GENERAL MEDICAL COUNCIL

FITNESS TO PRACTISE PANEL (MISCONDUCT/PERFORMANCE)

On:
Thursday, 5 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 Four)

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. I am Sandra Sturdy, I am Chairman of the Fitness to Practise Panel hearing inquiring into the allegation against Dr Skinner. For those of who you have not been here before today it is important to maintain the anonymity of the patients and should their name be mentioned in error please do not refer to them the outside of this room. Also mobile phones, I am sure everybody has turned them off. If you do feel the need to talk please could you do it outside the room.

MR KARK: Madam, we are going to begin by giving you copies, by agreement with Mr Jenkins, of Professor Weetman's report. I have to say that is not something I always do because sometimes it is preferable for you to listen to the evidence as it is given orally but this is undoubtedly a complex area and I think it will help you in due course to have the report. Also I am going to stick fairly closely to the report and so if you are making notes it may be easier for you to have the report available so you can make notes on the report if you wish to.

THE CHAIRMAN: This will be called C3. (*Same handed*)

MR KARK: Obviously it is important, if I may say so, that even though you have the report in front of you it is the evidence that is given that obviously matters. May I then call Professor Weetman, please.

ANTHONY WEETMAN, affirmed
Examined by MR KARK

Q Professor Anthony Weetman. Is that right?
A Yes.

Q Could you tell us something about your qualifications and your occupation?
A Currently I am Professor of Medicine and Dean of the Medical School of the University of Sheffield. I have been on the specialist register in general internal medicine and diabetes and endocrinology since 1987. My main area of clinical practice is endocrinology and I specialise in thyroid disease. I was a founder fellow of the Academy of Medical Sciences, I am a fellow of the Royal College of Physicians of London and Edinburgh and I am a member of the European, the American and the Latin American Thyroid Associations. I am President of the British Thyroid Association, having been elected to that post and I have also been elected to the Executive Committee of the European Thyroid Association.

Q Your main area of clinical practice is endocrinology. You better tell us what exactly that is?
A Endocrinology is the study of glandular diseases, that is the glands that secrete substances known as hormones that have general effects on the body through their carriage through the bloodstream and also local action within the tissues.

Q I think you have lectured widely and you have also been published fairly widely?
A That is true. I have published over 200 original papers on thyroid disease and related diseases. I have written the text book chapters in the two most poplar text books of medicine in the world: the *Oxford Textbook of Medicine* and *Harrison's Textbook of Clinical Medicine*. I have been an editor of *Clinical Endocrinology*. I have been associate editor of *Endocrine Reviews* which is the highest ranking journal in the

endocrinology field and I am currently on the editorial board of *Thyroid*, which is the journal published by the American Thyroid Association.

Q I want to start, please, with some basic explanations, if you would help us, about the functioning of the thyroid gland and also then we will move on to the pituitary. Could we start, please, with the thyroid gland. Help us where the thyroid gland is, first of all?
A The thyroid gland lies in the neck on either side of windpipe in about *this* location.

Q What does the thyroid gland produce?
A The thyroid gland makes two hormones: thyroxine, otherwise known as known as T4 and tri-iodothyronine otherwise known as T3.

Q For the members of the Panel if they want to have reference to it I am on page 4, paragraph 4 of the report. The two thyroid hormones T4 and T3, tell us about T4, please, first of all?
A T4 is chemical which is two tyrosine molecules, that is how the molecule is made, two amino acids which have four iodine atoms attached to them, hence the T4, the 4 standing for 4 iodine atoms. That substance is not active in the body. It is the predominant secretion by the thyroid gland that but hormone is inactive at the cellular level.

Q T3?
A T3 is made from T4 by deiodination, that is the removal of one of those iodine atoms, thus T3, and 80 per cent of the T3 in the body is derived from T4 which is secreted by the thyroid gland. The other 20 per cent is directly secreted by the thyroid gland.

Q The conversion of T4 into T3 happens where in the body and how?
A It happens within the thyroid gland but predominantly it happens to convert the 80 per cent of T3 which we use, because this is the active hormone, that occurs at the tissue level. In all tissues in the body, largely in the liver, but each tissue has its own set of enzymes able to convert T4 into T3 and thus regulate the amount of T3 which is supplied at the tissue level for the functioning of the cells.

Q You say for the functioning of the cells. How important is T3 in our body?
A T3 is very important indeed. Virtually all tissues have thyroid hormone receptors and these are able to translate the function of T3 into effect in all tissues in the body. So T3 affects every tissue in the body and determines the metabolism of the individual cells. You have heard previously it has been likened to a motor, the thyroid. I would regard it more as a regulator of metabolism.

Q There has also been mention in the papers of free T4 and free T3. What is the *free* related to?
A Again, another mechanism that the body has adopted in order to ensure that thyroid hormone supplies are kept at an adequate level is that the vast majority of T4 and T3 is bound to proteins in the bloodstream which act, if you like, as a reservoir for thyroid hormone supply. In fact, only 0.03 per cent of T4 is actually free and available for conversion at the tissue level and only 0.3 per cent of T3 is free and available for utility at the tissue level. The rest of it is trapped into proteins and there available to be released as necessary should there be any deficiency at any stage.

Q So are we looking in this case, when we see the T4 and T3 levels in the blood samples, by way of example, are we looking there at free T4 and free T3?
A We are looking at those because those represent the accessible parts of thyroid hormone and therefore they are more relevant physiologically.

Q I want to move on to the function of the pituitary gland. The thyroid produces T4 and T3. Does it produce those two hormones at a regular rate or not?
A There is a very small diurnal variation, that is a variation from morning to evening, but it is not regarded as significant in terms of blood level monitoring.

Q What triggers the amount of T4 and T3 we have produced by the thyroid gland?
A It might help if I use the chart.

Q Yes, certainly.
A (*The witness demonstrated on chart*) So the thyroid gland is a bilobed structure and it makes T4, as we said, and T3 and those have effects on the tissues as I have described. They also have an effect on the pituitary gland which is a pea sized gland lying roughly centrally in the brain. The pituitary makes a number of hormones but in particular and relevant to the thyroid it makes a hormone called TSH which is thyroid stimulating hormone. This stimulates the thyroid gland. T4 and T3 on the other hand have a negative function, an inhibitory function on the pituitary gland. This is a feedback mechanism. A classic example of a feedback mechanism. So the TSH goes up to stimulate the thyroid gland, the thyroid makes more thyroid hormone and that turns off TSH levels and therefore the TSH levels declined, thyroid levels fall, as they fall that inhibition is removed, more TSH is made and this feedback pathway keeps TSH levels -- TSH levels are stimulating the thyroid, that keeps the thyroid hormone levels constant.

Q So in general terms if your T4 and T3 are higher your TSH will be reduced?
A Precisely. If, for instance, your thyroid gland becomes overactive which happens in certain diseases like Graves' disease, then this excessive T3 and T4, that will switch of the production of TSH and that will fall to an undetectable level. Conversely if the thyroid is damaged by autoimmunity or it is removed through surgery then there is no T3, T4, no inhibition and the TSH levels will go very high.

Q But rather redundantly?
A Redundantly but they are attempting to stimulate the thyroid gland. There is one other feature I should point out which is slightly technical but it is very important that you understand. There is a so called log, logarithmic, linear relationship between these two sets of hormones. Put simply what that means is that a very small change *here* produces a very large change *here*. So endocrinologists use the pituitary as a very sensitive indicator of how much thyroid hormone there is in the circulation because of this amplification that I have mentioned. So tiny perturbations *here* are reflected in really quite large changes *here*.

Q While you are there, before I ask you to sit down again. If one inserts into the body T4 and T3 by way of medication does that have the same effect on the pituitary gland as if it were being produced by the thyroid?
A Precisely because these are the same chemicals. Therefore, a small amount will simply cause a reduction in TSH and the thyroid hormone will stop making its own thyroid hormone but very large amounts of T3, T4 taken by mouth will, of course,

suppress the TSH just as disease would.

Q Thank you, take your seat. That is one of the functions of the pituitary gland. I will ask you about the others because they may be relevant, I think, later on in your evidence. What else does the pituitary produce?
A The pituitary might be likened to be the master regulator of most of the endocrine tissues in the body. Not all but most. It makes a number of crucial hormones. I have mentioned TSH. It also makes a hormone called ACTH. Do you want me to give the full name?

Q Yes.
A Adrenocorticotrophic hormone. This is crucial as it stimulates the adrenal glands, two small glands that lie above the kidney, to make a hormone called cortisol. Cortisol is essential in the body's response to stress. Without ACTH or without cortisol a patient will become seriously ill and die.

Q What else does the pituitary produce?
A It produces luteinizing hormone or LH and follicle stimulating hormone or FSH and these are responsible for oestrogen production for women for the ovaries; testosterone production in men for the testes; and for egg and sperm production in the respective sexes. It also makes growth hormone which is obviously essential for growth in children, but has recently in the last decade been found to have significant effects in preserving well-being in adults. It makes a further hormone called prolactin which is responsible for milk production.

Q I want to turn to the issue of hypo and hyper-thyroidism. Can we deal with hypothyroidism first of all? We are halfway down page 4 of your report where you mention autoimmunity as one of the causes. Help us with autoimmunity.
A Autoimmunity is a common cause of disease and thyroid disease is the commonest, longest established type of autoimmune disease. The body's immune system is normally there to defend us against viruses and bacteria through a number of different mechanisms. Occasionally the body makes a mistake, instead of recognising the body as self, it thinks it is foreign and therefore attacks it and so in the same type of mechanisms that we use to get rid of viruses and bacteria are deployed against the body and disease results.

