daily. However, our results require confirmation in a larger study. The improvement noted anecdotally and in open studies may be due to the placebo effect shown in our study."

Again, I have only read parts of that but I hope the relevant parts. Can I take you to rapid responses? You will know that the BMJ has an online means by which people can put a
H rapid response, and I have put some of them in the pages that follow. If we look at the first one. It is from, I think, a lady, Pat Davis, and it is dated 19 October, which was the

day before the BMJ was actually published, but can you confirm that the BMJ is actually available before the date of publication?
A Online, yes.

Q She says as follows:

> "Not once in this article is it recognised that thousands of correctly diagnosed Hypothyroid patients throughout the world feel very little benefit from any amount of Thyroxine ... yet when they explain this situation to their GPs or Endocrinologists they are ridiculed and their situation is ignored in the totally rigid belief that both Thyroid Blood tests and Thyroxine are perfect."

She talks about the FDA. Just tell us that. That is the American agency dealing with food and drugs?
A Yes.

Q

> "The FDA are not happy about the quality of Synthroid (thyroxine) which is a grandfathered drug which has never been tested but just assumed to work ..."

What does she mean by a "grandfathered drug"?
A I do not know.

Q

> "Researchers in Spain have proved that it's what's happening at a cellular level that needs evaluation but currently there are no available tests to prove how a patients cells use or respond to Thyroid Hormone, or indeed tests to prove whether the patient is actually able to convert Thyroxine T4 into the T3 their cells need. Reverse T3 testing is not done so false assumptions are made and thousands of patients who are genetically resistant to Thyroid Hormone and thereby exhibit hypothyroid treatment go ignored and untreated."

and she goes on to deal with other matters and in the next paragraph talks about armour desiccated thyroid, saying that:

> "Some patients only respond to either T3 Cytomel or Armour desiccated thyroid ... both of which are denied to UK patients. Thyroid patients in the UK are treated like idiots who do not know just how rotten they feel or just what a poor quality of life they have all because of one influential person's rigid doctrine that Blood tests and Thyroxine are perfect."

She goes on to talk about her husband's condition, and says:

> "... who despite 10 yrs of optimum doses of Thyroxine and so-called perfect blood tests is very far from well or able to enjoy life and being on the end of a helpline. I sure know the subject and the suffering better than the majority of doctors."

Is it right that there are views expressed as to the efficacy of thyroxine in all patients?
A As in all fields of medicine, there are patients who take different views to those expressed by scientific medicine, yes.

Q Is it a concept you have come across before that some patients do not get on with thyroxine and that other forms of thyroid replacement therapy such as Armour Thyroid are more efficacious?
A We are talking now about patients who are biochemically hypothyroid?

Q We are talking about patients who are treated, yes, for symptoms and signs of hypothyroidism.
A I do not patients for symptoms and signs of hypothyroidism, I treat biochemical hypothyroidism and in that situation I certainly have come across patients who feel that they wish to change their medication.

Q Let us go to the next one, and again I am giving you the opportunity, I hope, to comment on these.
A Then if you wish me to, I would be very happy to.

Q Please do.
A Yes. First of all, this is typical of the sort of comments that I have seen.

Q From patients?
A From patients and expressed on websites that patients have run. Let us just deal with
the third paragraph amongst the many things one could deal with. Researchers in Spain. I am not sure exactly which researchers are alluded to, but I would think that this is a group who have worked on thyroid hormone effects in the brain, and those experiments done in animals can be translated into humans with exactly the same predictability that one would expect. She goes on to say:

> "There are no available tests to prove how patients' cells use or respond to thyroid hormone."

Clearly, that is simply wrong, since by measuring the TSH one is measuring the pituitary cells' ability to convert T4 to T3 and then to sense the appropriate level, and I have mentioned the high sensitivity of the pituitary in this regard. So when we are using TSH, we are using the response of a cell, namely a cell making TSH, in its ability to convert T4 to T3 and to make TSH. She goes on to say that reverse T3 testing is not done. Reverse T3 is an inactive form of hormone, it is the way that Thyroid Hormones are metabolised. Of course, reverse T3 testing has been done in the past; it is of no value diagnostically, but she then goes on to muddle this with genetic resistance to thyroid hormone.

Thyroid hormone receptors have been well characterised in the last 15 years, much is known about them. One can show very precisely when there are genetic mutations of the thyroid hormone receptors. In each of those cases there are unequivocal abnormalities in the biochemical tests. Such patients are euthyroid simply because cells are unable to sense thyroid hormone, unable to respond to it, due to this resistance, which is talked about here, signalled back to the pituitary, TSH levels rise, three T4 levels rise, easily detectable biochemically, and the patient is then euthyroid.

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The worst thing one can do to a patient with resistance to thyroid hormone is to treat the patient. To mistake this for thyroid toxicosis, which is what the blood tests tell you, to take the goitre out, and one is then left in a desperate situation. But the research in this is profound. There is no doubt about what thyroid hormone resistance is, there is no doubt about its genetic basis, and there is no doubt about the biochemical consequences of it, and to say that such patients go missed when one does biochemical testing is simply outrageous.

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Q That is your view of one patient's response?
A No, it is not. Can I correct you. It is the scientific view that every thyroidologist and every endocrinologist would hold. It is not my own view.

Q We will look at other doctors in the study in the rapid responses, all right? Let us look at the next one.

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A Hang on a minute. We are talking about scientific medicine here. If one wants to talk about thyroid hormone resistance, one would need to talk to Professor Chatterjee from Cambridge. He is the country's leading expert on thyroid hormone resistance and if you want to know what thyroid hormone resistance really is about and you doubt my word then you can talk to Professor Chatterjee about it and he will confirm what I said.

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Q I am not the one who chooses which witnesses the GMC call. They called you.
A Yes, but you are hinting that my views are not representative.

Q I am saying there is a wide debate and you are at one edge of the debate, one edge of the argument. There are other sides of the argument?
A No.

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Q Which perhaps you are not reflecting accurately?
A No, we are talking specifically here about thyroid hormone resistance and I am challenging you to find another endocrinologist who would depart from my views that thyroid hormone resistance cannot be diagnosed both biochemically and genetically.

Q I am going to move on in the paper, but of course you must have further opportunity to comment on any of the other rapid responses. The next one is from a patient, June Hyslop. She says:

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> "What does this study mean for patients with hypothyroid symptoms who are within 'normal' reference ranges on thyroid function tests? I do not think the picture presented in this research is at all clear. The sample is, as the authors acknowledge, very small and the findings do seem at odds with other published research in this area. The study may therefore ultimately be viewed as of limited value."

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She says:

> "Some information which I would consider useful is not discussed. For example, did either of the patient groups exhibit any ill effects from taking the thyroxine as opposed to the placebo and if not why not? Did the researchers consider that the dose of thyroxine may have

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been too small to make a difference, and what investigations did they make to ascertain what would be the optimal dosage?"

Can I break off? We saw yesterday that the BNF suggest that a dose should be between 100 and 200 micrograms. The dose chosen here for this paper was 100 micrograms, which, would you agree, some would suggest is insufficient?

A I have no idea what dose would be appropriate to test in this situation and therefore it seems a reasonable dose in this trial to choose. It certainly avoided over-treatment.

Q Is it properly testing thyroxine in those patients then if you are not using an appropriate size dose?

A Well, as I have talked extensively yesterday, I am sure if one used a dose of 200 micrograms then one would over treat some of the patients and then they would feel some of the symptoms and benefits that we discussed yesterday.

Q How can you say you have properly done a trial if you have not given the treatment that might be considered appropriate to deal with the symptoms?

A What I am saying is that in the trial they have chosen what would be a standard replacement dose for the average sized person to try. I go right the way back to what I said at the beginning, that I am not saying, nor have I ever said, that this is the definitive study. One could waste time and money doing many more studies on this area, of course, but what I indicated to you yesterday, and I have reiterated this morning, is that if one had such funding, and that is difficult enough to get in the present climate, I personally would devote those resources to sub-clinical hypothyroidism, for the reasons I have stated, which would have an indirect effect on assessing this particular problem.

Q We have explored your view yesterday on whether there may be hypothyroid patients but with normal chemistry. You do not believe there are such patients, so it is entirely understandable why you would not want to explore it?

A But we went into this yesterday too. If you believe that normal biochemistry is the same as being hypothyroid, and, as I pointed out to you yesterday, that is the same someone who is five foot six is short stature. They simply are not. Every laboratory test is based on a reference range and one has to have limits within which one regards the healthy population.

Q Every laboratory test deals with a number of individuals and the person whose TSM you are looking at is not one of those individuals in the reference range, are they?

A No, and that is why one needs to construct a reference range from a sufficiently large group of people in order to determine that that is valid. For instance, one can take the National Health and Nutrition Examination Survey from the United States that was published in 2002, where they examined over 13,000 healthy individuals and arrived at a TSH reference range, which is remarkably the same as that produced in laboratories in smaller sized samples. You will also see the National Academy of Clinical Biochemistry guidelines, which are probably the best in the field, talk about the sample size necessary to generate reference ranges. This is based on constant review and experience in a wide variety of biochemical scenarios.

Q So for any given patient who might come to the doctor and say, "I do not feel well", and they may have a long list of signs and symptoms, the endocrinologist in your

position would be saying, "Compared with 95 per cent of a normal healthy population you are perfectly well, there is nothing wrong with you, you are healthy." Forgive me, let me put to the proposition to you. The patient may then say, "You are comparing me with not everybody else but with a large group of other people. I do not feel well. I have got signs and symptoms." How are you able to say that you are perfectly healthy, because that is the approach you take, is it not?

A Two things there. First of all, you made a mistake in saying that I would say that the patient is perfectly healthy. What I said was that the patient did not have... under those circumstances would not have evidence of hypothyroidism. I would be very concerned in that situation, and to me this is by far the most concerning aspect of these four cases, not the treatment, which I have said very clearly would not have any short-term effect. The biggest concern I have about these four cases is that the patients were not biochemically hypothyroid, had very profound symptoms, and therefore it was highly likely that alternative diagnoses existed, should have been sought, and were not. Sooner or later a patient will have a serious illness and be misdiagnosed as hypothyroidism based on this approach and suffer consequences.

To then go to your other point, I have already made the point several times, but let me reiterate. I am aware of patients who have seen me in the past as children, who have complained of short height. They are complaining about their perception of their height compared to their peer group. When you put them on to the growth charts that you yourself mentioned yesterday and show them that they are within the 99 percentile range, the 95 percentile range, or whatever it is that one cares... whatever point they are, one can then assure them that their height is normal. Those patients may still leave concerned that their height is short. It is the same situation.

Q The patients we are talking about are not short children, they are adults who are able to say, "I am imprisoned in my life. I felt differently before. Something has changed in my health". So you cannot simply say, "Here is the reference range, you are the same height as everybody else, do not worry about it." It is a false analogy.

A Mr Jenkins, once again you are trying to get me to say yes to something that I was very, very clear about yesterday and I will continue to hammer away at as long as you wish me to. I have never said at any point that such patients are healthy. I have just told you that my major concern is that these patients are not just not healthy, alternative diagnoses are being missed.

Q I am going to read on in the article and you hammer away as much as you like. You have to make the decision how much hammering is required, all right?

> "It would have been interesting [she says] to have had a further group take Armour Thyroid and/or T3 and conduct the same tests and measurements as there is evidence that this improves cognitive function and general wellbeing for people for whom thyroxine does not work. I would also point out that in my experience, thyroxine may help alleviate hypothyroid symptoms for a short period of time and then some kind of resistance, like insulin resistance, kicks in and symptoms return. It is not known whether this has been accounted for in the study."

A Can I stop you there, Mr Jenkins?

Q Please do.
A Because once again we have this whole concept of resistance creeping in. Insulin resistance is mentioned here. Insulin resistance is again a biochemically defined situation. One can tell when a patient is insulin resistant based on either genetic studies or antibody studies or whatever, and in each of those cases in which insulin resistance occurs there is an elevated insulin level, biochemically measured, and one is looking at insulin there which is very high compared to the reference range. It is precisely the same situation for insulin resistance. So here we have a paradox of a patient saying perhaps in thyroid disease we are missing a condition like insulin resistance. But insulin resistance differs not from the situation in thyroid disease. One could not make a diagnosis of insulin resistance without proper biochemical measurements and showing that insulin levels are outside of the reference range.