Q For instance, yesterday we heard evidence from Dr Stewart that he had done an autoimmune test looking to see whether there was any sign of autoimmune disease.
A The first markers ever discovered of autoimmunity in any disease were in the thyroid. The discovery of thyroid antibodies was 51 years ago, so these are well-established tests to determine the presence of inflammation within the thyroid gland which can progress to cause thyroid disease, but not inevitably.

Q What is second main cause of hypothyroidism?
A Round one per cent of people develop an overactive thyroid gland which itself can be autoimmune and in the course of treating an overactive thyroid, the patient may have to have their thyroid gland damaged either by radioactive iodine or by surgery because an overactive thyroid is a very dangerous condition and therefore to swap and overactive thyroid from underactive thyroid is regarded as very reasonable.

A Q I want to see if you can help us, please, between the difference between primary and secondary hypothyroidism and you deal with this again at the bottom of page 4.
A A primary disease is that that affects the target organ, so in this case a disease affecting the thyroid. So you can see that if your thyroid gland is damaged by this autoimmune process that I have mentioned, you will end up with no thyroid hormone.

B When endocrinologists talk about secondary types of disease, in this case secondary hypothyroidism, we are talking about a defect at the pituitary level. So imagine one common cause might be a very large pituitary tumour which presses on the cells and stops TSH secretion, that will also have the effect of reducing thyroid hormone levels. Here the thyroid gland is perfectly healthy; it is the pituitary that is at fault. So a primary disease is where there is an effect at the peripheral level; secondary is where it is at the pituitary level.

C Q Thank you. If a pituitary is damaged presumably or presumably by disease and cannot therefore make TSH, does that mean that the thyroid itself will stop producing T4 and T3 because it is not receiving the TSH?
A Indeed, there is nothing wrong with the thyroid gland, but it is not receiving the necessary signal and therefore the hormone levels decline and indeed this is good evidence that we have the TSH is the essential regulator of thyroid function.

D Q You say this in your report:

> "Although uncommon, such *secondary* hypothyroidism is important as the normal blood test used to test for the presence of primary hypothyroidism (namely the TSH level) can be misleading."

Now why?
E A *(Demonstrated on chart)* Well very simply, as I have said, we rely on this feedback loop where we have got very common primary thyroid diseases because if you remember if you remove this arrow *here*, if the thyroid gland fails, T4 levels decline and that leads to this large increase in TSH. I have mentioned this relationship by tiny changes *here* they are reflected by very large changes *here*. So we use this as a very good tool to mark primary thyroid disease, but very rarely, as I have mentioned, you can have pituitary disease in which case there is no TSH signal. The TSH levels there will be
F misleading; they are not elevated in this condition.

Q Would you still get TSH produced?
A That is very variable. Essentially it can be produced, but it is not functional TSH and you will pick up those cases by looking at the T4 levels.

G Q What would you expect to see?
A You would expect to see a low or normal TSH and a low 3/T4.

Q That should be a signal, should it, for pituitary disease?
A That would be an absolutely classic sign that the patient needs to be investigated for pituitary disease, but there will usually be other features of pituitary disease. These
H people will also not be making the myriad of other hormones that I have mentioned.

Q Which can also be tested for?

A Exactly and present with symptoms and signs.

Q Let us turn to symptoms and signs. First of all, what is the difference between them?
A A symptom is something that the patient complains of; a sign is a feature that a doctor usually elicits during examination.

B Q So an example might be that a patient says, "I'm always hot, doctor."
A The doctor might feel sweaty palms, might take a temperature and find it elevated.

Q Let us deal, please, with the symptoms of hypothyroidism and turning to paragraph 5 of your report. We have heard a great deal really already in the evidence about certainly what patients consider to be their signs of hypothyroidism and you list some of them here. You say: "Common complaints include fatigue and lethargy, cold sensitivity," so the
C patient says, 'I always feel cold, doctor'.

> "Dry skin and lifeless hair, impaired concentration and memory, increased weight with poor appetite and constipation."

You mention,

D

> "A hoarse voice, tingling of the hands, heavy and, later, absent periods, deafness and joint aches."

You mention that:

> "In childhood there may be delayed development and in the adolescent precocious puberty. The elderly may develop 'myxoedema madness' or
E depression."

Myxoedema madness is?
A It is the colloquial term for the psychosis, the altered perception of reality that these people can sometimes have.

F Q You say:

> "In rare cases coma can occur, resulting in death if left untreated. Signs include slow movements, 'Myxoedema facies'."

A Facies.

G Q

> "Facies' in which the face looks puffy due to the accumulation of subcutaneous fluid, cool dry skin, slow pulse rate, thinning of the hair including the eyebrows, slow tendon reflex relaxation time, slow pulse rate and hoarse voice."

You then mention the possibility of a goitre. Why does a goitre form?
A A goitre forms largely due to the accumulation of the white cells which are
H mounting the autoimmune process. These are the things that defend us against viruses and bacteria, but in an autoimmune process the white cells accumulate at the site of injury and the thyroid gland is replaced by white cells in hypothyroidism caused by

autoimmunity. There are rarer causes of hypothyroidism where again a goitre can occur due to excessive TSH stimulation of the gland trying to get it to work. So it grows even though it is not functioning.

Q A goitre may be seen or presumably it may be simply palpable?
A Exactly.

Q You say that:

> "It is important to emphasise that nowadays patients often are diagnosed at an early stage of disease, due to increased awareness and improved biochemical testing."

Again we heard, I think it was from Dr Stewart yesterday, about that that one does not often see overt signs of hypothyroidism and I want to ask you about that. What has changed in the years, as it were, since the blood tests have been discovered?
A Well improved blood testing has made the diagnosis far easier and therefore one can apply blood tests and identify this at an earlier time. I think there is increased awareness as well: increased awareness by the public who may be coming forward and asking for thyroid function testing; increased awareness by the GPs; and very recently there has been an initiative by the government to increase thyroid screening at the general practice level. So even if this was not happening in every general practice, it now is. There is remuneration for conducting thyroid function testing.

Q How effective and accurate are modern blood tests?
A I think it might help the Panel if I gave an analogy. Clinical biochemistry is also called chemical pathology. It is a branch of pathology and if you went to see a doctor with a breast lump and the doctor simply said, "You have got signs and symptoms of breast cancer and I am going to remove your breast," without a histopathology diagnosis I think that doctor would be clearly irresponsible. It is precisely the same with blood tests as far as endocrinologists are concerned. These are as precise in terms of making an endocrinological diagnosis as a tissue sample is to make a histopathological diagnosis.

Q At the bottom of page 5 you are really dealing with this same area. You say:

> "In addition, none of the symptoms or signs just listed is sufficiently sensitive or specific for a diagnosis of hypothyroidism, even when combined together."

Now I expect that you and Dr Skinner are going to depart at this stage, but help us, why do you say that?
A I think it is well recognised through many studies, but perhaps the best I can quote is the one that I have mentioned here, which is a paper which was designed to produce a very detailed scoring system. So this was not just an assembly of features that were taken at random through a history, this was a carefully constructed questionnaire of symptoms, the conclusion of this, which was applied to a large group of patients, was as follows ---

Q Is this appended to your report?
A It is not. It is the reference I mention in my report, Journal of Clinical Endocrinology and Metabolism. You will see that at the foot of page 5. If I could simply

read out the conclusion of that to back up my statement:

> "Faced with the variability of the clinical findings in overt and subclinical hypothyroidism, we cannot recommend the use of the new clinical score for the purpose of establishing the diagnosis of hypothyroidism." *(Not provided)*

So here is a group who have assembled a very detailed score, not simply taking a view overall of what the patient was like, but have put scoring numbers to the different symptoms and even applying that degree of precision, scores were inadequate in making the diagnosis.

Q Staying with that for the moment, I think you deal with this at the bottom of page 5 where you say this:

"It turned out that 6% of health individuals with normal thyroid function had clinical scores which were in the frankly hypothyroid range."

Does that mean that they had a number of those signs and symptoms?
A Precisely. As I think we have heard from several of the general practitioners but I will reiterate, the signs and symptoms of hypothyroidism are non-specific and occur in a large number of other conditions. It is a fact that many people do not feel completely well even when completely healthy and these are the scores that people were giving that simply tells us that there is a lot of perceived ill health in the general population.

Q 23% had scores in an intermediate range. You say this:

"On the other hand, only 62% of all patients with clear-cut overt hypothyroidism…"

When you talk about clear-cut overt hypothyroidism, does that mean on the basis of their blood tests?
A Overt hypothyroidism is a precise endocrinological term. It means that the TSH is elevated and the free T4 levels are low, below the reference range.

Q "…frankly, hypothyroid clinical scores."
A What this tells us is that over a third of patients who, despite unequivocally abnormal biochemistry did not have the highest scores in this system.

Q "4% had scores that did not suggest hypothyroidism at all." In other words, presumably, no signs or symptoms?
A Exactly.

Q "The remainder 34% had scores that were in the intermediate range", so presumably some signs and symptoms?
A Exactly, showing how imprecise signs and symptoms are.

Q Let us turn in a moment to the accurate diagnosis of hypothyroidism but I want to deal, please, with paragraph 6 of your report and the treatment of hypothyroidism. We have heard a lot, of course, about thyroxine. That is also known I think, is it, as Levothyroxine?
A Yes.

Q Is that a current standard thyroid replacement treatment?
A It is.

Q That is recommended, I think, in the BNF?
A It is.

Q It can be had free, can it, on the NHS?
A Yes.

Q You talk about a half life of seven days and this, under the heading of Thyroxine, we are talking about T4, yes?
A Yes.

Q You talk about a half life of seven days. Can you help us with what a half life is, please?
A This means that if one took a tablet of Thyroxine and measured it in the circulation, half of it would still be in the circulation seven days after ingesting that tablet, and another seven days later a quarter of it would be there and so on.

Q You say it is readily converted into T3 by the process that in fact you have already described to us. You deal also I think later in your report with armour thyroid. Can we just deal briefly with that now? Armour thyroid I do not think is available in this country?
A No, it is not within the British National Formulary. It can be imported.

Q It is normally imported from where? The US?
A America.

Q Right. We have heard that it is a so-called natural product in that, is it normally from pigs?
A Yes.

THE CHAIRMAN: Mr Kark, are we on page 10 now?

MR KARK: Yes. This is 6.7. I am trying at the moment just to give a thumbnail picture and then we will come back to a more detailed examination.

Q It is desiccated thyroid extract from pigs?
A Yes.

Q Is it used in the USA?
A I think it is.

Q Again, a thumbnail sketch, why is it not normally used in this country?
A The concerns have been that, firstly - and I think this was perhaps a problem earlier – that obviously being derived from a natural source, a pig, levels of thyroid hormone within the pig thyroid gland may fluctuate due to variation in the food stuffs the pigs have been fed with etc, and there are details which have been reported which are batch-to-batch variation between the preparations, so some preparations may have slightly more thyroid hormone, some may have less.

Q You said that was a problem earlier. Is that a problem still?
A I do not think that is so much of a problem now. I think that the products are standardised and in any case one can use thyroid hormone testing, provided one uses blood tests one can titrate according to batch.

I think the bigger problem for endocrinologists – and again I am afraid this is a little detailed – is that the normal range of T4 to T3 – and here we are talking about a molar ratio, I do not want you to get concerned about the 80% I just mentioned – the normal ratio between T4 and T3 is 14:1 in the human thyroid gland, so 14 parts of Thyroxine to one part of T3.

In armour you will see I have mentioned here, towards the bottom of 6.7, the amounts and you will see that the ratio is close to four parts or five parts of T4 to one part of T3, so to summarise, there is proportionately more T3 in armour thyroid extract than in the human thyroid gland and that is pretty simple. Thyroid from pigs contains more T3 than human thyroid glands and therefore when one gives this preparation one is giving really quite large doses of T3.

Q I want to come back, please, to paragraph 6.2 and ask you for your help about the goal of treatment with Thyroxine. You say:

"The goal of treatment in primary hypothyroidism"

- so in other words hypothyroidism which emanates from problems with the thyroid gland directly, yes?
A Yes.

Q

"…is to normalise the blood TSH level."

First of all we are going to hear about such differences as there are between medical practice in the US and in the UK, but first of all as an objective goal, is that recognised to be the goal in both Britain and the US?
A Yes.

Q You say:

"The blood test is successful in establishing the correct dosage of Thyroxine because there is the feedback loop"

and you have described already how that works. You say:

"Between the thyroid hormone in the blood and the pituitary, it is such that when the thyroid hormones"

- meaning T4?
A And T3.

Q And T3:

"… are low, TSH levels rise. Conversely when the hormone levels are high the TSH levels fall. The pituitary is very sensitive to changes in circulating thyroid hormone levels and the amount of TSH it secretes is therefore taken as a yardstick to measure how much thyroid hormone the whole body is exposed to."

I asked you earlier about the regularities of secretion of the thyroid gland at T3 and T4. You have described how the feedback look works with the pituitary gland, but in a normal, healthy individual, is the TSH produced at a regular rate throughout the day or does it fluctuate?

A There is a slight rise in TSH at midnight and that, since we never test TSH at midnight, is irrelevant. The National Academy of Clinical Biochemistry in America, which has produced the most extensive guidelines on laboratory testing for thyroid disease and which is quoted in my report later, has stated unequivocally that there is no need to take into account this diurnal variation provided testing is conducted during daylight hours.

Q You deal with a consensus statemtn published eleven years ago now stating that, at the bottom of page 6:

> "The correct dose was one which relieved symptoms and would in most cases result in a normal or raised T4, a normal T3 and a normal or below normal"
>
> - meaning below the reference range –
>
> "TSH."

Has medical practice moved on since then?

A As I mention exactly over the page, practice has developed since this publication and I think most endocrinologists now are very cautious about suppressing the TSH below the reference range

Q You deal with the reasons for that. Can you just help the Panel, please? You say:

> "This is because it is known that prolonged periods of over treatment with thyroid hormone associated with a reduction of TSH levels below the reference range increases the risks of developing atrial fibrillation."

Is that the same as a pounding heart?

A No, it is a specific type of pounding heart where the heart beats in an irregular fashion and it is particularly dangerous because it can be associated with a risk of stroke.

Q Also you mention here bone thinning. What is the evidence behind that?

A The evidence is summarised, as I have mentioned, in the JAMA article. This is the Journal of the American Medical Association and just to give you some idea of the background to that report, the American Thyroid Association, the Endocrin Society of America and the American Association of Clinical Endocrinologists, got together a group of experts who were not just endocrinologists but experts in public health medicine and epidemiology, to review 195 separate publications on thyroid disease and to produce a consensus statement.

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If I can just summarise from their table in this publication which I have mentioned here – this is the JAMA article – there are two types of suppression of TSH. So the TSH might lie *(witness demonstrated on chart).* We have heard that the lower limit of the reference range is 0.4, so 0.4 to 0.1 or less than 0.1. They classified these into two groups, so this was just a little suppressed and this was very suppressed TSH.

B

On the side *here* where the TSH is just a little suppressed their summary of that evidence was that there was insufficient evidence to conclude there was a risk of atrial fibrillation or cardiac dysfunction and no evidence for reduced bone density. On *this* side there was good evidence of an increased risk of atrial fibrillation, fair evidence of cardiac dysfunction and fair evidence of reduced bone mineral density.

Q Just staying with those figures for the moment, the figures on the left, 0.4 to 0.1?

C

A Yes.

Q Are you saying it is only when you go below 0.1 on the TSH that there is then evidence of those potential problems?

A The evidence at this stage was that there was insufficient evidence to say there was a risk here, good evidence or fair evidence here for effects on the heart and the bone when the TSH is very suppressed. However, there are other publications which have emerged

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since which do suggest that the risks may be greater in this area than we imagine and continuing research is necessary.

Q All right. You say at the bottom of the first paragraph on page 7:

"Finding at least 0.5% of the older population may develop mild thyroid overactivity and in them excessive thyroid hormone replacement instituted previously could be sufficient

E

to cause serious thyroid toxicosis."

Does that apply even if they have stopped taking Thyroxine?

A No. The point I am trying to make here is that if one gives thyroid hormone at slightly excessive doses, imagine this situation *here* but one out of 200 of the elderly will develop intrinsically an overactive thyroid gland, that could make the situation worse.

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Q Now why do we not use T4 and T3 levels as a basic monitoring level?

A Are you talking about monitoring treatment?

Q Both treatment and monitoring before treatment. Let us deal with before treatment?

G

A Laboratories have different strategies for thyroid function testing. Some laboratories test only TSH, other laboratories offer TSH and free T4 together. The laboratories that only offer TSH in initial testing do so simply because of economy. Since the vast majority of have primary hypothyroidism that is what one is primarily trying to pick up and that will always be marked by an elevated TSH. You can then go on and do a free T4 as necessary if the TSH is elevated. Of course, that strategy would miss rare patients with secondary hypothyroidism. Therefore, other laboratories preferring not to

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do that offer both tests but at twice the cost.

Q What about the laboratories that do offer the T3 and the T4? We are looking at

people before they have received any medication, before they are on thyroxine. Is T3 and T4 in those circumstances a reasonably accurate test or not?
A I do not know of a laboratory which routinely offers free T3, so let us stick with free T4. Free T4 assays are as reliable as TSH. Let me be clear on this, there are a number of factors which will interfere with these assays which are well recognised by endocrinologists and have to be taken into account. Provided one does that then the assays are equally reliable.

Q What about once the patient is taking thyroxine?
A If I can just continue on the last point. One of the reasons for not relying on the free T4 is that in the earliest stages of thyroid failure, so called sub-clinical hypothyroidism, the TSH levels go up but the free T4 levels remain normal. In that situation you have a partially damaged thyroid gland. If I go back (*The witness demonstrated on the* chart) If there is slight damage to the thyroid gland the TSH levels will rise in order to stimulate the gland.

Q In order to compensate?
A Exactly and do so in the majority of patients. So they end up maintaining free T4 which is normal at the expense of the high TSH which is stimulating the gland and that is why you can sometimes have the situation of an elevated TSH but a normal free T4.

Q I think we do see that in some these cases. If you have an elevated TSH but a normal T4 within the reference range, is that a signal - it is not diagnostic presumably - but is that a signal of thyroid problems?
A It is. It would certainly need follow up.