Q Do not think that I am putting forward the concerns of each of these contributors as correct. There are a number of observations that are made, some of them are mutually inconsistent. I am just putting them forward to see the sort of responses that came to the Pollock paper and as an illustration that there is a wider debate, almost all of whom, where the contributors call for more research.
A If the point that you wish to make is that there is the need for more research in this area, I think we have debated that extensively. I think you are making other points besides, however, and it is those that I am trying to comment on.

Q I understand. Can we go to the bottom two paragraphs:

> "In summary this research appears to raise more questions than it answers and a more extensive study in terms of both participant numbers and treatment options appears warranted."

She then declares her interest, she is a patient who is clinically hypothyroid but whose thyroid function tests are within the 'normal reference range'.

> "I do not know what is normal for me, however, as my thyroid function was never tested when I was well. I have had tremendous difficulty getting what I consider to be appropriate treatment for my condition on the NHS. I am however currently functioning very well on a combination of armour thyroid and T3, NHS homeopathy and a wheat free diet."

What do you know about armour thyroid? Have you ever prescribed it?
A Yes.

Q You have?
A Yes.

Q In this country?
A Yes.

Q To what range of patients?
A To patients with biochemically diagnosed hypothyroidism who have been on

similar websites, have been inculcated with some of the beliefs of the type of patient that you are reading out and who are not persuaded that synthetic Thyroxine is satisfactory. As I said to you yesterday, when faced with a patient who will not take the best available treatment and hypothyroidism biochemically confirmed, one is in the difficult position. Any thyroid hormone in that situation is better than none and I would be prepared to prescribe armour thyroid in that setting. However, I would always counsel a patient on the risks of such treatment, I would monitor the patient frequently and in post menopausal women I would perform bone mineral density estimates.

Q Let us look at the next, from an American doctor. I take him to be an American doctor. "It's the Thyroxine, Stupid!" is the title of his response:

> "Dear Sirs,
>
> Excuse the somewhat insulting title but it is hard to believe that rational well trained doctors are so endocrinologically blind as to still be using Thyroxine only in their hypothyroid patients. Almost all of these patients have problems with T4 to T3 conversion and many other have refractory T3 binding sites. Clinical experience overwhelmingly demonstrates immediate response to either Armour Thyroid or Thyrolar (mixed T4/T3) in the majority of these patients. STOP"

- he writes in capitals –

> "STOP treating the Lab values and start treating the patient!"

I take it you disagree with the approach that he suggests?
A Yes, simply because he is an MD. We do not know what his speciality is and we do not know how current he is in his practice. I have mentioned already but I will mention again that we completely understand now what T3 receptors are – that is what he means by binding sites. They are defined at a molecular level, genetic defects have been identified and there can be absolutely no doubt that there is any refractory binding sites in patients such as these because refractory binding sites or abnormal receptors are always signalled by abnormalities in the biochemistry.

Problems with T4 to T3 conversion again we have covered. We have talked about the physiology of this. There is no evidence that there is any impairment in conversion. Were there, one would see absolutely classic changes in the biochemistry again.

For instance, when one takes a drug called amiodorone it interferes with peripheral conversion of T4 to T3. This produces a very distinct, reliable and reproducible biochemical pattern. Furthermore, we know from the eleven studies which I cited yesterday where there have been combinations of T4 and T3 tested against T4 alone, that there is no benefit from adding T3 in, which would be the implication of this statement.

Furthermore, the conclusion of that last meta-analysis was very clear in stating that further studies in this area simply were not warranted because we have already got enough evidence.

Again, these are two statements which are simply refutable.

Q I am not going to read much more of these responses.
A Good.

Q I will be asking the Panel to read them in due course. The one I am going to deal with is the last one.

MR KARK: I am sorry, before Mr Jenkins goes on, can I just ask what the purpose of this exercise actually is? We are far removed from the four patients with whom this case is meant to be concerned and at the moment we are simply reading, effectively, letters from either patients or doctors about whom we do not know the qualifications, about their random views on this topic and I just wonder where this is actually going or getting the Panel in relation to the charges they have to consider.

MR JENKINS: Yes, of course. What the Panel have to decide in relation to the four specific patients whose details they are considering, are whether Dr Skinner's approach and prescribing particularly was inappropriate, unnecessary, irresponsible, not in the best interests of the patient or whether it placed the patient at risk of harm. Those are the general topics that you have to consider.

In order to determine for any given patient whether the prescribing was appropriate or inappropriate or placed them at risk of harm, you need to know, plainly, details about that specific patient. You have got them and we have discussed them, but you do need to know whether it is appropriate and in what circumstances it might be appropriate to prescribe the drugs that Dr Skinner was prescribing.

We have to look at the wider debate. We have to look at what people such as Professor Weetman have to say and we need to look at what others have to say. It may be that the patient's voice is an important voice in all of this. What we have heard from Professor Weetman is that what he treats is an abnormal chemical result. We know that there are scores of patients who feel that all that the doctors are treating is their blood result, they are not treating the patient. That is the result we need to have and that I am trying to have through this Professor. That is why I raise the questions that I do.

What has been said about this particular article is, it is the best evidence that we have that it is inappropriate, that there is in benefit in treating patients who have symptoms and signs consistent with hypothyroidism but who have normal chemistry. I am exploring whether there are valid criticisms to be made with that paper. I have read some of the rapid responses; I am going to come to others. What I have suggested is that I was going to deal with one more, which is the last one on the last three pages of this bundle, which is a critical appraisal by a Sheffield GP and a number of vocational trainees – junior doctors who were undergoing their vocational training in looking at how to critically appraise a paper and they have a number of criticisms. That is the one I want to deal with.

That is my response to Mr Kark's question. What is the relevance of this? It is the debate about whether it is appropriate to treat with thyroid replacement therapy patients who have signs and symptoms. Professor Weetman takes one view but there are many others and for you to determine whether it could be appropriate or irresponsible for Dr Skinner to have treated the four patients in the way that he did you need to know the full picture, or at least a fuller picture than you have had so far.

That is my response, but you may be invited to rule on it.

THE CHAIRMAN: Mr Kark?

MR KARK: First of all the paper, the research, is quite different to the responses to it by way of letter on a website. It is right that we have heard that this research is the best that we have, imperfect as it is. That is not to say that everything on the website is part of the research. It is not. These are simply the responses.

Secondly, we know nothing about these patients at all. We do not have their medical records, we do not know what they were treated with. We do not know what their TSH values were at the beginning of the treatment. We know absolutely nothing about them.

Thirdly Mr Jenkins has, as we understand it, an expert and has no doubt been through this report and if he wants to put specific criticism of the report to Professor Weetman, he is no doubt in a good position to do so, but I do ask again whether this is an exercise that has any value at all given the problems that I have just indicated.

MR JENKINS: My response is that medicine must require patients' involvement and if there were no patients there would be no doctors.

THE CHAIRMAN: Mr Jenkins, I wonder if I could just make a comment?

MR JENKINS: Please.

THE CHAIRMAN: I feel myself I would like to discuss with the Legal Adviser but to my mind online comments about research papers are testimonials rather than straight evidence in this case, so I would just like to confer and I will get back to you.

MR JENKINS: Would you permit me to respond to that? They are not testimonials about Dr Skinner, although certainly one of the patients says they feel much better having met Dr Skinner and taking treatment from him.

What I would like to do is deal with the last three pages which, as I say – perhaps you would like to look at the first paragraph or two and consider whether it is appropriate for me to deal with that with Professor Weetman.

What I was in the process of saying before Mr Kark stood up – and I make no criticism that he did – was that I was not going to read the others from patients and doctors save for the last one, but that I did not want to deprive Professor Weetman of the opportunity to make any comment that he might feel appropriate and I wanted to ensure that he had that opportunity without me going through and reading every letter.

I am sorry to interrupt you.

MR KARK: May I just make a point procedurally, which I am sure the Legal Assessor is going to make? You should not receive any advice that is not made public and so I think, with respect, that the idea of one member of the Panel conferring with the Legal Assessor is probably inappropriate and we ought to hear the Legal Assessor's advice publicly.

THE CHAIRMAN: Thank you for that.

THE LEGAL ASSESSOR: In fact I was just about to say, I have already said at the beginning of this hearing this is not a debate. This is a fitness to practise hearing of an allegation made against Dr Skinner and the allegation is made upon the paragraphs of the allegation which you have before you.

You decide that allegation upon the evidence that is put before you. There are specific rules of evidence. In this case you have heard from the various patients who form the allegations. You are hearing from an expert who is entitled to give evidence opinion because of his expertise. In the course of his evidence that expert is being quite correctly cross-examined about various papers but one must remember, although he can be cross-examined about the paper, once one starts putting to him as assertions of fact responses to a particular paper made by people who are themselves giving opinions although with no indication of their degree of expertise, it may well be, although you have a wide range as to the evidence that you hear, that you may think that those opinions that are being put in relation – because it is one stage further, in relation to a paper – to an expert become increasingly valueless.

What is relevant here, you may think, is not so much the paper and the responses to it; it is the evidence that you hear from the witness table and the responses particularly from the witness at the moment.

MR JENKINS: Can I deal with that? What we have been told is that the best evidence is in this paper. I am trying to explore whether it is paper upon which one can place a great deal of reliance and it seems to me that where there have been criticisms of the paper one should look at those. I am not placing the criticisms as factually correct. I have taken care to suggest that there may be contradictions between the criticisms, but in order to examine Professor Weetman's assertion that this is a paper that one can place reliance on, one really has to look at the criticisms of it.

I agree entirely with what your Legal Assessor has suggested, that the further removed one gets from the paper or the research the less value one can place on opinions, but these are opinions on this very paper. This is the best evidence that is being placed before you on the question of whether it could ever be appropriate to treat patients with hypothyroid symptoms and signs with thyroid replacement therapy.

I agree this case is not a debate but it involves question of when might it be appropriate to treat patients. You are being invited to say, by Mr Kark and those he represents, that you can be sure that it was inappropriate to treat patients A to D as Dr Skinner did.

You have to look at in what circumstances might it have been appropriate to treat them. You have to look at the evidence that is being placed before you, by Mr Kark's own witness, as evidence to say it would never inappropriate to treat them. All I am inviting you to do is to listen to Professor Weetman's responses and to the responses and the criticisms of the paper.

What I have done, and I hope I have been scrupulously fair to do so, is to ensure that Professor Weetman has every opportunity to come back on each of these. As I say, the

last one I want to look at is the VTS critical appraisal, where some junior doctors went through this paper with a more senior doctor just to see what flaws there might be. It was a training exercise for them so that they would hone their critical faculties, but I say it is a useful exercise for you to follow to see what they were doing, but, plainly, you will want to consider the advice of your learned Legal Assessor.

THE LEGAL ASSESSOR: Let me just repeat again, as Mr Jenkins as said, these are opinions being expressed about a paper. The only persons entitled to express opinions in these hearings, and that is by specific permission, are experts. There does not appear to be any expertise attached to these opinions. Should valid criticism wish to be made of this particular paper it is open to the defence to call an expert to critically evaluate that paper, but it may be, as I say, of no value or little value, it is a matter for you, to hear from a number of people who say, "I did not like that paper when I read it."

THE CHAIRMAN: Mr Kark.

MR KARK: Can I make a suggestion that might help? As the Legal Assessor has said, it is the expert witness's evidence that matters, and I am sure Mr Jenkins would agree with that, and I think he, perhaps, made a slip of the tongue when he referred to these letters as the "best evidence". It is not evidence.

MR JENKINS: The paper is the best evidence.

MR KARK: Thank you. I have no objection to Mr Jenkins putting what he posits as the flaws in this paper, and if he gleans those flaws from various documents here that he has read, obviously, I could have no objection to him doing that. It is important, in my respectful submission, you do not regard these letters as evidence. They are not evidence of anything. If Mr Jenkins says it would help you to follow the questions that he puts to have, for instance, the last letter before you for the moment, and that will help to you follow what is being put, then I do not think I would object to that, with the caveat that you must not regard it as evidence. It is the answers that Professor Weetman gives in response to the criticisms that matter.

In due course, I would invite you to ignore the responses that you now have before you. You have been invited to read them through at your leisure. I am not sure what the purpose of that is. Again, as I said, it is not evidence and I think Mr Jenkins agrees it is not evidence. So if he wants to use this paper from which to put questions to Professor Weetman at this stage I have no objection to that happening, but, in due course, I will submit that of course you can keep the research itself but the comments on the website should not be left before you.

MR JENKINS: Can I take that up as a sensible way forward for the moment, that we look at the last three pages of this document and I ask some questions of Professor Weetman about the way in which the study was conducted, and we can say for a future day what you should do with the other letters, whether you should read them and then ignore them or not read them at all? That, I think, we can save for a day which is not a Friday, if I can put it that way.

THE CHAIRMAN: Proceed, Mr Jenkins.

MR JENKINS: Thank you. (*To the witness*) It might be helpful to look at the last three pages of this bundle of material, Professor Weetman. Again, as I have said, this is a

group of training GPs looking at the paper in order to critically appraise it, it would seem, as I have suggested, to hone their skills. They say:

> "To begin with some us were unclear about what the actual research question aimed to answer, 'to determine whether high thyroxine treatment in patients with symptoms of hypothyroidism but normal TFTs is effective.'"

Do you agree with the criticism that the objective of the paper, going back to the first page, is not clear? They do not indicate what would be effective.

A I am not sure how far this is going to get us, Mr Jenkins, but for what it is worth as a ex-journal editor and present editor of the *Quarterly Journal of Medicine* I would say that the initial objectives, as stated there in full rather than in part as quoted in this letter, are acceptable and I would accept those as an editor. It goes on to say:

> "... to investigate the effect of thyroxine treatment on psychological and physical wellbeing in healthy participants."

I think that makes the aim of the study clear.

Q If you are looking at dealing with symptoms do you need to measure them? I am looking at the last sentence in the second paragraph of the VTS critical appraisal.

A One is measuring objectively and there are a number of ways that one can do this. Obviously, they have used whatever measures they had available to them, and we discussed yesterday a paper which has evolved a new clinical scoring method which might be used in the future in studies of sub-clinical hypothyroidism.

Q There is no scoring system in this paper for the various signs and symptoms that the patients were complaining of.

A No, but they have gone on to say exactly what it is that they are doing. They are looking at psychological and physical wellbeing in healthy participants.

Q Are we told precisely what they are looking at in judging psychological and physiological wellbeing?

A Part of the danger of this, of course, is that you are approaching it not as a scientist, if I may say, Mr Jenkins. The abstracts are there to help people but one should read the paper in full and, of course, it may be that if I was given sufficient time - and the paper has been put before me and I have not read it for a quite a number of years now, but if I was to go through it I dare say that we would find that if we read it properly in detail there would be amplification of the statement in the abstract. I think to simply say the abstract is not sufficient is more of an editorial comment rather than a comment about the study itself.

Q Professor Weetman, my first question of you this morning was, "Are you very familiar with this article?" Your answer was in the affirmative. Do not let me take you at any disadvantage. If you feel you need time to read it again you should say so and I am sure the Panel would break for a short time.

A Well it depends what questions were going to be asked on it, but perhaps I could amplify what I said to you earlier. You will have seen in my report appendix 6, in which I wrote an editorial. I was invited to write an editorial based on this paper, so when I said to you this morning that I was familiar with the paper, of course I was. When I wrote the editorial in 2002 I was very familiar with it, having been through it very carefully.

It might short-circuit a lot of discussion if I read out bits of this appendix because I myself was critical of the study, as you will see. I said:

> "Are there any problems with the study?

MR KARK: I am sorry, just pause there. I think the Panel actually have the appendix.

MR JENKINS: I do not know quite what the Panel have of Professor Weetman's report and what they do not.

MR KARK: You have a copy of the same ---

MR JENKINS: Of the full report I have, but ---

MR KARK: I think we passed you a ---

MR JENKINS: A redacted copy.

MR KARK: Yes.

THE CHAIRMAN: I believe the Panel have appendix 6. Do you, Mr Jenkins?
MR JENKINS: I certainly do in the original.

THE CHAIRMAN: May I just confirm that we are discussing the initial report on page 1 of D6?

MR JENKINS: Yes.
A If people have this appendix 6 you will see it is a commentary which is in *Clinical Endocrinology*. It is a comment which, as I have said, I was invited to prepare by the editors of the journal to look at the study. It you turn to the second page, that is page 26 of the article, second paragraph down you will see that I say:

> "Are there any problems with the study, or has this notion of biochemical euthyroidism with clinical hypothyroidism finally been laid to rest? The authors do not tell us the power of their study, and indeed recruitment size appears to have been limited by resources. Although a minor effect of thyroxine may therefore have been missed, there was no obvious trend in the results, and we can have confidence that a major effect of thyroid hormone treatment, previously described anecdotally in this setting, has not been found. As only a quarter of patients with sub-clinical hypothyroidism have a symptomatic response to thyroxine",

- and to remind you, that is the situation where the TSH is elevated and the T4 is normal -

> "it could be argued that thyroxine would help fewer than this proportion in a group individuals with normal TSH, but even if it were only, say, 10%, this effect would be important. Such reasoning can be countered by the fact that the patients here were selected on the basis of their symptoms: the great majority, if not all, should therefore have improved if a subtle deficiency of thyroid hormone was responsible. However, complete certainty would require a larger trial to establish whether there is any benefit in a small percentage of patients with the highest 'normal' TSH levels."

A I then go on to say, if you miss the next paragraph:

> "There are still important questions to be answered about thyroxine treatment and Pollock *et al* show the importance of suitably controlled trials. I believe attention should now focus on sub-clinical hypothyroidism, as there are remarkably few trials in this area, to determine whether subgroups of patients can be identified who would definitely benefit from treatment."

B This is what I have meant all along, in saying if one was to do future research this is the group one would look at because messages from that would actually have an implication for this group where it is uncertain. I go on to conclude, if you just go further down the page to save time:

> "Should a beneficial effect be shown",

C - in patients with sub-clinical hypothyroidism -

> "only then would it be worth looking more closely at individuals whose TSH was in the 'high normal' range, in whom",

- for instance -

D

> "there may be subtle alterations in endothelial function of uncertain significance ... For now, though, a normal TSH and free T4 rule out hypothyroidism and thyroid hormone treatment is not indicated for suggestive symptoms in such individuals."

I think that makes both my position clear but also draws, I think, attention to some of defects in the study which I have no doubt the authors of this letter will have alluded to.

E MR JENKINS: It was my misunderstanding. I did not appreciate the Panel had the appendices to your report. I thought they just had the body of the report with the last parts redacted. I do not have a problem with it, but I did not know that the Panel had seen what ---

A If I could, Mr Jenkins, then on page 11 of my report, which the Panel definitely had, you will see at the foot of page 11, when I talk about this study, you will see that I say:

F

> "Only one formal study has been conducted to assess the possible benefit of thyroxine treatment in euthyroid individuals",

- I mention the study -

G

> "In this controlled trial there was no effect of thyroxine. This is not an absolutely definite trial as I have commented on elsewhere, especially as the sample size was modest",

- and I allude to the appendix.

So it is there in the report as well.

Q What do you say about the concerns expressed as to the methodology? I am looking at the fourth paragraph of the VTS critical appraisal.

H

"The symptomatic subjects recruited for the trial were hospital subjects, GP referrals, hospital clinician referrals or by self selection through an article in the local rag",

- as it is described, and we do not know what the details are or what the article said.
A But the whole point of the study, if one reads it carefully, was to take precisely the group of individuals that Dr Skinner is dealing with and see if in them thyroxine treatment would have any benefit, and perhaps you did not understand what I wrote in my editorial when I read it out to you, but the line of arguing would be that if one takes those patients with the most extreme symptoms who volunteer for such a study, the patients such as the very ones we have been discussing, and treats those with thyroxine and finds no benefit then one has tested the most extreme group and, therefore, a more general trial of, let us say, everybody in this room, potentially, asymptomatic, hopefully all with normal TSHs, would be expected to have even less benefit.

Q What is the power of a study? Is that to do with the size of the study and the quality of the methodology?
A That is the number needed to treat and, I have mentioned in my editorial, the power of the study seems to me to be sufficient to exclude a major effect but one would need to estimate what kind of minor effect one would be looking for.

Q This is a tiny study, is it not, when looking at patient numbers?
A No. Again, if you would let me finish, it is a rather technical area and so please bear with me.

Q I am sorry, what is technical? The number of people in the study?
A No, describing what power is. That was the question you asked me so please let me go into it because I think it is relevant.

Q I do not want to shut you up, Professor Weetman. Do not think I do.
A I just got the impression there that you did.

The power of the study is determined by the size of the effect that one wishes to measure, so one sets, initially, the kind of effect that one is looking for. Perhaps it is easiest for the Panel if I describe this in terms of a drug. Let us say we have a drug that we think will cure an infection. It is an infection which is fatal. So if we save one person out of ten we would be very happy to have that drug. We set the power by saying we are looking for an effect to save one person in ten. That is important. Another drug one might test one might be looking for an effect which is on 50 per cent of the population. Another drug one might be looking for an effect on 100 per cent of the population.

What we have seen in the cases that Dr Skinner has described, and, again, it is my experience from seeing many of these patients, are very profound effects. We have heard from some of the patients. So here we are looking at a treatment which is purported by Dr Skinner and also mentioned in his paper as having a very major effect. We have heard that, and I think the Panel will be fully aware of the size of the effect claimed both by the patients and by Dr Skinner and in his paper.

The reason for pressing this issue is that the larger the size of the effect that one is trying to establish the smaller the sample size necessary, and that is only common sense. If one is looking for a tiny effect one needs to look at a very large group of people. If one is looking at a treatment which, as Dr Skinner has said, is almost universal effective, every

patient Dr Skinner seems to treat with thyroxine gets better, from very profound symptoms to very good health quite rapidly. In that situation the power of the study means that you have to study very few individuals.

Now, as they say here, they do not tell us what the power of the study was but my guess would be that they were looking for a significant effect. They have mentioned Dr Skinner's paper and, therefore, they would be aware of the kind of effect claimed for thyroxine. Therefore, although I cannot tell you in exact number, this is a statistical calculation, what I am confident of, as I wrote in my editorial, is that the kind of major effect claimed is very unlikely to exist, based on a study even of this size.

Q Let me suggest that the criticisms of this study are, firstly, that the numbers are tiny, the manner in which the patients for study is selected is questionable and the manner in which the controls are selected for the study is questionable. The objects of the study are not made clear. They are looking at whether treatment is effective and they do not spell out what effective treatment would be. In looking at signs and symptoms they are not measuring them in a way which is appropriate for a study like this. You have suggested in other studies of people who quantify put a numerical value as against various signs and symptoms. Other studies, that is what has been done. It has not been done here.
A I said one could do that if one wished. We are looking at a number of other measures here, which the investigators have chosen, I cannot be blamed for the measures that they chose, but these are very good scales to estimate how well a patient is performing.

In my view, rather than, as you have said, not stating the aims clearly, from an editorial point of view to me, as stated in the abstract, the objectives are clear. They have said what they are going to look at, psychological and physical wellbeing, and they have used appropriate scales and they have known no benefit and I find it - I was about to say difficult, but I find it impossible to believe that patients can have the kind of improvement and symptoms we have heard about and not have improvement in these scales that have been used in this study simultaneously.

Q I have given six criticisms already. The last one is that the size of dose that is given to the patients may well be insufficient to demonstrate any effect.
A I have told that I think this is a safe dose and, obviously, higher doses could have been used but that would bring in exactly what we discussed yesterday. Namely, if you make the patient thyrotoxic you will undoubtedly have a pharmacological effect of the treatment because you are giving an excessive amount.

Q Let me move away from the paper. Do you ever treat clinically hypothyroid patients?
A Do you mean clinically hypothyroid but with normal thyroid function?

Q Yes. I am sorry. It is my fault for not making it clear.
A I have mentioned yesterday and I will say again, in the situation of patients who have been to see Dr Skinner or others practitioners like him who cannot be persuaded to come off thyroxine and, in my experience, those are few, I would continue with thyroxine at a dose to keep the TSH within the reference range. I have not changed my views since yesterday.