Q I was going to come on, if we have finished that area, to dealing with using T3 and T4 as a test once the patient is on thyroxine?
A The problem with using free T4 measurements if a patient is taking thyroxine is that the level fluctuate after taking thyroxine treatment. Therefore, within the few hours after ingestion there can be a ten or fifteen per cent level difference in level compared to twelve to twenty four hours after ingestion. The second problem which is frequently encountered by endocrinologists is that the patients may not adhere to their treatment very strictly and may remember to take a tablet before a blood test which will give them normal T4 levels and might have omitted their tablets over the preceding weeks. Because of the sensitivity of the pituitary that can be identified by raised TSH but a normal free T4. Therefore, TSH, because it is measuring a response of the body, in this case the pituitary gland, it is by far the best measure of the nature and degree of thyroid hormone replacement.

Q You spoke earlier about the goal of treatment, which was both in the US and the UK, to ensure that there was sufficient T4 but that the TSH was kept or brought within certain levels. Is it fair to say that the goal of treatment, the goalposts are slightly different in the two countries?
A Absolutely and this is something you may wish to expand on later about the differences in assays and the way that things have evolved over time but there is no doubt that when I qualified in 1977 the upper reference range for TSH was eight to ten. So assays have improved and that is one reason for the changes and the constant revision of guidelines over time. The other development, I suppose, has been further research which has suggested that we might be better off trying to treat people to get their TSH within the

lower half of the reference range, that was a suggestion that came out of the National Academy of Clinical Biochemistry.

However, even more recent research has shown that adjusting the thyroxine level has no objective benefit. So this is still an area that requires further investigation. It seems prudent to bring the TSH down into the reference range. If the patient feels well that is fine, if the patient still does not feel well to then give slightly more thyroxine to bring to the TSH down to within the lower half of the reference range below a value of 2.5 or 2. Then one could be absolutely confident that one knows the patient is getting their maximum amount of thyroxine which is safe. The reason for this, to press the point a little bit, is that one does not know where that patient's TSH was when she was healthy. For instance, the patient may have had a TSH of 3.5 which is certainly normal and does not require treatment in health but when her TSH goes up to 20 and you are confronted with it for the first time with a blood test then you do not know where to bring her TSH down to. Therefore it is prudent to go to a value below 2 or 2.5 in that individual depending on which guidelines you read. The majority of people in my experience do very well just by bringing their TSH to within the reference range.

Q The reference range, I just want you to deal with that. You say half way down or two-thirds of the way down page 7:

> "The US National Academy of Clinical Biochemistry has indicated that ideal treatment may consist of maintaining the TSH level in the lower half of the reference range, that is between 0.5 to 2 or 2.5."

Is that standard across the USA now or not?
A It is in these recommendations and in other recommendations.

Q At the bottom of the page you say this:

> "The most recent UK guidelines published by the Association of Clinical Biochemists and the British Thyroid Association states simply: the aim of treatment should be to restore and maintain the TSH within the reference range."

For the purposes of treatment in the UK what is regarded as the reference range for treatment; the goal?
A As it says here, the UK guidelines which were produced by a group of endocrinologists and biochemists and then there was consultation within the two societies, so all members of the societies were invited to consult. So these have met the scrutiny of every member of these two societies before their publication. It is simply to maintain TSH within the reference range, that is whatever the local laboratory reference range is.

Q Can you take up the patient notes and turn to tab 2, page 16. I have taken this relatively at random. This is in relation to Patient A, this was the first blood test that was received back after Dr Skinner's first meeting with Patient A and it shows that the T4 for Patient A was 12.2. So that is measuring the free T4, is it?
A Yes.

Q The TSH was 1.4 and also can you help us with the measurements: "T4 - 12.2 pmol/L"?
A Picamols per litre.

Q I am not going to ask you for an explanation of picamols.
A Thank you.

Q I expect we will be here for a long time if I did. TSH equals 1.4?
A Milliunits per litre.

Q You understandably winced each time I referred to microunits but it is milliunits per litre. Then we can see the reference range for this laboratory down on the left-hand side, T4 reference range between 9.0 and 20.0. TSH reference range - 0.5 to 5.5 . We can see elsewhere that sometimes those reference ranges differ, not by a huge amount but sometimes they differ. Help us, please, how do laboratories get these reference ranges?
A Again it might be helpful if I use *this*. (*The witness demonstrated on the chart*) Let us say *this* is the TSH level. *This* is the percentage of the population. So one would typically take 300 or 400 healthy individuals and one would measure their TSH and you will get a curve which looks like *this*. It is what is called a skewed curve in that there are slightly more people lying in *this* tail than in *this* tail but it is a similar curve to the distribution of heights in the general population. One so called normalises this curve by a log transformation, I will not go into the technical details, but one can make that curve look like the normal heights in the population by log transformation. One then says that the mean is *here* and there is a statistical figure called the standard deviation which measures where the population is. One standard deviation on either side of the mean contains 66 per cent of healthy individuals. Two standard deviations on either side contain 95 per cent of healthy individuals. Those are the limits. So one laboratory might have 0.4 to 5 as its TSH.

The important thing to emphasise, I think, is the 2.5 per cent of the healthy population will lie outside of those reference ranges. If one measured them again one might find that they just pop back in *there*, or it may be that their TSH values are really slightly above or slightly below the reference range. I think that is important because if we look at this cut off it is actually constrained. It is meant to pick up only 95 per cent of the healthy population, not 100 per cent of the healthy population. We know that some healthy people lie on either side.

Then there is the question of why the range might be different in a different laboratory. This is very simple; different assays are used. An analogy I might give you is that if you go to into three different high street shops to by a T-shirt in a medium size you will get a medium size T-shirt which will vary in size slightly. If you went into the same shop to buy a medium size T-shirt it would always be the same size, it would not vary from one day to the next in that shop. So as long as you are using one particular assay and are used to the reference range then there is no need to worry about perturbations.

The last thing to emphasise is that all UK laboratories are subject to external quality assurance scheme, a national external quality assurance scheme. This distributes on a monthly basis samples for every anolite, every chemical that that laboratory measures. It works out whether that laboratory is able to meet a particular standard and it will deliberately give the laboratory a slightly high, a normal and a slightly low TSH, or

whatever it is that they measuring and will measure that laboratory's performance then report back. So each laboratory in the UK measures that sample and can say whether it is abnormal or not.

So the reference range differences are really not helpful to the discussion. As long as the laboratory has established a reference range on one particular machine using one particular assay kit that is fine. That is then validated by the external quality assurance scheme.

Q At paragraph 6.4 of your report you deal with optimisation of the treatment, which is the area that we are still dealing with. Page 8. You said:

> "The precision with which TSH levels must be adjusted is therefore a controversial area."

Before we go on I want to underline the word *treatment*. This is not the same as what you are looking for before you start treatment?
A That is true.

Q So this is once you have diagnosed hypothyroidism what you are aiming to achieve. Is that right?
A Yes.

Q

> "In my clinical practice I would attempt to bring TSH levels below 2.5 but above the lower limit of the reference range when faced with a patient who has known hypothyroidism and who still has symptoms despite taking thyroxine at a dose sufficient to merely normalise the TSH. It is important to stress this is not the same as treating a healthy individual whose TSH levels are in the upper half of the reference range with a view to reducing levels to the lower half. In the case of a hypothyroid patient the doctor can never know what the TSH level was in health."

You have explained that already which is why you have to have this goal, as it were, that you are aiming towards because you did not know what the patient was before you started?
A Exactly. Otherwise one would have to regard precisely 50 per cent of the population as having thyroid disease which is clearly nonsensical because precisely 50 per cent of the population will lie above the median and 50 per cent will lie below and that median will be around about 2.5.

Q

> "Therefore it is possible to reason that the doctor should give the hypothyroid patient the benefit of the doubt if the symptoms persist and tailor the TSH dose to below 2.5 but above the lower end of the reference range"?

A Yes.

Q So if you are dealing with a patient who on the TSH is within the reference range when they are being treated but is still having or exhibiting the symptoms and signs of hypothyroidism would you then be willing to increase the dose?
A Well, one caveat before I answer your question and that is, just to go back to my last point, if the reference range in a different laboratory to the one I use was 0.4 to 3 then we would be talking about a TSH of 1.5. So again that level of treatment depends on your own laboratory, which is why we have the figures of 2.52 and so on. One has to use local knowledge.

I think I have laid down what I would do and that is to bring the TSH down to the lower half of the reference range, which is below 2.5 in my laboratory's case; treat the patent for three months which is the maximum it takes for all symptoms to then disappear if they are due to thyroid hormone deficiency. If the patient still had symptoms at the end of that and the TSH was within the lower half of the reference range I would then conclude that the symptoms have an alternative cause.

Q I asked you a great deal about your background, your qualifications. I did not ask you about your own clinical practice and seeing the patients. Do you still see patients?
A Yes, I have one thyroid clinic a week; one general endocrinology clinic a week, whish is largely thyroid patients; one thyroid cancer clinic a month and I take a lot of consultations from colleagues over the phone who seek advice on a weekly basis.

Q So when you talk about what you would do with a patient this is something you do in practice?
A Every week.

Q You deal with the issue of an impaired feeling of health or impaired health at the bottom of page 8 where you say this under the heading:

> "Well being in patients receiving thyroxine.
>
> A recent study of well being of hypothyroid patients on thyroxine replacement is relevant: at first sight, it seems to contradict the view that thyroxine is adequate treatment for hypothyroidism. This study showed that even when TSH levels are within the reference range, a feeling of impaired health, as assessed by a General Health Questionnaire, occurs in 26 % more of the patients than in controls."

You say:

> "There are several possible explanations for this result. Firstly, patients may require T3 replacement as well as T4."