Q I am going to deal with the four patients but in very few sentences indeed. Again, you have never seen any of them apart from Patient A on videolink and Patient D across

this room earlier in the week. Yes?
A Yes.

Q Patient A was a lady who showed improvement on a prescription of thyroxine. That is what the documents show, she was feeling better. We can look at the pages if you want to, but I do not think it is necessary.
A I think when I heard the lady talk, the question was put to her, "Did she feel she needed to continue on thyroxine?" and we did not have any evidence at that stage, as at present, that she was certain that it was having continued benefit.

Q No. Forgive me. We can look at the documents if need be, I had hoped it was not necessary. It is the large bundle, tab 1, page 4. Do you have it? 26 February 2003, "Patient's condition improved on small dose of thyroxine." If you look further down the page, 15th April 2003, "Patient's condition same. Definitely felt better on small dose of thyroxine." 27th May 2003, "Patient's condition improved finds feels physically better on increased dose."
A Of course at that time she was thyrotoxic.

Q 30 June, over the page, "A lot better." A reference to her periods and her bowels being regular, more energy. Next entry, 2nd October 2003, patient feels well, periods better, no more constipation, seems likely dosage correct. This was a patient who felt much better and whose symptoms improved or diminished?
A I accept that, but that is not what I said initially. What I said initially was that when the patient was interviewed by videolink, my recall, and you will have to go back to the transcript, my recall is that when she was asked whether it was still doing her good, she was equivocal about it.

Q You cannot say this was a patient who felt supported by a hugely sympathetic doctor and that there may be some placebo effect because of his empathic approach. She did not like him, she did not like his bedside manner at all, she thought he was a horrible man.
A But she had also seen a reflexologist, who told her mistakenly that she had hypothyroidism, and therefore she had a belief that her thyroid was to blame. She received treatment and we have evidence that she is receiving slightly excessive treatment, and I mentioned to you yesterday that a clear reason for the benefit that Dr Skinner seems to achieve in his patients is overdosage of treatment. You may dismiss a placebo response, you may not think that this is something that is at all worthy, or you may rubbish it, but placebo responses clearly exist, which is why double blind control trials have to be done, and indeed Dr Skinner himself believes in the placebo response otherwise he would not have called in his paper for a placebo controlled, properly controlled trial of thyroxine to be done.

Q Patient B felt better. There are no records in Dr Blair's medical records, his medical records are signally deficient in mention of measuring signs or symptoms. He did not monitor her blood pressure or pulse, as Dr Skinner did, but the only evidence we have in relation to patient B once she started treatment with Dr Skinner was that she got better, she felt much better and her symptoms improved.
A Why then did she stop it?

MR KARK: I am sorry, that is simply not accurate, actually. If we look at patient's B's

notes at page 28, just underneath the entry of 23 March.

THE CHAIRMAN: What tab are you under?

MR KARK: Tab 3, page 28. Just under the reference to "thudding heart" on 23 March 2004, 5 August 2004 there is, "Decided to reduce thyroxine." The very last page of that bundle, page 122:

> "I have not noticed any difference since the pills finished, and feel I am well on the road to recovery."

It is not accurate with respect to Mr Jenkins to say ---

MR JENKINS: Can we deal with the period when she was actually on treatment. Dr Skinner's notes the Panel have at tab 4. "Energy, libido, and sore eyes better. Nails better. Hair less dry. Feeling better."

A But Mr Jenkins, one cannot have it both ways. Either a patient is hyperthyroid and requires thyroxine, and if Dr Skinner is right and clinical symptoms are all that are necessary and you give her treatment, then surely if the symptoms get better because the diagnosis is hypothyroidism then when one stops the treatment, the same symptoms would recur. I think this is quite important to understand because it goes back to a point that you made yesterday. You quizzed me about the studies which showed that patients with a normal TSH may over 20 years progress to hypothyroidism, and you indicated that you felt at that stage that some of those patients at the outset, not 20 years later, may have hypothyroidism, but the biology of this disease is it inexorably progresses and therefore when one stops treatment, as indeed it was stopped, then hypothyroidism would get worse, the TSH would be higher, and that is not the case in this patient. She would actually, because of the elapse of time, have been even worse off and when she stopped her treatment, not only would her symptoms have returned, they would have returned with a vengeance because her disease would have got worse.

Q Do you think there is some risk, if the GP is antipathetic to the treatment that Dr Skinner is advancing, do you think there is some risk that the GP may over interpret what the patient may say? By which I mean if the patient has come off treatment, no longer receiving treatment, and the GP thought they should not have been getting it, do you think there is a risk the GP will encourage the patient to respond, "I feel better now I am off it"?

A I cannot comment on that since I do not work in general practice.

Q Do you need to work in general practice to comment on that?

A Again, having been taken to task yesterday for speculating, I think that would be speculating outside of my expertise.

Q Let us turn to the third patient, the third patient C. It is fair to say that the GPs, after Dr Summers, were expressing concern about the prescribing by Dr Skinner for her and those GPs suggest that she was reporting that she was not getting any benefit. Yes?

A If you take me to the pages I am quite happy to look at them.

Q I do not think I need to. I think it is a longer exercise than I need to do, but the suggestion I make is that one has to take care sometimes when you are listening to the

witness, as it were, and considering whether or not they may have an interest. Perhaps it is a comment and you cannot deal with it. Let us turn to Patient D.

A Sorry, before we move off patient C, I think it is important to remind the Panel that when patient C stopped treatment she felt better.

Q That is what her GPs report her as having said.

A If you doubt the veracity of a GP's notes where are we ever going to be?

Q That is why I asked the question that I did, whether you would agree that a GP who is complaining about Dr Skinner has the patient in front of them, there is a risk the GP will encourage the patient to say, or will want to hear the patient say, "Yes, I feel better off the treatment", and that is then what goes down in the notes?

A I simply cannot comment.

Q It is just a comment on human nature, is it not, that I am asking you for?

A I am not prepared to comment on it, but I am prepared to say that much of what we have debated over this week has been based on notes. One expects doctors to keep accurate, contemporaneous notes. I do not expect a qualified medical practitioner to write down something inaccurate. I expect, if the patient said she felt better, he would record it. He would not write it down if the patient did not say that.

Q Well, if you were in the process of making a complaint to the General Medical Council about the treatment that has been given to your patient, you would want some evidence that you could produce to back up the complaint you made. It would be unsurprising if a doctor was keen to write in the notes: "patient feels better"?

A You are implying that doctor is dishonest.

Q Not at all.

MR KARK: That was not put to any of the GPs who gave evidence that they were writing inaccurate or deliberately inaccurate notes.

MR JENKINS: I have not suggested for a moment that it is deliberately inaccurate. I am saying that it is a mere fact of human nature.

THE LEGAL ASSESSOR: I think possibly we are veering away from the prime task.

MR JENKINS: I will return to Patient D, if we may, please. There is no doubt that Patient D's quality of life was improved immeasurably once she was treated by Dr Skinner.

A We have eloquent testimony from Dr Stewart too that she had severe personal difficulties at the time; it has improved since she had a new partner. We also have unequivocal evidence that she was thyrotoxic on treatment. I have described the benefits, and I would put those in inverted commas, the potential benefits of taking excessive doses of thyroxine, and we heard directly from the patient herself that as she has reduced the dose from an excessive amount to what would be a regular replacement amount of 100 micrograms a day she has started to feel worse again. So I think we have two alternative explanations for this patient's benefit. Of course there would be others, so again I will remind you this is speculation. But I would guess based on the patient's response to treatment that she described to us that the benefit was due to the fact she was

being treated with excessive amounts of thyroid hormone, we have strong biochemical evidence of that, and also that her circumstances improved simultaneously.

Q And is that an example, Professor Weetman, of you not wanting to listen to what the patient has to say and examining her critically? Patient D was eloquent herself as to how her life had changed dramatically. You do not want to hear what she has had to say, I suggest.

A I think this is a completely unsubstantiated assertion. I have been at pains to the Panel to point out that I listen very carefully to patients, I described to you yesterday my style of consultation, which is empowering. However, I would take you back to one significant thing that the patient said. The patient said that she had headaches initially. Headaches are not a feature of hypothyroidism of any kind. I have never come across a patient presenting with headaches and hypothyroidism where the headaches have got better on thyroxine.

Q Do you mean Patient A or D?

A I am talking about Patient D. Patient D said, and I took a note, "My headaches responded to treatment quite rapidly." Now, she indicated that the response to thyroxine was quite rapid. Since headaches are not due to hypothyroidism, that implies to me that she was getting, if you like, and I know you will not like this, a placebo response.

Q Lots of patients who complain of hypothyroidism have headaches, do they not, lots of them?

A It is not in any textbook of medicine that I have read.

Q It may be, as you said yesterday, that there is a lot more exploration in medicine that needs to be done and it may be that in future years people will look back at us now and think, "Gosh, they did not know very much then, did they?"

A Mr Jenkins, I think it is important for the Panel to understand that hypothyroidism affects one in a hundred people. It is an exceedingly common condition. It is something that every medical student and every practitioner is aware of. We know more about this condition than many others. I think that if headache was a signal feature of hypothyroidism, it would be in every medical textbook.

Q You are president at the moment of the British Thyroid Association?

A Indeed.

Q A recent past president was Dr Malcolm Prentice, who allies himself to the complaint about Dr Skinner?

A No.

Q Am I wrong?

A Yes, you are. He was secretary and treasurer.

Q Secretary and treasurer, I am sorry, but you see the point. Would you regard yourself as independent to act as an expert in these proceedings?

A In what sense?

Q Well, given that a colleague of yours on the British Thyroid Association is part of the group who are complaining about Dr Skinner, what comment would you make about

your independence here as an expert?
A I feel that I am completely independent, but I have made no secret of my presidency of the British Thyroid Association and indeed the Panel will have in their bundles the statements in the British Thyroid Association. Now, the statements that we produced that are on our website are those which are, first of all, promulgated by the entire Executive Committee; signed up to by them; distributed to the entire membership of the British Thyroid Association for comment; endorsed by the entire membership and then posted on our website. So it is very clear that anybody with an interest in thyroid disease will have, if you like, come to the same conclusions that I have, because they have all endorsed the statements that are on the website. So in that sense, there is ... All I am trying to say, and I am not able to put it perhaps more clearly than this: every thyroidologist, every endocrinologist in the UK would have a similar view to me, and I do not see any conflict of interest between Dr Prentice... Dr Prentice's involvement in whichever case it was was not made clear to me before I started to take this work on and I do not sense that I am not independent.

Q On the front page of the BTA website, is there a sort of warning, "We are the only reputable organisation"? I use my own words.
A I cannot recall what the website says.

Q But there is something to that effect, is there not? "Do not listen to others, we are the reputable people."
A I cannot recall what it says.

Q Is there something to that effect, whatever the words are?
A For the third time, I cannot recall what it says. When I access the website I know exactly where I am going. I cannot recall what it says.

Q Is there a warning on the front page to people who may be looking at the homepage to the effect, "We are the reputable organisation"?
A Mr Jenkins, if you have something in your possession that would help me then perhaps we might get on quicker.

Q I have not copied it, but I am suggesting that your association sees itself as fighting a war.
A I think it would be fair to say that we are concerned about the prescription of thyroid hormone to people who are biochemically euthyroid and have clinical symptoms. There is absolutely no secret about that. I have included in my bundle the joint statements produced not just by our organisation but the Society for Endocrinology, which represents all UK endocrinologists, and once again this is a statement that has been promulgated by that Executive Committee, endorsed by the membership of the entire Society for Endocrinology, it appears on their website too. This is not a war, this is simply trying to make the case of scientific medicine, objective medicine. Objective medicine is necessary to clinical practice. It is not sufficient for clinical practice, but it is fundamental and necessary.

Q Can I suggest that the criticisms you have of Dr Skinner's investigation of the four patients that we have looked at are overstated, that the suggestion you made yesterday that for each of these patients they should have been referred on to specialist after specialist, after various signs and symptoms have been reported to Dr Skinner, is simply

a gross overstatement of the position?
A I did not say for each patient they should be referred to a specialist.