In what circumstances would that arise?
A The reason I wrote this in my report to be clear is that this led onto a discussion of T3 and T4 that this type of information which this reference alludes to of the feeling of ill health that some people have on Thyroxine was one reason why these trials of T3 and T4 were first instituted because this was a hypothesis that although, as I have mentioned, 80 per cent of the T3 in the body is derived from T4 made by the thyroid gland or taken as a tablet, would it be possible that the body was incapable of converting the right amount and therefore needed the 20 per cent of T3 that was coming from the thyroid gland.

Q What is the answer to that? I mean, are there circumstances where in fact the body is incapable of converting T4 to T3?
A No – well, there are certain drugs and very rare conditions in which case there is a deficiency of these enzymes and in all of those cases that would be readily recognised by abnormalities in the blood chemistry. Indeed, we were confronted by a patient with bizarre biochemistry about five years ago that led to the discovery of an entirely new syndrome where there was a problem with DI ordination. So problems with DI ordination would be figured by really odd blood test results, but in answer to your other question, there have been two meta-analyses of all of the trials of T3 and T4 and meta-analysis, I am coming to it ---

Q Thank you.
A A meta-analysis is where a group of people objectively look at all of the data that have so far accumulated and try and produce an overall feeling, an overall summary of where that treatment has led. In other words, the more patients you include in any trial, the more reliable your results. So any one trial will give you one result or another, but if you take of all of the trials for a particular drug and summate them, you have clearly got the entire population that has been treated and you will get a far more precise answer about the outcome of treatment.

There have been two meta-analyses, but the latest one which was published in 2006 concludes as follows: "Given the conclusive evidence, monotherapy," that is single therapy with T4, "should remain the standard treatment for hypothyroidism."

It goes on to state:

> "It is doubtful whether further trials evaluating combination therapy are needed because the chances that accumulated evidence will change are low." *(not provided)*

In other words, the conclusion in this trial is we have already done so many trials on this, eleven, that there is no overall benefit. Nor if we kept doing trials would we show a benefit. So I think that is pretty definitive.

Q Are you saying that there is almost never a reason to treat a patient directly with T3?
A Yes, there are rare situations where I would use T3. In patients with thyroid cancer, we use T3 temporarily to allow us to withdraw treatment. This is really perhaps more detailed than you need, but there are particular reasons why we would treat thyroid cancer patients temporarily in order to allow treatment with radioactive iodine.

The other situation where I have given it reluctantly has been to patients who have refused to take Thyroxine when they have had classical overt hypothyroidism. So no doubt about the diagnosis, but for personal reasons have read information on the Internet or whatever and have determined that they will not take Thyroxine in which case T3 is a less than optimal substitute and it is better to have some thyroid hormone rather than none.

In each of those patients I would undertake a bone mineral density, I would repeat the bone mineral density and I would counsel the patients about the risk of atrial fibrillation

and I would write that in the notes.

Q Now why particularly is that relevant to T3?
A Because T3 does not have the smooth half-life of T4. I have mentioned this very prolonged half-life. T3 has a half-life of a day and that means the levels rise very high and then fall very low. Current tablet size of T3 is a 20 microgram size tablet. If you took someone's thyroid gland away, they might need 40 to 60 micrograms of T3 a day if you gave them no T4 at all. So if you were only going to treat with T3, that is how much you would need and you get very big peaks of T3 in doing so. Inevitably, at some point during the day when you give a 20 microgram size tablet you will have a level which is slightly above the reference range or quite high above the reference range depending on the weight of the individual and so ---

Q Why is that specifically relevant to atrial fibrillation and to bone thinning?
A Well this is theoretical, we have no direct evidence for it, but we do have the accumulated evidence that when you have a suppressed TSH that is harmful for the heart and I have summarised that. If you continually give spikes of T3 through the day, that will inevitably be having a direct effect on the tissues and, indeed, in these trials that I have mentioned in the eleven trials that were done, bone marker studies were done. Bone markers are measurements of the chemicals in the blood that come out of the bones and measure bone turnover. In two studies in which these bone markers were looked at when they gave T3 as well as T4 bone markers showed increased bone turnover within a matter of weeks of treatment. In the third trial, one patient developed atrial fibrillation while taking T3 and had to be withdrawn.

Q So is that directly relevant to the evidence you gave of Armour Thyroid extract?
A As I mentioned, this contains an abnormal level of T3 for the human equivalent. It is a ratio of four to five to one instead of 14 to one, T4 to T3.

Q I want to turn to page 11 of your report, paragraph 7. What I was hoping to do (I think we will be able to do it) is to deal with the general part, as it were, of discussions which I appreciate is quite dense material for anybody. I will turn after the break to his evidence about each patient. If the Panel are prepared to keep going, as it were, for ten minutes or so, but I am in your hands.

THE CHAIRMAN: You are contemplating a break at about what, eleven or thereabouts?

MR KARK: At about eleven.

THE CHAIRMAN: Yes, that is fine.

MR KARK: *(To the witness)* I wanted to turn to your comments that you make about thyroid hormone treatment in euthyroid individuals. First of all, euthyroid means?
A Normal thyroid function.

Q Normal thyroid function meaning on the basis of blood tests?
A Yes.

Q You say this:

A

> "At the heart of the cases referred to in Section 8 is the belief of Dr Skinner that thyroid function tests are unreliable in the diagnosis of thyroid failure. (In his words …"

As we have read I think twice at least:

B

> "'Good servants but bad masters.' Dr Skinner believes that people with symptoms of hypothyroidism but normal biochemical tests of thyroid function (such individuals are called euthyroid by endocrinologists) should be treated with thyroid hormone."

And you say: "There is no scientific basis for this belief."

C

Can we just come back to that? I think you deal with it again later. In fact, could we just go straight to TSH reference range to 7.2 and I am then going to come back, as it were, to those comments?

You say at 7.2: "[A] pertinent aspect in this discussion is the definition of the reference range for TSH." You talk about the laboratory tests and then you talk about:

D

> "In simple terms this means that 95 % of normal values will lie within the reference range, 2.5 % will lie below it and 2.5 % above it. This is why the term reference range is preferred to 'normally range'."

Now the reference range that we are now talking about is not the goal, as it were, of treatment that we were talking about earlier?

E

A No, as I have said, the recommendations most recently made by the BTA and the clinical biochemists is that one should simply bring the TSH to within the reference range and I have indicated that personally (and a number of other endocrinologists would do the same) confronted with a patient who continued to have symptoms despite bringing the TSH down to three, I would bring it down further still.

F

Q Let us deal with a patient who walks into your surgery, he is not on any thyroid treatment at all and you take blood tests and you discover that he is at the top end of the TSH. When do you decide you are going to start treating a patient with T4?

A I would only treat a patient whose TSH was above the reference range. If there was any doubt and if the patient was particularly concerned, I would repeat the TSH three months later because TSH can be affected by a number of factors, as I have already mentioned. A recent severe illness can affect the TSH and can cause an elevation or a suppression, so that if there is any doubt I would repeat the TSH and I would also measure thyroid antibodies because if those are positive, then I would certainly want to check that TSH more regularly, and if it became elevated and the patient had symptoms I would discuss with the patient whether they wanted to have treatment and if they did I would institute a three month trial of treatment and if they felt better I would continue with it.

G

H

Q Just using your chart for the moment, you have got a long tail there. I think it is described in your report as a long tail on the right-hand side. So those at the upper end of the reference range were still within in it. If a patient comes into you with signs and symptoms and they are part of the long tail, as it were, what do you do?

A *(Demonstrated on chart)* This is where there is some discussion and controversy as I have mentioned. We know from other trials if you take the group of patients who are going to become hypothyroid in the future, so they have been followed, you take a group of healthy individuals, you follow them for 20 years, some of them will develop thyroid disease and you will see *that* sort of thing happen. So you have got a group of people who go on to develop thyroid disease, their TSHs 20 years before will look a little like *that.* Some of them will have TSHs within the reference range and so we know that in this tail there are a group of people who are heading towards thyroid disease in the future in 20 years' time. Nobody yet knows whether if you went back 20 years in a time capsule and asked those patients would they have any symptoms, but all of the evidence that we have so far is that that is not the case that these people do not have symptoms, but this is where, if you like, some of the recent controversy has stemmed from. This survey that showed that an initial TSH above two was a risk factor for thyroid disease in the future. That is totally different saying that those patients have symptoms.

Q Do you treat those patients?
A No.

Q Do you treat those patients if they have got symptoms and if not, what are you looking for? In other words, what is the alternative diagnosis?
A Well there are many alternative diagnoses for some of the symptoms that we have heard about already.

Q Can we deal with alternative diagnoses? You have got your list of symptoms and signs and hypothyroidism back in paragraph 5 at page 5. Dr Skinner, I expect, will say that when you have got this list the first thing that you are looking at (I should not be putting words into his mouth) one of the things that he is going to be looking at is hypothyroidism. Yes? Hypothyroidism. Do you agree with that? One of the things you are going to look at.
A I am sorry, Mr Kark, I missed the question.

Q If you have this list of signs and symptoms which you set out in your paragraph 5, the patient comes to you and says, "Look, doctor, I am losing my hair, my eyebrows are thin, I have got tingling hands and a hoarse voice."
A In my experience, you would never get these severe symptoms of hypothyroidism without both an elevated TSH and a low 3T4. I mentioned this distinction between subclinical hypothyroidism and overt hypothyroidism. The overt hypothyroidism is where the TSH is high, the 3/T4 is low. That is also called clinical hypothyroidism because that is when clinical features present. So the biochemistry is unequivocal in patients in my experience who have these symptoms.