Q You got to about ten or eleven cases where they should have been referred off to this person or should have been referred on to that ---
A Let me just give one example to the Panel. Dr Skinner talks in Patient A about a condition called secondary hypoadrenalism. I can go to the exact page, if you wish me to, to highlight that to you. He talks about secondary hypoadrenalism. This is a serious medical condition, it is absolutely defined, you can look in any textbook of endocrinology, look up hypoadrenalism, look up secondary, and you will find a precise description of it. It is a life threatening condition. If Dr Skinner had truly believed the patient had secondary hypoadrenalism, there are only two courses of action open to him: he either investigates the patient himself or refers to an endocrinologist.

Not to do so would be unsafe. Last year I acted as the medical expert in the case of somebody who overlooked a diagnosis of hypoadrenalism in a 35-year old computer engineer from Windscale who was reduced to zero brain function and is now totally dependent on the state for his care because the diagnosis was missed. I simply point this out to you to show how serious that diagnosis is. One cannot as a medical practitioner entertain a diagnosis of secondary hypoadrenalism, write it down, and not do either the appropriate investigations or refer on. Of course the patient did not have secondary hypoadrenalism and any competent endocrinologist, or indeed any general physician, could have found signs and symptoms that would have excluded the diagnosis or made it so low in the list of probabilities as not to be entertained. But once a doctor writes down, "I think a patient has such a serious condition", then it is my contention that that patient must either be properly investigated by the physician or must be referred on.

MR JENKINS: Thank you very much.

<u>Re-examined by MR KARK</u>

Q First of all, Professor, how big is the membership of the British Thyroid Association?
A Around 200 members.

Q What is one's qualification, as it were, to become a member?
A Originally we extended membership to those who had either published scientific papers or peer review journals on thyroid disease or had presented papers to one of the Association's members. We have recently widened the membership to include those who have clinical care of patients with thyroid problems.

Q You have been challenged very generally but in relation to the specific patients with whom we are dealing in this case you have not actually been cross-examined about your evidence that Dr Skinner gave an inadequate examination, took an inadequate history, that if he suspected deficient B122 he should have taken action and that if he suspected secondary hypoadrenalism he should have taken action. As your view…

MR JENKINS: I have challenged it but not in detail.

MR KARK: Very well. Has your view changed from when you gave evidence in chief

about any of those features of your evidence?
A No, indeed my views have been reinforced because I was given by you a copy of Diagnosis and Management of Hypothyroidism. This is a publication that Dr Skinner has published and it is clear from this publication that it is both unscientific and muddled but there are several key features that I would draw from this publication.

Firstly, it is not just thyroid blood tests that Dr Skinner does not believe in.

Q The publication you are referring to now is what?
A Diagnosis and Management of Hypothyroidism by Gordon R B Skinner.

Q This is Dr Skinner's book?
A Yes.

MR JENKINS: There are copies for the Panel if Mr Kark wants the Panel to follow the point.

MR KARK: I think let us just hear from Professor Weetman and then we can discuss the book at a later stage.

THE CHAIRMAN: Could you just completely clarify where you are getting your facts from so that everyone understands?

THE WITNESS: So I am now talking about the book. Do you want page numbers from it?

THE CHAIRMAN: No, just that you are talking about the book written by Dr Skinner and the title is?
A Diagnosis and Management of Hypothyroidism.

THE CHAIRMAN: Thank you, of which we do not have any copies?
A No, but if you bear with me, my anxieties are strengthened by reading the book because Dr Skinner doubts not only thyroid function testing but also the wisdom of testing for Vitamin B12 deficiency by blood testing, doubts the utility of synacthen tests which are the standard means of diagnosing adrenal disease used by endocrinologists, and even doubts whether diabetes can be excluded by proper blood tests.

He goes on himself to say:

> "As always in medicine it is necessary to be alert for any diagnosis irrespective of the nature of the referral."

Later on he describes the need to…

MR KARK: I am going to ask you to pause because I do not want a general treatise on the book. Dr Skinner may give evidence supporting those views in due course.
A OK. Let me simply summarise by saying the book itself gives evidence that it is not only thyroid function tests that Dr Skinner dismisses as having any utility. He also goes on to assert in the book that – let me just, if you bear with me, one thing which I think is the most important part of the book and I will read this out because I think it is

important. This is page 18 of the book:

> "The diagnosis of hypothyroidism should be made on clinical grounds. This is the most important statement in this book."

That is against any guidelines one cares to mention because all guidelines say that even if they include clinical grounds, biochemical testing has to be performed.

Q All right. I wanted to ask you about another matter about which you were cross-examined and that is people feeling better and people feeling worse. I just want you to explain once more why do you say that a patient will feel well or better when they actually become thyrotoxic?
A We see this in patients who have spontaneous thyrotoxicosis due to disease – not always but some patients who one makes euthyroid – restores normal thyroid functioning – complain. They complain because their weight that they have lost goes back on, they have had an advantage in terms of weight gain, they sleep more, they have less energy because having excessive amounts of thyroid hormone can have this apparent "benefit", and I would put "benefit" in inverted commas. It can speed up metabolism, therefore people are able to do more. It is an artificial state, it is a harmful state.

Q The corollary is, why do they feel worse on reduction from a state of thyrotoxicity?
A Then they are comparing themselves with what they felt like before and the converse applies.

Q In the report that we looked at, one of the criticisms of the report…

THE CHAIRMAN: Which report are you now looking at?

MR KARK: I am sorry, this is the Stobhill Report which is D6.

Q Do you have it?
A Yes.

Q One of the generalised criticisms - I think this was from the junior doctors – was that one did not know the starting point, as it were, of the symptoms. I just want to see if we can glean – I appreciate you have not read this for a while – any assistance from the report. On the first page, which I think the Panel have, the bottom right-hand corner:

> "Methods.
> Participants.
>
> Patients were required to have had at least three of the following symptoms for six months: tiredness, lethargy, weight gain or inability to lose weight, intolerance to cold, hair loss or dry skin or hair."

Those were the symptoms and signs, as it were, that they appear to have been looking for in their patients. If we go to the second page – and I am not going to go through the report because equally I am afraid I have not had time to read it in full – the bottom right-hand corner we see "Physical and Psychological Evaluation." Again the criticism was

made that there was no starting point, as it were. If we look at the last paragraph on the page:

> "Psychological and physical wellbeing were measure by using two questionnaires, the hospital for anxiety and depression scale assessed emotional disorder and SF36 health survey measured five health concepts."

Over the page:

> "Statistical methods.
>
> Baseline characteristics were summarised by means or counts and percentages as appropriate."

Can I just ask you, do you accept that particular criticism? I know you have others but do you accept that particular criticism that one does not know what the starting point of these patients was in terms of the problems that they exhibited?

A To be perfectly honest I have got my copy of the paper and I have not got the copy with those comments to hand.

Q I think it was handed to you?

A I had a copy but I have put it somewhere and I cannot find it. *(Same handed)*

Q You will recall that one of the criticisms was that the methodology and the selection of the control group and what, as it were, the baseline was, the symptoms and signs that they were examining, I just want to know from you whether that is a criticism that you accept?

A The business about selection of the patients I think I covered because they were out to recruit the kind of patients who refer themselves to Dr Skinner and I have mentioned the potential benefits of that to the study rather than that being a potential detriment.

The baseline element of your question I am afraid I am struggling to identify in the letter. If you could point me to the paragraph I would be happy to comment on it.

Q I am afraid I cannot now remember if it was in the doctor's – they start by saying:

> "To begin with some of us were unclear about what the actual research question aimed to answer"

and you dealt with that. Then they criticise the small size of the study and you have dealt with the power of the study?

A Yes.

Q Then they move on to methodology:

> "The symptomatic subjects recruited for the hospital were hospital subjects"

and so that is the selection of the patients, as it were.

A I think on the second page they talk about, at the foot of the second page they talk about outcome measures and they say there – perhaps this is what you are alluding to:

> "If there were measurements of the original symptoms that was not made clear."

Q I am grateful, yes.

A I think that this is back to the point that Mr Jenkins made – was this a paper where they evaluated symptoms and looked at symptoms at the outset and then at the end? No, they did not. They used instead a surrogate measure which are these scales. You will recall that I said to Mr Jenkins that even if they did not measure symptoms it would be difficult if not impossible for me to conceive that the symptoms would improve and the scales would not, so the scales are an objective questionnaire which can be marked and which is reproducible and therefore they have chosen that, if you like, instead of a symptom score. It is not perfect but that is how they did it.

Q In the study can you help us with this – they treated as we know both their control group and their patient group with a standard dose of 100 mcg Thyroxine and obviously we have seen that Dr Skinner doses his patients at a starting dose of 25 mcg very often and then there is an increasing dosage. What do you say about taking 100 mcg of Thyroxine?

A I think as Mr Jenkins has said, one could imagine any sort of combination of treatments that one could use in such a trial. In a trial such as this then 100 mcg is a reasonable dose to give.

Q If you were dealing with a patient who was in fact hypothyroid, biochemically hypothyroid, would 100 mcg as a standard dose be a reasonable dose, or is there no standard dose?

A I think I mentioned yesterday that slightly contrary to the BNF I would give for someone with complete hypothyroidism who is healthy and young, a starting dose of between 100 and 150 mcg of Thyroxine a day because this is dependent on body weight but, of course, let me emphasise again, these patients did not have any degree of thyroid hormone deficiency. They had normal thyroid function tests and therefore that higher dose that I have just mentioned I think would have been inappropriate and I think 100 mcg would be a safe dose.

Q If they had overdosed these patients and put them into a state of thyrotoxicity, would you have expected then the patients to have felt some benefit?

A Based on what I have said then yes, but I think that the dose chosen was such that it did not, although we are not given, looking at the information, sufficient detail to look at how many patients fell outside the TSH reference range.

Q That is the next question that I was going to ask you and then I was going to leave this report. Do we know if they treated patients to a point where they fell outside the TSH reference range, or were they always treating with the standard goal, as it were, remaining within the TSH range?

A If we look at the paragraph on page 893, the bottom left-hand column, it says in both groups the serum TSH concentration decreased but it does not say if any TSH values fell outside of the reference range. I think the difficulty you have to appreciate is that in

the British Medical Journal they are so short of space that they often ask authors to exclude what would be interesting data, so I do not think this paper actually includes that.

Q Just for clarification, you made reference at one stage of your evidence to reverse T3 testing. There was something of an assumption that we all understood what that was. What is reverse T3 testing?

A Reverse T3 is a molecule in which an iodine atom is removed from Thyroxine but in a different position to the iodine atom which is removed from T3. Reverse T3 is therefore a way of getting rid of thyroid hormone from the body. The body turns over thyroid hormone in the liver, so it converts T4 into reverse T3, then that is excreted in the urine and to a tiny degree in the faeces.

Q Is it a way of treating hyperthyroidism?

A No, it is just a normal part of the biochemical pathway for thyroid hormone metabolism. It has no effect. It is not of any benefit in diagnostic testing. You will not find any mention of reverse T3 in the National Academy of Clinical Biochemistry guidelines as a means of diagnosing hypothyroidism. It is just a red herring.

Q You were asked – and I am not going to take you to it, although I am going to go to it – tab 4 page 11 of the main bundle – I had better take you to it.

THE CHAIRMAN: File 1, tab 4, page 11?

MR KARK: File 1, tab 4, page 11. You were asked about this. I just wanted your clarification, please. There is reference to back stacking. You have already dealt with that and I am not going to ask you about it again. Can you help us with this? Why if a patient is thyrotoxic do they fail to convert T4 to T3, or is that just not right?

A It is just not right. I do not understand the logic behind this but, again, speculation would be that what Dr Skinner is saying is that in this patient there is a high free T4 reading and that was the free T4 reading from 9 December which was 39. On his methods he felt that the patient was clinically hypothyroid and so his presumption was that the T4 was ineffective.

Q So it was not being converted?

A It was not being converted into T3 and what I am saying is that that does not occur and the reason that the patient still had signs of hypothyroidism was that this was not the appropriate treatment for her. There was a different reason for her allegedly hypothyroid symptoms.

Q You were asked this question: is it reasonable to start a three month trial, and the answer you gave was, well, provided you remain within the TSH reference range, yes, it is reasonable.

A I do not think I said that, Mr Kark. I think what I said was that it would be safe. I said I did not think it would be reasonable.

Q No, you are absolutely right, because you say you do not treat somebody who is not clinically hypothyroid.

So far as treating a patient with thyroxine is concerned, you have dealt with the issue of differential diagnosis and the danger of missing. The primary differential diagnoses, if

you are able to list them, would be what?
A The list would be exceedingly long, but top of the list would be depression and chronic fatigue syndrome. Dr Skinner himself has mentioned the possibilities of adrenal failure and vitamin B12 deficiency, particularly in those patients who had otherwise unexplained tingling in their fingers, anaemia, malignancy of any system. With regard to headaches, as I have mentioned, some space-occupying lesion within the brain, pituitary diseases, inflammatory diseases such as lupus. I could go on.

Q All right. Finally, I want you to help us with the German study that you were referred to, and we heard that there was a suggested reference range from one study in Germany. I think it was between 0.3 and 2 on a TSH.

MR JENKINS: From a laboratory in Germany.

MR KARK: From a laboratory, yes. (*To the witness*) Was that the Pomeranian study?
A No, I think the bundle that Mr Jenkins was referring to, which was very lengthy but, fortunately, I recalled, was a set of biochemical tests which had been done and the result sheet was provided and the reference range was provided alongside. Is that right, Mr Jenkins?

MR JENKINS: Yes, it is.
A It was simply to make the point that in some parts of Germany they have a very narrow TSH reference range and I think that that might be down to the local circumstances, that if they test their local population that is what they come up with, but, as I mentioned to you, that is why in the UK we have our own reference ranges established with the laboratories and then these are checked through the National Quality Assurance Scheme, so we can be confident that the UK reference ranges are those that you should apply to the UK population and, indeed, that is gone into extensively in the National Academy of Clinical Biochemistry guidelines.

Q Finally this. Mr Jenkins put this to you fairly earlier on. You define hypothyroidism by chemistry. I am giving you the shorthand of the question, but you define hypothyroidism by chemistry, and it was put to you that, in effect, you are at the extreme edge of that particular view. You and who else?
A As I have mentioned, I think, previously, every endocrinologist in this country who is in the specialist register would have exactly the same views as me and the reason that I am able to state that is that I have shown you the Society for Endocrinology statement alongside the BTA statement, (British Thyroid Association statement) which has been signed up to by UK endocrinologists. It is also a position which is held by the European Thyroid Association, of which I am a member and a member of the executive committee, and it is also a position which is held by the American Thyroid Society, of which I am a member.

MR KARK: Thank you. Would you wait there, please.

THE CHAIRMAN: Thank you, Professor Weetman. We will now break and what we will do is we will have a 20 minute coffee break and then we are going to give ourselves half an hour to have a private session to discuss the expert witness's evidence and then we will return at quarter past twelve. Thank you.

(*The Panel adjourned for a short time*)

Questioned by THE PANEL

MR PAYNE: First of all, I am going to say this to you, that I am a layman of this Panel. I have no criticism of your testimony whatsoever and the way you have explained things but from a layman's point of view I found some of the language is not something I would normally use and I found some of it quite difficult to understand. At the end of this I am part of this team that makes a decision, which could be quite a serious decision, so I want to make sure in my own mind that I have got what you said. I am sure you probably answered some of the questions that I am going to ask you already but please bear with me because I want to understand them in the language I understand them in.

A I full appreciate the difficulties.

Q Thank you. Exhibit C6, that particular graph. Am I right in saying that the graph you have shown us, which says "TSH" at the bottom, is a graph taken by people who are well? They are not suffering from thyroid problems at all?

A Yes.

Q Just either side of that, that only takes in 95 per cent of the people and 2.5 either side are still well but fall outside of that particular graph?

A Yes. This is a statistical method which is applied to any reference range for anything we measure.

Q If someone came to yourself with symptoms of a thyroid problem and you did a blood test and that test fell within those boundaries of 0.4 and 5, then you would be looking for the problem elsewhere?

A Yes.

Q If it was outside those boundaries, say they came with the same symptoms and outside those boundaries and say it was 5-plus to the right-hand side of that graph, then it would be fair to say the problem was a thyroid problem?

A To be precise, there is some dispute at the range of a TSH of, let us say, 5 to 10, and I have mentioned that dispute, but I personally would still treat such patients and see if their symptoms improved. There is no dispute, once the TSH is above 10, that treatment should be instituted.

Q You also talked about - was it the [Wye] report? The [Wyke] report that you mentioned?

A The Wickham report.

Q The line that goes outside on your graph there, that is the line that goes out over a 20 year period?

A Just to be clear, if you take people in this town in the north east of England and you measured their TSH and then followed them for 20 years, if their starting TSH was above 2 there was a very slight risk that a fraction, a very small fraction, of those people would go on to develop true hypothyroidism over the next 20 years. The vast majority, however, would remain with normal thyroid function.

Q You said only a small minority, and I have taken a note and I thought that it was 20 per cent.

A No.

Q Thank you for that, because I was under the impression that it was 20 per cent.

Within those people that go from that ---
A I am sorry, could I just clarify that last point? The risks, if your TSH was 2, would be very small indeed. The risks would be slightly higher if your TSH was 3. It would be slightly higher still if your TSH was 4, if you take that group of people. There is a mathematical way of expressing that and that is in the paper that was quoted, but I still think, overall, trying to take all of that group whose TSH lay between 2 and whatever the upper limit of the reference is, that group would be less than 20 per cent. The reason that I say that is as follows: obviously, half of the population would have values around 2 or above, the healthy population. We know that, ultimately, only 1 in 100 people develop hypothyroidism, only 1 in 100, so it could not be that 20 per cent or 50 per cent go on to develop hypothyroidism.

Q So those people, you are saying, the 2.5 per cent beyond the 5, even though they are well now, would be more likely to develop it than someone who only has a 2 now?
A That is right.

Q Thank you. That is very helpful. Could not the signs appear before the actual development of the illness? Could not the signs of the illness start to come in - they may still be within the readings but could not they still start to get the signs of the illness coming in?
A That, of course, has been part of the postulate but that is not the case. We know that for several reasons. One of the key reasons is that if you take the group of people whose TSH is between the upper limit of the reference range and 10, there is considerable controversy as to whether treatment is of any benefit. Out of five studies which have looked at this in detail only one has found a benefit and the other four have found either no benefit or, indeed, as I mentioned, in one case an increase in anxiety scores.

So if you take those people who have an unequivocally raised TSH, beyond the upper limit of the reference range, in four out of the five studies there is no objective evidence of any benefit of treatment and, therefore, it seems very unlikely indeed, based on that bit of reasoning, that symptoms would be present in the group whose TSH was between 2 and 5. We also have the paper that we discussed at length this morning. Despite its imperfections, that shows that treatment has no objective benefit.

Q So you are also saying that as from 5 to 10 there is also doubt as to whether the treatment is effective as well?
A Exactly, and I have mentioned the controversy between endocrinologists in this area. I am somebody who would give somebody a trial of thyroxine if their TSH lay between 5 and 10, and if they felt better I would continue it, but in many cases they do not feel better and I would not continue it.

Q Could those people then have the signs? Could they quite comfortably come to you and have the signs and then if you do not feel it is better after a short trial then you would look for an alternative diagnosis?
A Exactly, and that is the whole point in treating sub-clinical hypothyroidism. Here one has an unequivocally abnormal result and, therefore, I take the line, if you like, that, practically, you would treat that abnormality you have discovered and if the abnormalities persist, if the patient still has symptoms, then, obviously, you would seek an alternative course.

Q Within your graph there is a dotted line that goes from top to bottom and then one side is lined off and the other side is not. The blank side, and correct me if I am wrong, is

what some endocrinologists and some thought in America should be the limit that you would work to?
A Yes.

Q Would it be fair that elsewhere in the world people who fall from, say, beyond 2.5 to 5 to 6 are being treated for this problem where they are not being treated in this country?
A I have mentioned in my report - and I can turn to this if you would like - but there is debate on this. Somebody has suggested that one would treat a TSH above 3. Provided the TSH is consistently elevated, that is one does a TSH reading, then one checks it again several months later and if it is still elevated one could institute treatment, particularly in the presence of positive thyroid antibodies. That, in my view, is the most extreme view on that side of the argument.

There are arguments on the other side, which I think are obviously difficult for a lay person to follow, but that is when one takes a group of entirely healthy people who have had every conceivable current test for thyroid disease performed on them, in whom there is no suspicion of any future thyroid disease developing as far as we can tell at the present time, and looks at their TSH reference range one finds that the TSH reference range is the same as in any random population that one uses to construct the reference range. So that tends to give the lie to the suggestion that the TSH reference range needs to be narrower.

Q The only way then that you can identify the problem is through a blood test?
A That is the view of all endocrinologists, but you can turn the matter around and consider the diagnosis of chronic fatigue syndrome, or, as Dr Skinner terms it, ME (myalgic encephalomyelitis). The definition of chronic fatigue syndrome, as produced by the Royal College of Physicians of London and a working group set up by them in 1996, says that chronic fatigue syndrome can only be diagnosed when you have excluded other disorders, including thyroid disease, by means of a blood test. So you cannot have it both ways.

Q Yes, I understand that. Thank you for this, because you are making it clear to me. I worked in an industry where there were guidelines, and you had a problem and this is the way that you were supposed to overcome it, but there were other times, because of the conditions that we worked in, you could not do it that way and you had to find an alternative method to overcome the problem. Could it not be said that Dr Skinner is being confronted with these signs and symptoms and to make someone better he is using an alternative method to make them better?
A There are two problems with that approach. My main concern in all of these cases is that by all accepted criteria these patients do not have thyroid failure. They have, however, very profound symptoms and signs. These are all recorded. These are serious issues. There is no doubt that these patients felt very unwell indeed and, therefore, there must, by conventional reasoning, be an alternative cause for those signs and symptoms. That is my main concern. There is not an alternative type of endocrinology. There is only one endocrine system, there is only one defined set of blood tests, and if you fall within those parameters and you have profound symptoms then you need to look for another cause. That is the position that every endocrinologist and physician would take.

The second thing is about treatment. This would then be empirical treatment outside of any recognised guidelines and of course doctors do occasionally embark on unlicensed or empirical treatment. However, the principle of such treatment should follow one of the earliest concepts a medical student learns about treatment, "First do no harm", and here

we have evidence that patients are being over treated and some of the benefits that they are deriving are from over treatment.

Q Right. I am led to believe that the boundaries of medicine are pushed by people who are looking outside and thinking outside the box and looking for alternatives and one thing and another. That is how it has progressed, and I am just wondering if perhaps Dr Skinner might have been able to say that that is the way he is looking at this and other endocrinologists are saying the same. You quoted at page 12 of your report, 7.2, about some endocrinologists think the same as Dr Skinner. I think it was with regard to the "viewed in the lower range of the TSH". Are people in your profession now looking to find an alternative way forward or an alternative measurement?

A No, I do not think... Unfortunately I may not still have been able to explain this to you to your satisfaction, but can I just reassure you that on page 12 I am not saying anywhere that an endocrinologist would treat in any way other than I have described. I have mentioned the extreme view of people like Len Wartofsky who might treat patients with TSH values above 3 on two occasions, particularly in the presence of thyroid antibodies, but can I remind you that in none of these patients was the TSH above 2.5 even, let alone 3.

Q I have taken that on board. Believe me.

A So I fully accept the need for doctors to continually challenge dogma and, where dogma has been challenged, I have made that clear in my report. I have mentioned the extreme views of people like Wartofsky, I have mentioned the dispute there is about the treatment of sub-clinical hypothyroidism. I do not think it is fair to say that endocrinologists have been idle in terms of trying to push the boundaries, but we have something here which is way beyond what makes rational sense, if you like, in terms of a hypothesis to investigate.

Q Right, okay. One other question and it is not in that particular area, but the actual test that you take, is it an exact test for that particular moment in time, or when the blood test is taken, or is it an average test to say, "This is what the levels have been over a three-month period". I have a blood test on a regular basis for my diabetes and it can tell me what it has been for the last three months on average. Is this a similar type of test or is it a spot test at that moment?