Q What are the alternative diagnoses?
A Well a large number depending on the individual symptoms which patients present because very, very few patients have the whole gamut of symptoms and signs I have recorded here. Obviously, as we have heard already, depression would be high on the list of alternative diagnoses.

There are a number of conditions which group together under the heading of functional somatoform symptoms which are exceedingly common. Twenty-five to 35 per cent of outpatient consultations in the UK and in Holland are for patients who have symptoms

which have no reliable current explanation. That is not to say that these people do not have an illness, far from it, it is simply that we do not understand the nature of that illness.

One typical functional somatoform syndrome is chronic fatigue syndrome or ME. I see a lot patients with chronic fatigue syndrome or ME. I have absolutely no doubt that these people are ill. I am equally sure that further research will uncover the cause of what that illness is, but the Royal College of Physicians' definition of chronic fatigue syndrome produced in 1996 states that the diagnosis can only be made by three months or more of chronic fatigue in the exclusion of all other known causes of fatigue. The College of Physicians, therefore, expects that hypothyroidism is excluded by biochemical testing. You cannot make a diagnosis of chronic fatigue syndrome in the presence of hypothyroidism and vice versa.

Q You deal with this going back to where we were before at page 11, halfway down under paragraph 7.1, you say:

> "I have described above in Section 5 how inadequate symptoms are in assessing whether a patient is hypothyroid, even when a sophisticated scoring system is used,"

Which you referred to the research there.

> "Mere clinical history and examination without such formal scoring is likely to be even less precise, and especially so if Dr Skinner adds to his list of possible diagnostic signs one which is new as far as I am aware, namely the perception by the patient that there are grey objects in the peripheral vision. I have never encountered this in patients with hypothyroidism."

Putting that aside for a moment, the basic premise of this is that your stance is that mere clinical history and examination, whether with or without formal scoring, is not a diagnostic tool for hypothyroidism?

A That is right, but I think there is a corollorary to that which is important. Some guidelines are produced which state that the diagnosis can only be made by biochemical testing or clinical assessment. This is not the same as saying that clinical assessment is essential in making a diagnosis. As I mentioned, biochemical testing can be inaccurate in certain settings and one needs the clinical examination in order to interpret the biochemical tests correctly.

Let me give you one simple example amongst many. When a woman is pregnant the TSH level falls normally during the first third of pregnancy. To merely look at the blood test and say the THS was suppressed without taking a history would obviously be foolish in that setting. One needs to know that the patient is pregnant in order to say that that TSH which is low is in fact entirely appropriate for the situation. So that is where clinical examination history taking is essential.

Q You finish that paragraph saying this: "In summary" this is page 12, a third of the way down:

> "In summary, the existing data shows that there is no significant benefit from

thyroid hormone replacement in biochemically euthyroid individuals and there are also good physiology reasons to believe that such treatment is futile."

Why do you say good physiology reasons to believe that such treatment is futile?
A I have already mentioned that the thyroid gland is able to compensate for mild degrees of deficiency by the pituitary secreting TSH. I have mentioned a very large reservoir of T4 which is holding T4 in the circulation. I have mentioned the regulation at the tissue level which allows the right amount of T3 to be made from T4. We know that such patients, as mentioned in this trial, who have symptoms and who have been treated, do not benefit.

Q At the bottom of page 12, please, and we are back to the TSH reference range which you say is crucial. The very bottom two lines of page 12:

"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 5.0."

Can you just help us with that? Are we talking there about the upper end of the reference range?
A Yes. Again, if you bear with me, this is a slightly complicated story but I will try and simplify it. I have mentioned that there are data from 20 year follow-up studies that a TSH above 2 might give an increased risk over 20 years of developing hypothyroidism. Based on that information the NACB, whose guidelines are quoted extensively – that is the National Academy of Clinical Biochemistry – suggested but did not stipulate – suggested – that the TSH upper limit might be 2.5 rather than four or five.

There have subsequently been four studies to test that hypothesis, so the NACB have put forward a postulate that has been tested four times where people have taken individuals to construct their reference range who have no thyroid abnormality whatever.

Instead of just taking 300 people from off the streets, they have taken 300 health individuals who have no family history of thyroid disease, no thyroid antibodies and have had their thyroid glands examined by ultrasound, which is a sensitive way of picking up whether there is any inflammation or tumour or anything else within the thyroid gland.

This is what is called a constrained population. This is a group of people for whom present testing has shown absolutely no evidence of thyroid disease now or likely to develop in the future.

In three out of those four studies that constrained population reference range was virtually the same as the random population that had not been so tested. In the one study that did not show that, the study itself was performed in an area of Germany where there had been an iodine deficiency problem previously, and that is not the case in the UK population. The consensus amongst European thyroidologists quoted in appendix 2 to my report – and I am one of the authors on this paper – is that based on this information there is no need to shorten or narrow the reference range. The TSH reference range based on these three studies in iodine sufficient populations like the UK, show that it does not matter how you choose your reference population, you will get the same TSH reference range.

Q In the US, is the general view of endocrinologists that the range should be lower?
A No, there is a controversy in the United States. Some endocrinologists will argue it should be and I have mentioned the leading protagonists of this – Professor Len Wartofsky. There are many others who would argue it should not. I have given you the evidence that shows from Europe – studies in Denmark and in Germany - which have shown that there is no need within Europe to narrow the reference range.

Let me just add to that, Mr Kark, if I may, that even if one is a protagonist of this narrowing of the reference range, as Len Wartofsky is, the recommendations for treatment are, as I have laid out on page 13 and even the leading protagonists would only recommend Thyroxine replacement if the TSH is above 3 and that is on repeated values above 3, particularly if the patient has thyroid antibodies. None of the patients that we will consider after the break had a TSH above 3.

Q I was just about to ask you exactly that. Even if one took that, even if one were to accept that as the standard, as it were, which is not accepted in the UK as you tell us, even if one were to accept that lower top limit of the reference range as the point at which one would start treatment, none of these patients are above that level?
A I would go further – none of the patients were above 2.5.

Q We have dealt, I think, at 7.3 with secondary hypothyroidism and you have explained that that is not a disease directly, as it were, of a gland, of the thyroid gland, it may be as a result of disease of the pituitary. You say at the bottom of that, just to clarify:

> "Therefore it is unacceptable for a diagnosis of hypothyroidism to be made on the basis of a low free T4 level but normal TSH, since this combination implies the presence of pituitary disease and in this setting endocrinological assessment is mandatory."

That is for the reason that you described earlier because that is a flag, as it were, a signal that there may be something wrong with the pituitary.
A Yes and that is particularly relevant to Patient A.

Q We will turn to Patient a in a moment. You finish this section of your evidence, I think, at 7.4 by saying:

> "In summary I do not believe that there is any reliable scientific support for treating individuals whose thyroid function tests are within the reference range with thyroid hormone."

I am now going to turn to your observations in relation to Dr Skinner's treatment of each of these four patients and I suspect that that would be a good moment. You understand, Professor, that I cannot speak to you and you cannot speak to anybody about your evidence.

THE CHAIRMAN: Thank you, we will break until 11.30

The Panel adjourned for a short time

THE CHAIRMAN: Mr Kark.

MR KARK: Before we launch into Patient A, as it were, just in relation to the flip charts that you have produced, so that we can have reference to them later, have you done two or three?

A Two, I think. Three.

Q Could you turn them back and I will just ask you to mark them, if you would. Could you put at the top right-hand corner of the first one C4, the second one C5 and the third C6.

I want to turn to Patient A and you will need, obviously, the bundle of patient notes. Patient A's bundle of medical notes. If you could go to tab 2 page 9, which is the referral. We heard from Patient A that she was tired all the time and she had been to see a reflexologist who had suggested Dr Skinner. As we can see Dr Cooke therefore wrote a referral and he included in the referral letter the recent blood test reports, one from 2001 which showed that her TSH level was 1.49mU/L and a further TSH on 13 May 2002, TSH level of 1.45, so very similar from one year to the next on her TSH level. When we see the word "serum" TSH level, does that make any difference?

A No. That is the liquid compartment of the blood.

Q So that is the information in terms of blood tests that Dr Skinner had and then over the page of the referral letter, the last two lines:

> "The patient wonders if could be eg auto immune thyroiditis, has had chronic"

is it Epstein Barr –

-

> "viral infection. Ask opinion Dr Skinner who has an interest in this."

If there were concerns about auto immune thyroiditis, what is the test that could have been done?

A Thyroid peroxidase antibody.

Q We then go back to Dr Skinner's note which we have typed up at the beginning. Can I just mention that in the report you will find some of the tab references have been changed. It is simply because Professor Weetman had a much bigger bundle of other documents than you have and we have amended it so that I hope now it should refer to the right tab and the right page number. We have the notes of consultation.

Can we deal, please, with the typewritten version which I think in respect of this patient is fairly full, if not full. We can see that the information that Dr Skinner received was in relation to the three children, that she was complaining that since 1995 she was feeling "knackered, flat and lifeless".

THE CHAIRMAN: I am sorry, Mr Kark, where exactly are you?

MR KARK: Dr Skinner's note, the typed version, tab 2 right at the beginning.

THE CHAIRMAN: Page?

MR KARK: It does not have a page number. It is the typewritten note that we put right at the beginning.

Q

"Complains of feeling knackered, flat and lifeless.