A It is a test of the TSH secretion at that particular moment in time, but, as we discussed in detail yesterday, to remind you, provided the test is taken during daylight hours there is no fluctuation that needs to be taken into account. Put it another way, if I checked your TSH today and I checked it on Monday, the values would be the same.

Q Right.

A Furthermore, if I could just press the point a little further in terms of treatment, which is the analogy you have drawn with diabetes, this is where the TSH value comes into its own because indeed the TSH reflects what has happened over the last few weeks with treatment. Thyroid doctors use it much the same way as the test that you are alluding to in diabetes to indicate how much thyroxine the patient has been exposed to over the course of weeks rather than that particular day, so that is why it is such a useful test in determining how thyroid hormone replacement should be adjusted.

Q If you just bear with me a second, I want to check I have asked everything I want to.

A Of course.

MR PAYNE: Those are all the questions I have, thank you very much. Thanks for the clarification.

THE CHAIRMAN: Mrs Catherine Whitehill.

B MRS WHITEHILL: Good afternoon, Professor Weetman. I want to talk about, really going back to a question I asked yesterday, about the relationship between symptoms and biochemistry. Patient D, she was taking 200 micrograms of thyroxine. On 18th November she had a T4 of 27.2 and a TSH of 0.1. I presume that is negligible.
A It is undetectable.

Q Yes, undetectable. We have heard that you said that is thyroid toxicosis.
C I suppose I am still struggling with, if she was on such a large dose of thyroxine, is that a high level of thyroid toxicosis or is it a minimal level of thyroid toxicosis?
A I think that would be in the lower third of patients that we see whose thyroid glands have become spontaneously overactive, so it is a mild level of thyroid toxicosis.

Q Would you generally expect symptoms of that level?
A If you like, this is the obverse of what we have just discussed with sub-clinical
D hypothyroidism. I mentioned to you there that when the TSH is only slightly elevated then patients can have very few, if any, symptoms. Indeed that is why it was originally called sub-clinical. Doctors, some endocrinologists, believe it is not worth treating because there are no symptoms associated with this. So it is exactly the same when you look at the other side, when the TSH goes low and even when the T4 rises and the T3 rises. I see patients, I cannot give you an exact figure, but I guess about 10 per cent, who have no symptoms whatever despite higher levels than this.

E

You will remember we went through another study score, just to back that up, the scoring system where there were a group of patients there who had very profound hypothyroidism, unequivocal hypothyroidism, and yet I think a small fraction, 6 per cent from memory, had no symptoms at all. This is because people adjust to their thyroid biochemistry, so what happens is that the T4 has gone up gradually in this lady and she has become adjusted to it and may not notice evidence of over activity. Alternatively, she
F could actually be deriving a benefit, as we have mentioned, from the excess of thyroid hormone. She might lose a few pounds in weight, she might have more energy, and these could well be signs of over activity that she interprets as a beneficial effect of the treatment.

G Q But if you look at the BNF, the side effects, I accept the issue about loss of weight and the general feeling of wellness. It is interesting she did not report a loss of weight, did she? She reported her weight increased. But the BNF talks more about the sweating, flushing, headaches, and tolerance to heat. Would a person on that level of thyroid toxicosis report none of those symptoms?
A It is possible that that is the case. As I have mentioned, this is mild thyroid toxicosis and it is possible to have that and not have any signs at all. Other people, who
H might be more sensitive, would have signs and symptoms such as the ones you have just mentioned. Just a word about the weight: thyroid hormone not only helps to stimulate metabolism of cells, it also stimulates appetite, and 10 per cent of patients who have

hyperthyroidism, whose thyroid glands are spontaneously overactive, report weight gain rather than weight loss. So the fact that this lady reported weight gain could well again have been a sign of excessive thyroid hormone in her case stimulating appetite more than it stimulated metabolism.

Q Now I would like to move on to Patient A. On 16/01/03 Dr Skinner writes in his examination note, that is the first page behind tab 2, that Patient A's thyroid was palpable.

This is just a very basic question: is everybody's thyroid palpable?
A No.

Q Right, okay. Then we have on 08/04/03 Professor Franklyn says there is no goitre and that is tab 1, page 56. My question there is: can goitres disappear very quickly?
A When did she see Professor Franklyn?

Q The letter is written on 08/04/03.
A So three months roughly?

Q Yes.
A Not in my experience.

Q Right. Usually their resolution takes a longer period than that?
A Yes.

Q If a person is hypothyroid biochemically, as you have described, and they begin treatment with thyroxine, do all their symptoms resolve with the treatment?
A No, some patients continue to feel symptoms.

Q Why is that?
A Obviously the patient goes initially to see the doctor, as we have seen with these cases, with a number of symptoms. The doctor takes a history, does an examination, and does a series of blood tests. Thyroid disease is very common, as I have mentioned. One in a hundred women will develop an underactive thyroid. Therefore it is perfectly possible to have a combination of symptoms and turn up either coincidental hypothyroidism or hypothyroidism which is partially responsible for the symptoms, but not all of the symptoms. So depression is a very common condition, chronic fatigue syndrome is a very common condition, and it is therefore not unexpected that one might have patients who might have combinations of these common diseases and treatment of one therefore will not relieve all of the symptoms.

Q But if the symptoms were due to hypothyroidism and treatment was commenced you would expect those symptoms to resolve?
A In my view any symptoms that remain three months after the TSH has been normalised and brought into the lower half of the reference range cannot be due to the thyroid.

MRS WHITEHILL: Thank you. Those are all my questions, thank you.

THE CHAIRMAN: Dr Margaret Elliot, please.

DR ELLIOT: Good afternoon, Professor Weetman. I have three general questions to ask you before I ask you specifically about two of the patients. The first one is about the British Thyroid Association. I think you have told us a little bit about who was eligible for membership of the British Thyroid Association, but I do not seem to have total recall of that. I wonder if you could remind me, please.

A We used to restrict membership to those people who had either published scientific papers on the thyroid in peer review journals or had presented scientific work, clinical or basic scientific work at meetings of the association. We have recently widened the membership to include those who have an interest in the treatment of thyroid disease and therefore essentially endocrinologists either in training or as established consultants.

Q And do you have a patient representative in the association?

A No, not per se, but we work incredibly closely with the British Thyroid Foundation, which is the largest representative group for patients with thyroid disease that I am aware of, and they in fact handle all of our mail; we work so closely with them and we have a member of the British Thyroid Foundation on our Executive Committee so that again, when we release statements such as the ones that we have discussed, those have been seen and had an input into by the BTF, British Thyroid Foundation, which is the patient group. Indeed we also offer members joint membership of both organisations and many members of the BTA are also members of the BTF.

Q Thank you. The next thing I want to ask you about are risks, the risks in particular of thyroid toxicosis. I think we are aware of what we have been told the risks are of thyroid toxicosis, of atrial fibrillation, and subsequent stroke, of osteoporosis, heart problems and so on. But what I am not clear about is what the actual risk to an individual patient is and in particular a patient who has been made thyrotoxic iatrogenically. What is the actual risk to that patient?

A As I think I said yesterday but, if not, forgive me, in the case of atrial fibrillation there are no good studies which have looked at iatrogenic hypothyroidism, that is hypothyroidism caused by excessive thyroid hormone alone. However, this is the commonest cause of sub-clinical hypothyroidism and therefore in studies which have looked at the risks of atrial fibrillation in sub-clinical hypothyroidism, the major cause in those studies is iatrogenic hypothyroidism and the risk specifically for atrial fibrillation is between two to threefold increase over a ten year period in patients over the age of 50. The risks with osteoporosis, as I mentioned, there are no good studies showing that there is any increased risk of fracture. But, as I mentioned, more recent research has shown that bone markers are increased when thyroid hormone levels are raised.

I mentioned the studies in meta-analysis when T3 is added to T4 and we have yet to see what the long-term effects really are, I think, over a long enough period of time. We ourselves conducted a study in patients with thyroid cancer who have, as I mentioned, deliberate over treatment with thyroid hormone, not sufficient to raise their T3, we always keep the T3 normal, but just sufficient to stress their TSH. We found reduced bone mineral density in a group of women who were so treated in the post-menopausal group and I think that is the evidence that is now pretty consistent. Those women over the age of 50 are more likely to have a reduced bone mineral density, but I cannot give you, I am afraid, off the top of my head an exact figure in terms of risk.

Q I had understood you to say that in the meta-analysis which was reported in the Journal of the American Medical Association that there was not good evidence of an

increased incidence of complications unless the TSH was unrecordable?
A Below 0.1, yes. Just to reiterate, if you wish me to go through the list again, the risk was cited as fair for reduced bone mineral density in that group, and for fractures insufficient evidence.

Q Okay. And for atrial fibrillation, sorry to ask you, in the group where the TSH was still within the reference range or ---
A Just below the reference range.

Q Yes.
A Insufficient for that group and then good when the TSH is below 0.1.

Q Thank you. The final general question I want to ask you about is... I am not talking about the effectiveness, but is there any risk in oral vitamin B12, in patients taking oral vitamin B12?
A Not that I am aware of, but I have never prescribed it.

Q Thank you. I just want to go on to Patient A now. You might want to have file 1 and I think most of the things I want to ask you about are actually behind tab 2. You said that you felt that Dr Skinner's notes from his consultation were inadequate in that he did not mention an abdominal or respiratory neurological examination, for example. Dr Skinner did have available to him when he saw Patient A the GP's referral letter, which is behind tab 2, page 9, which does document that the patient has had a number of investigations including hospital referrals over the last months and years. Would you consider that, for example, the fact that she had had a very recent gastroenterological referral and examination would be sufficient evidence that there was not any abdominal abnormality?
A I personally would not because, as you will appreciate, diseases progress and in the case of a patient with otherwise unexplained tiredness one is looking for a disease, and because one physician a few months ago found nothing does not mean that a few months later signs may not be present in the abdomen. Dr Skinner himself says in his book, the one that I mentioned before we broke for coffee, that an abdominal examination is essential.

Q Dr Cooke, Patient A's GP, does specifically say:

"Ask opinion of Dr Skinner who has an interest in this",

- for example, in autoimmune thyroiditis.

So he was being asked specifically about the patient's potential thyroid problems rather than general opinion?
A I think I mentioned yesterday, but, again, I find it difficult to understand the position that Dr Skinner is in ---

Q I appreciate that.
A He is not a consultant and, therefore, my standards may very well not apply, but I think that any prudent physician confronted by somebody who has asked to have a thyroid opinion, if you like, "Are these symptoms due to thyroid disease", has two options open to them. They either say, "No this is not thyroid disease, the biochemistry is entirely normal", or they investigate the symptoms and find an alternative cause. Of course,

Dr Skinner himself was not adverse to doing this, in that he sought diagnoses such as cortisol deficiency and B12 deficiency as explanations for the patient's symptoms.

Q I am really trying to steer away from the controversial debate and concentrate on the management of these individual patients, which I believe is what we have been asked to do. So I am trying not to get involved in that. I just want to ask you then about Professor Franklyn's opinion being sought about the same patient, Patient A, which I think is behind tab 1, page 56, and, indeed, page 55, which is Dr Cooke's referral letter. Dr Cooke's last sentence of his letter to Professor Franklyn:

"I would thus value your kind opinion both in diagnosis and management here."

I appreciate Professor Franklyn's reply is not a case record but it is a letter, and Professor Franklyn does not mention abdominal examination and neurological examination or examination of the respiratory system. I just put that point to you to compare Professor Franklyn's record and Dr Skinner's record. I know it is comparing apples and pears a little, but would you comment about Professor Franklyn's letter?
A All we have is a letter. I would not routinely say in my letters that I have examined every system, but I would it, as I said yesterday, in my notes.

Q The next thing I want to ask you about was one of the things you mentioned about Patient A either complaining of or having visual symptoms elicited during the course of the examination, and you commented that you felt it was mandatory that her fundi should have been examined and her visual fields examined as a result of those symptoms. I appreciate there is nothing in the notes, but the patient himself did say that she thought she recalled the doctor examining her eyes. We heard Patient A saying that, and I can take you to the part in the transcript.
A I do not have the transcript before me, but I am not sure what examination of the eyes was undertaken.