In bed from 10 pm. to 7 am but insomnia, scattered aches and pains, tightness of hands, brain in slow motion, forgets names, side vision hallucinations, asocial and weepy, paraesthesia of hands and feet"

- paraesthesia?
A Tingling.

Q

"No libido, blurred vision, looking through smokescreens through a veil."

I will come back to that.

"History:
Glandular fever, sees Reflexologist---

Examination.
Temperature peripheral, less than 32oC axilla 36.8oC, pulse 56 per minute, voice hoarse, yellowish pallor, loss of outer half of eyebrows, tongue slightly enlarged, eyes slightly bloodshot, skin dry with cracked heels, thyroid palpable (+). Blood pressure 105/60

Generally seems out of things and in a world of her own.

Treatment
Oral B12 1000 micrograms."

Let us just deal, please, with that note. It does not appear as though Dr Skinner had anything like her full medical notes but he may have had the letters that we see in the bundle leading up to the handwritten note at page 12?

MR JENKINS: He did have them and that is why they are included in the notes at tab 2.

MR KARK: Thank you.

MR JENKINS: Those are his records, as it were, what he had.

MR KARK: First of all if this note accurately reflects the examination that Dr Skinner performed what, if anything, do you say about it?
A I do not think it is complete.

Q Why not?
A As I mention in my report, there is no specific social family or drug history which

is taken and checked off and, as I mention, it is difficult to discern whether her past medical history has been checked against the GP record which is at page 9. As we heard from the patient yesterday, she had a significant history of postnatal depression which, looking at this letter again, does not appear in the GP letter and had Dr Skinner taken a full history from this patient and a complete past medical history, he would have been able to record that.

Q Would that have been potentially significant?
A A past history of postnatal depression is a significant marker for the likelihood of developing depression in the future.

Q You say in your report there is no record of any examination of the abdomen or of the respiratory system. Can I just ask you to pause for a moment. A number of the GPs – you were sitting here – were cross-examined by Mr Jenkins, "Did you check the heart, did you check X, Y and Z." What is Dr Skinner's position when he sees each of these four patients? Is he in the same position as the GP or is he in a different position?
A I think Dr Skinner is in a position which is unusual as far as I am concerned. All I can speak about with certainty is my own practice as a consultant endocrinologist and as a consultant physician. I think when a patient seeks a second opinion from a consultant complaining of tiredness which is eluded diagnosis by certainly a GP and in this case I think two other consultants, then I think one has to start again, one has to go through a comprehensive history with all of the detail I have mentioned, one has to undertake a comprehensive examination of each system and then perform the appropriate testing based on one's knowledge of what has gone before. It is only then that one can make a diagnosis and, of course, at the heart of the matter is the fact that this patient did not have thyroid disease because she has two normal TSH levels. The only type of thyroid disease she could have had would have been secondary hypothyroidism and if that had been the case, then a proper history should have been taken to elicit signs that might be features of pituitary disease, for instance.

Q Such as what?
A Such as looking at the visual fields, such as looking at the fundi.

Q One of the notes that he makes is blurred vision; looking through smoke screens; through a veil. What should that have signalled, if anything?
A It is not a symptom that I am familiar with but if the patient spontaneously of that then I would certainly want to look in her fundi and examine her visually fields irrespective of any suspicion of pituitary problem. This is a patient with unexplained visual problems. There are a number of possible causes for constriction of peripheral visual fields. One common cause would be glaucoma but there are other causes such as a pituitary tumour. One would need to do the appropriate testing.

Q You mentioned specifically in your report an examination of the abdomen or of the respiratory system. First of all, why the abdomen?
A There are a number of causes of tiredness which emanate from abdominal disease; one might pick up a lymphoma or a leukaemia by enlargement of the liver or the spleen; one might pick up liver kidney disease; one might pick up kidney disease by enlarged kidneys, etcetera, etcetera.

Q Respiratory system?

A Again, respiratory disease can sometimes present with fatigue. One might have fibrosis of the lungs that might present with crepitations. Pulmonary hypertension might be elicited.

Q You say heart sounds are not recorded. What is the significance of that?
A This is simply again standard medical examination would include examination of the heart to make sure there is not a heart murmur. This patient might have mitral valve disease or aortic valve disease, which is a rare but sometimes diagnosed surprisingly out of the blue as a cause of tiredness.

Q We can see that the examination demonstrated, I do not know if you understand this, we may have to wait to hear from Dr Skinner if we do. Temperature peripheral less than 32 degrees. Do you know what that is a reference to?
A In the handwritten note it does not state axilla although it does in the transcribed note. Dr Skinner has taken the temperature at two sites, one in the axilla or the armpit; one which is 36.8, he does not state where that is recorded from. My guess it would be an oral temperature but I do not know where that was taken from. Certainly the temperature of less than 32 is low even for an axillary temperature.

Q There is then reference to a number of what we are going to hear, I expect, as signs and symptoms of hypothyroidism. First of all, how many do you recognise? Voice hoarse you have mentioned. Yellowish pallor?
A Yes.

Q Loss of outer half of the eyebrows?
A Yes.

Q Tongue slightly enlarged?
A Yes.

Q Eyes slightly bloodshot?
A Very rarely patients with hypothyroidism might develop thyroid eye disease but if that was a suspicion further investigation would have been necessary.

Q Skin dry with cracked heels?
A Yes.

Q Thyroid palpable?
A Yes.

Q In other words he can feel the high thyroid and it was enlarged?
A Yes.

Q Can I ask you this, thyroid palpable, enlarged thyroid, how does that square with the blood tests?
A In the presence of normal blood tests and in the absence of thyroid antibodies we have a patient with euthyroid goitre. This is relatively common and might be found in five to fifteen per cent of the population depending on the age or sex of the individual. Typically such goitres will either regress as the patient gets older or progress to nodular thyroid disease. So it is perfectly possible to have a goitre and to be euthyroid. Indeed,

this is common.

Q What causes it?
A Nobody really knows, surprisingly for such a common condition. However, modern molecular techniques have shown that increasing numbers of these people can be assigned to different subtle enzyme disorders, or other diseases of function within the thyroid where the thyroid works a little harder in order to secrete the right amount of thyroid hormone and so you end up with a slightly larger thyroid gland than normal producing a normal amount of thyroid hormone.

Q There is no reference here to thyroxine but there is a reference to oral B12, 1,000 micrograms. 1,000 micrograms of B12 as a prescription, what is the point of that?
A It is difficult to understand this prescription. There is a common cause of vitamin B12 deficiency known as pernicious anaemia. Pernicious anaemia is another autoimmune disease. In this case the body's immune system attacks specific cells in the lining of the stomach. Those cells make a molecule called intrinsic factor. Intrinsic factor is essential for the absorption of B12. One cannot absorb dietary B12 in the absence of intrinsic factor. It helps to transport the B12 across the gut and into the blood stream. People with thyroid disease, autoimmune thyroid disease have a higher frequency of pernicious anaemia. This is because the same underlying process - autoimmunity - is driving both diseases. It is by no means an inevitable accompaniment but the risks are slightly higher. These people are more like to attack components of the body. The diagnosis of pernicious anaemia is important, therefore, to suspect in any patient with *bona fide* hypothyroidism. This patient did not have it but perhaps Dr Skinner was thinking if she did have hypothyroidism she was at greater risk of pernicious anaemia. However, the diagnosis of pernicious anaemia cannot be made by signs or symptoms alone. Again, blood tests are essential to make the diagnosis. The reason its important to make the diagnosis is that if the patient truly has pernicious anaemia then oral B12 is largely ineffective for the reasons I have explained - intrinsic factor is not present and it is highly likely that the B12 will not be absorbed. The British National Formulary states that oral B12 can be given for the treatment of PA but this is unlicensed and the appropriate treatment recommended by the BNF is vitamin B12 by injection.

Q This was Dr Stewart yesterday?
A Yes. We also heard on the first day from Patient A's GP who saw a lot of pernicious anaemia. There is a further complication which is important to mention and that is that pernicious anaemia is associated with a higher risk of gastric cancer. Therefore, this is not just a diagnosis which can be made flippantly, it is a diagnosis which needs to be made because having been made then the patient presenting in the future with signs might be appropriately investigated and obviously might needlessly be investigated if she pernicious anaemia.

Q We will see references to B12 with later patients as well. We will see if you comments apply equally to those. Dr Skinner has, as we can see from page 14 of this section, began treatment with thyroxine, 25 micrograms per day for seven days followed by 50 micrograms per day for four weeks. He wrote to the general practitioner at page 15:

> "Thank you very much for letting me see this nice led lady and your helpful results."

In the second paragraph he deals with her symptoms. He says in the last two lines:

> "I think it is really quite likely that she is hypothyroid and perhaps B12 deficient with yellow lemon tint to her skin and serious paraesthesia in both her hands and feet.
>
> I know that she has had one or two highish TSH readings but unfortunately nobody seems to have carried out an FT4."

Can we just go back to page 9, please. The July 2001 TSH level was 1.49. The May 2002 TSH level was 1.45. In your view in any sense could either of those be regarded as highish TSH readings?
A No.

Q In fact, they are below the lowest high level, as it were, below the 2.5?
A However one wants to look at it these are entirely normal.

Q Nobody has carried out a T4. He says:

> "I really thought there was a good case for institution of thyroid replacement having taken a blood test and I have laid out a programme of thyroxine replacement and in fact given her a prescription to get her on the road so to speak."

Was this treatment by thyroxine, in your view, at that stage justified?
A No.