Q She said she did not have a clear recall of the whole of the examination but she thought she recalled the doctor, and I believe she specifically said, "looking in [her] eyes".
A Simply looking in the fundi would not be complete. One would need to do a visual field examination which is very rapidly done. Again, I take the view, and you may take a different view, but my view is that the fundoscopy and the examination of the visual fields is not recorded in the notes; we have no evidence it was undertaken.

Q The next question is about, again, Patient A. Patient A was started on thyroxine 25 micrograms a day and she said she developed a headache almost immediately and after four days or so contacted Dr Skinner. In your experience have you ever found that thyroxine in that dose caused a headache?
A No, but, of course, I have never treated someone with normal thyroid function *ab initio*.

Q No, but you have treated people with that sort of dose of thyroxine?
A Yes, but they have had hypothyroidism and, therefore, they may have a different response to treatment.

Q Yes. Do you think it is likely that it would have been a side effect of thyroxine?
A No. As I think I said yesterday, I think it is unlikely that that would be the case, although, as I said also yesterday, thyroid hormone can cause anxiety and anxiety can

cause headaches, so one cannot rule the possibility out completely.

Q Do you think it is likely?
A I have already said, I do not think it is likely.

Q About the issue of B12 and adrenal cortisol function, I just wanted you to confirm - again, this is in tab 2, page 15. This is Dr Skinner's letter to Dr Cooke, which is at tab 2, page 15. He has not carried out any investigations for B12 deficiency but he has mentioned his suspicion that that might be the case to the GP in this letter. You would accept that?
A I do.

Q Do you also accept that under some circumstances one might ask a GP to investigate certain conditions rather than doing them oneself? Is that something that does happen in clinical practice?
A Of course, but just to be specific in this case, if I may, the letter says - this is still page 15:

"Serious paraesthesia",

- that is serious tingling -

"in both her hands and feet."

So these are not trivial symptoms, and I mentioned the need to conduct a proper neurological examination to determine whether this is nerve compression or the neuropathy of B12 deficiency or some other cause.

It seems to be the case that Dr Skinner recommended oral B12. If the GP did not know that then the GP might request a vitamin B12 level, which is the best way to make the diagnosis of pernicious anaemia. That investigation would be confounded by the oral treatment, in that the patient, if they did not have B12 deficiency or had a partial B12 deficiency, could conceivably have a vitamin B12 which had just been raised into the reference range. So one does not want to have a patient already on B12 when one is trying to investigate them.

Q But you would not treat pernicious anaemia with oral B12 anyway, would you?
A Precisely. So what I am saying is it simply muddies the waters. If you are implying that the GP should be investigating this, first of all there is no investigation plan and it is not ordinarily the case, nor recommended, that you should start treatment before you do the test because it muddies the water.

Q The other letter I just wanted to take you to was on page 24, the letter to Patient A herself, in which Dr Skinner suggests that Dr Cooke will arrange a good endocrinological opinion. Again, he seems to be suggesting a second opinion to the patient. Would you agree with that?
A Yes, indeed, and I think we heard from Dr Cooke that he did get such an opinion.

Q Yes. Finally on Patient A, both Professor Franklyn and Dr Cooke, and you yourself, I think, said that - or Professor Franklyn and Dr Cooke by their actions and you, by your evidence, have said that you accept that under certain circumstances a pragmatic solution of continuing the prescription of thyroxine, even in a patient in whom you

believe it should not have been started in the first place, is the one solution to the problem.

A If a patient flatly refuses to do otherwise then yes, but, of course, there are consequences to that. The patient needs continued monitoring. There are implications for any future pregnancy. One is costing the NHS and every penny wasted, as Patricia Hewitt said, is a penny stolen from the patient. So there are important ramifications even of continuing.

Q I understand that. Do you then think it is unethical to continue to pragmatically treat people with thyroxine? Do you think it is dangerous to continue?

A Provided the TSH is kept within the normal range I have made it clear that I would do so myself. I am simply saying not that it is unethical but there are consequences. There is no free ride in this. There are consequences for continuing to do it.

Q I just want to go on to Patient D now. Patient D had very strong family history of high thyroid disease. Could you tell me what you think the risks are of her developing thyroid problems in the future?

A Very low, given that she has negative thyroid peroxidase antibodies, and her family history is not unusual. I have been chairman of the International Genetics Consortium, which has conducted the largest ever genomic analysis of any autoimmune disease in the case of thyroid disease, so we have collected almost 800 different families with thyroid disease running in them and this sort of pattern skipping a member of a family is very common. We know from the Wickham study, the one we mentioned earlier, this is the North of England study where they looked at 1800 or so individuals and followed their TSH, that if your thyroid peroxidase antibody is negative and your TSH is below 2 then the risk of developing thyroid disease in the future is virtually nil.

Q One final question. Again, it is really just asking you to confirm something which I believe you have said. Have you found any evidence that any of these four patients were harmed?

A Not directly.

THE CHAIRMAN: Thank you, Professor Weetman. My question is related to all four of the patients and, basically, I am sure you have covered it in your report, which is very thorough, but my question is this: has this treatment, relating to all four patients, been in their best interests and has it, perhaps, put them at harm with these treatments? I just refer to your page 29. At 8.6, halfway down the paragraph, you use the term, "prolonged period of time", so if you could use that phrase and, perhaps, enlighten me further about whether you feel that the treatment has not been in the patient's best interests, and also, might it have put them at risk of harm?

A I have mentioned here the need for a prolonged period of time in order to see effects, and I have mentioned figures of ten years, for instance, in the context of atrial fibrillation.

I think, as I have said previously, my main concern is that alternative diagnoses were suspected that, fortunately, turned out not to be the case, such as adrenal failure, and that by continually assigning patient symptoms to hypothyroidism and not following up adequately other possibilities there is a risk of harm to newly presenting patients. Not, fortunately, to these patients.

The third thing I would mention is that we heard from Dr Stewart that, to paraphrase what he said, some of the misconceptions around this had affected the GP/patient relationship.

Q Could you enlighten me a bit more on that one?
A I think Dr Stewart was in the difficult position of seeing Patient D with regard to her asthma and not being aware of what her thyroid status was. So, for instance, let us imagine that the patient continues to be thyrotoxic. He has finally managed to get blood tests from her and confirmed that she is still thyrotoxic, I believe, although I have not seen the test results, and is beginning to manage her thyroid disease now. That could have been achieved earlier had the patient/relationship with the doctor not been strained by what had happened.

THE CHAIRMAN: Thank you very much. Mr Kark, do you have any further questions?

MR KARK: I think it is Mr Jenkins, first.

MR JENKINS: I do not, thank you.

Further re-examined by MR KARK

Q Just dealing with the Chairman's questions. You are saying, as I understand it, that the primary risk of harm, if there is one, is the danger of missing the differential diagnosis as opposed to the treatment with thyroxine itself?
A Yes.

Q Does that apply so far as Patient D is concerned, who appears to be still on thyroxine over a more prolonged period than the others?
A Well, obviously, the longer she is on it the more the risk accumulates. To go back to some of those statements that I made earlier based on the consensus guidelines that were published in the *Journal of the American Association*, they have concluded there is insufficient evidence, and I think as Mr Jenkins said earlier, absence of evidence is not evidence of absence and, therefore, one is concerned about continued over-treatment in these patients.

Again, to flesh that out, if you would like me to, the main reason that doctors feel concerned about treating those patients whose TSH levels are above the reference range, subclinical hypothyroidism, is that many of them end up slightly overtreated. That was the thing that steered the guideline writers away from recommending treatment if your TSH was above 4 or 5 and that is why they wrote in their original guidelines that the TSH should be treated only if above 10, because of the risks of over-treatment.

Q In relation to the patient who becomes thyrotoxic, you told us earlier that that patient may feel better, as it were, in themselves because they are thyrotoxic and so it becomes harder for the GP to wean the patient off?
A Yes.

Q Can I just ask you something about - I think it is the questions that Mrs Whitehill asked, and we were in the area of what evidence there was in relation to bone density, et cetera, and we were dealing with those patients who were in the area of being below 0.1 in the TSH range where I think you said that the evidence was good?
A If they are below, “reduced bone mineral density, TSH 0.1 to 0.4, none”, and fair if below 0.1.

Q If the TSH is reduced down to that very low level, as we see in some cases here, as

to be undetectable, and we have not really covered this, but does it mean that no T4 is going to be produced naturally by the thyroid gland?

A If you take a person with a normal functioning thyroid gland and you gave them thyroxine then their own gland would stop making thyroxine, and if you suppressed the TSH then no thyroxine would be made by that person's thyroid gland.

Q So that is what is happening as we see in some patients here?

A Yes, they are reliant on the T4 that they are ingesting.

Q The medication?

A Yes.

Q Does the problem with bone density come from the lack of TSH, the lack of natural 4, or do we simply not know?

A No, it is very simple, that this is the excess of thyroid hormone. We know that if you take patients who have a thyroid gland which is diseased and is producing too much thyroid hormone, a condition which is very frequent, these people end up with osteoporosis.

Q So it is the excess of T4?

A It is the excess of T4, and the reasoning is: it does not matter whether that comes from the thyroid gland or from a tablet, they are after all identically the same chemical and therefore are going to have identically the same effect.

Q You were asked questions by Mr Payne and you were referred to your report, specifically to page 12. You were being asked about those who, as it were, think outside the box and are pushing the frontiers of science, et cetera. On the very last line on page 12, I just want to ensure that we have understood it, is saying:

> "However, even those endocrinologists who have argued most strongly for a lowering of the reference range do not advocate treatment if an initial TSH level is between 2.5 and 5."

As meaning the upper range, yes?

A Yes, that is taken as one reference range, but you could say 4 or whatever.

Q Those who are arguing for a lower reference range, are they arguing for a lower reference range for the initiation of treatment or a lower reference range for the goal once treatment has started?

A It might help the Panel if I slowly go through the history of this. The Wickham study was published quite a while ago and showed for the first time that if you had TSH above 2 and you followed that patient for 20 years, there was a tiny increased risk of thyroid failure in the future and that risk got higher the higher your initial TSH. That led the National Academy of Clinical Biochemistry, when it was considering the evidence, to wonder whether the reference range for diagnosis should be narrowed; their reasoning being that perhaps some of these people, as I mentioned on my graph, had thyroid disease beginning; that is, they might have thyroid antibodies, they might have thyroid abnormalities, which were not being picked up in the typical reference range.

They therefore made a suggestion - not an insistence but a suggestion – that the TSH

reference range in the future would be narrowed.

I have talked at length about the four European studies that have been done where highly selected individuals have been used to look at the reference range and told you that our present reference ranges for countries like the UK are satisfactory, but then based on the National Academy guidelines some endocrinologists went even further and said, if we the TSH reference range in the future really was to be narrowed, then what would the implications be? The implications would be that anything above 2.5 or 3 would represent sub-clinical hypothyroidism so *(demonstrated on C6)* if you did that you would still end up then treating those patients rather than patients out *here*. *This* is the sub-clinical hypothyroidism group as now where the TSH is elevated and T4 is normal and obviously, if you move your curve *here*, then you bring back that whole conundrum, so that is how we got to the situation which I mentioned on page 12.

Q Pushing the bounds of science or not, your position is that nobody would - no endocrinologist would - treat a patient or any of these four patients – let us just be specific, any of these four patients – with their TSHs as they were with the initiation of treatment with Thyroxine?
A Yes.

MR KARK: That is all that I ask.

THE CHAIRMAN: Thank you and thank you, Professor Weetman. You can go now. I think we are really concluding the Panel for the day. We will commence on Monday at 9.30 and am I correct that you have a witness then, Mr Kark?

MR KARK: I hope to have Mr John Lynn.

THE CHAIRMAN: Thank you very much, everyone, and we will see you on Monday morning.

Just to remind everyone, the reason why we are finishing early is that there are no further matters that we can clarify today. Is that correct?

MR KARK: That is right. I have spoken to Mr Jenkins about that and there are issues that will arise later in the case potentially but we do not feel that those can be dealt with properly this afternoon.

MR JENKINS: There is some reading that you will be asked to do in due course but now, I think, is not the right time to ask you to do it. There will be a later time for doing it.

THE CHAIRMAN: Thank you.

(The Panel adjourned until 9.30 am on Monday 9 July 2007)