Q We know, let us deal with this now, that she carried on with thyroxine. She seems to have changed her dosage but later on she was given thyroxine by Professor Franklyn and Dr Cooke?
A I think it was continued by the general practice. I think Professor Franklyn did not give any thyroxine and, indeed, indicated it was not necessary.

Q What do you say about that aspect of her treatment?
A I think Dr Franklyn was confronted by a problem that I have seen very frequently. Patients who have even started on thyroxine unnecessarily with normal blood tests and the patient wishes to continue on thyroid hormone despite the evidence to the contrary. As we have heard from one of the general practitioners it is usually possible to get these patients off such treatment and they go on to have normal thyroid function but certain patients refuse to come off thinking they have benefit from it in which case it is correct to take the pragmatic approach that Professor Franklyn has taken and that is to continue with T4 if the patient wishes to have it provided the TSH is maintained within the reference range. The danger with this, as I think we have seen with two of the patients, is that patients taking thyroxine do tend to adjust the dose as they see fit rather than according to the blood tests. Therefore that policy, although pragmatic, does run the risk at the TSH can become suppressed over a long period of time unless properly monitored.

Q This patient, we know, did have a blood test and Dr Skinner says in his letter: "…having taken a blood test". The results of that blood test we see at page 16. Her T4

was at 12.2 and her TSH was at 1.4. Is there anything unusual about either of those readings?

A No. Although Dr Skinner says in a letter to the GP that the T4 reading is lowish, it is not lowish. There would be approximately fifteen per cent of the healthy population with T4 values around that or lower. I am simply approximating to give the Panel some sort of feel but there would be, yes, perhaps ten per cent around that figure.

Q Sorry, ten per cent or fifteen per cent?

A It is difficult to tell because unless one looked at the laboratory reference range one cannot construct the curve. What I am saying, not to put a figure on it and then have that flung back at me, simply to say that there will be other people who will be equally healthy who have free T4s which are lower, let us say 9.1, 10, 11 and there will be a significant of number of those. So this is not lowish.

Q We heard from the patient. She started her thyroxine. She thought it did not agree with her. Whether she is right or wrong about that. She got headaches. Does that seem relevant to you or not?

A It is difficult to tell since I have not been in this situation where I have given thyroxine to people with such normal thyroid function tests. I think that there is one study which has shown that when you treat people who have a high TSH but a normal free T4, what we could sub-clinical hypothyroidism, there is an increase in anxiety scores after treatment. No evidence of benefit but an increase in anxiety scores. It is possible to conjecture therefore that the thyroxine given could have made this patient anxious, anxiety can precipitate tension and headaches.

Q She talked about feeling emotional tense?

A She did indeed. So that is one possible explanation. However, in a patient presenting with a new and serious headache the only line of approach is that the patient is seen and examined to make sure that there is not a serious cause for the new and serious headache. So she should either have been seen by Dr Skinner or by her GP.

Q The patient phoned the surgery. I think she said that after trying to get hold of the surgery she was given another number. She was told by somebody other than Dr Skinner really to stop taking the thyroxine. Do you have any views on that?

A I would not let somebody who is not medically qualified alter treatment in my patients with the exception of my endocrine nurse. If I can expand on that. I think that if you have a patient who has new symptoms on a medication then either the patient sees the specialist who has prescribed that, one of his staff members, one of his team and if that fails then the recommendation has to be to see the GP.

Q The patient wrote a letter and we have that at pages 20, 21 and 22 and she says this and she repeated it in her evidence that there was a discussion about desiccated thyroxine, I think that is five lines down on page 22 and Dr Skinner agreed to that. Can I just ask you if that sort of suggestion come from a patient, first of all, what would you expect the doctor to do?

A Well, in this situation we have someone with normal thyroid function tests who does not need any thyroid hormone treatment full stop.

Q They should not be on it in the first place?

A Yes.

Q Then?
A That is the full stop. There is not an alternative. This patient would have to have an alternative cause for her symptoms. This patient should have been seen and fully investigated and an alternative explanation found for her symptoms but to substitute one thyroid hormone for another when it is not necessary is simply not appropriate

Q If you go to page 24 we can see what Dr Skinner did plan to do. He says:

> "I think the best plan is to take 25 micrograms of Thyroxine as of now (not 50 micrograms) and order the Armour Thyroid by fax - it may come before your holiday - if not we can forward some to you by some means. After two weeks, take one tablet of one of the HALF Grain tablets (they should send seven) and then contact Dr Cooke."

Now I expect that you are saying he should never have started in the first place. What would have been the potential effect on the patient of starting Armour Thyroid?
A Again, I am in a difficult position since I have never done this, but one can only conjecture that if she was feeling anxious on thyroid hormone (and that is pure conjecture, I cannot say that she was) but if she was, that certainly would not abate and would likely to have been made worse by Armour. Of course, it is perfectly possible her head aches had alternative causes and I am simply speculating. I cannot say any more and I do not wish to be drawn on this.

Q All right. If we go to page 28 we can see how things moved on.
A Mr Kark, I only have a page 27.

Q I am sorry, 26, I misread it. When Dr Skinner writes to Dr Cook and this is in relation to the blood test that he had received which we looked at a moment ago, he writes:

> "The clinical features and the lowish FT4 reading do I think suggest this that lady may be suffering from hypothyroidism and while of course her FT4 is within the 95 % reference interval is significantly below the average for healthy patients and I would be very disappointed that we cannot return [her] to optimal health with some form of thyroid replacement."

Do you accept it is significantly below the average for healthy patients?
A No, I think this is important because it is either low or it is normal in my book. Dr Skinner could interpret this as being low, but if it is low and the TSH is normal, then there is only one diagnosis which needs to be excluded and that is pituitary disease. There will be other explanations for that combination of blood test, but high on the list or top of the list would be a pituitary problem.

Q Now just pausing for a moment, is this referring back to the comments you made earlier about secondary hypothyroidism?
A Exactly.

Q So if this is what was being looked at, in other words a low-ish T4 but a normal TSH and you would say this was an unequivocally normal TSH, Dr Skinner perhaps

disagrees with you, but if that is seen to be the problem, as it were you, you would be looking for pituitary disease?
A Yes. If all of the features recorded by Dr Skinner were there, ie suggestive but not diagnostic of hypothyroidism and if the 3T4 was low, then the explanation on a thyroid basis would be secondary hypothyroidism. That is the only type of thyroid disease that would cause symptoms which are definitely due to thyroid disease and a combination of biochemistry which is low 3T4 and a TSH.

Q What should he have down?
A He should have either conducted investigations himself if he felt that this was appropriate or, I would suggest, he should have referred her to an endocrinologist and those are the recommendations of the Royal College, which I have mentioned, patients with suspected pituitary disease should be seen by an endocrinologist. Of course, as it turned out, the 3T4 was not low or low-ish, it was normal and therefore no referral on that basis was necessary.

I would add one thing, this patient had a head ache and one of the features of a pituitary tumour is a head ache. So one can start to see a thread of argument here that if one really believes the symptoms are all there for hypothyroidism, a patient with a head ache, and one really believed, I do not, but one really believed the T4 was low-ish, then that is even more suggestive of a pituitary tumour.

Q When the patient comes back to Dr Skinner by telephone and says, "Look I am getting these head aches," first of all would you expect a doctor to make a note of that conversation or not if he had just received a call like that from a patient?
A I always endeavour to record such conversations.

Q You may do, but is it a requirement in your view or not?
A I think it is best practice.

Q If, having started a patient on Thyroxine, you do receive that call, is it sufficient to deal with it over the telephone?
A I do not think we have got sufficient information here to comment, but all I can tell you is that in general if a patient rang me complaining of a head ache and a new head ache at that, then I would certainly want to take more information over the phone to try and determine what this might be and, as I have said, if I had concerns about it, as clearly the patient did, then either I would arrange to see the patient myself, get her to see one of my team or ask her to see the GP and the degree of urgency with which those would be done would depend on the history I elicited over the telephone.

Q You made reference earlier to Professor Franklyn's advice we had better look at that briefly. Tab 1, page 57 - 56/57. This, of course, is post Dr Skinner, as it were, the patient has gone back to Dr Cook and has then been sent on, it would appear, to Professor Franklin and she writes:

> "As you know you asked me to address the question of diagnosis of hypothyroidism and appropriate management. Having read that some of her symptoms might fit for Hashimoto's thyroiditis, she was subsequently seen by a practitioner outside the NHS and began treatment with Thyroxine."

At the bottom of the page:

> "Clinical examination from a thyroid point of view is unremarkable, in particular she has no goitre."

Over the page:

> "She [brought] along thyroid function tests. T4 was normal at 12.2 and TSH was 1.4. I did explain that given this extremely normal TSH one can be confident about ruling out a diagnosis of hypothyroidism."

Then she deals with the position where the patient wanted in any event to continue with Thyroxine.

It may be suggested, I do not know, that you are out on a limb or in an ivory tower et cetera. Do you deal with this sort of patient?
A Yes.

Q Do you concur with Professor Franklyn's view in relation to this?
A Yes. I have already described the fact that I see many such patients who have been put on Thyroxine, not just by Dr Skinner, but by other practitioners and I try and take the patients off and often patients have an unallayable anxiety to continue with treatment and I would agree with Professor Franklyn that under those circumstances one should be pragmatic, but not over-treat as she specified.

Q Finally, in relation to this patient, I just want to go back to the note, the first page at tab 2. You say, as I understand it, that there was not a sufficient examination, first of all?
A Yes.

Q No examination of the abdomen, respiratory system and no indication that he examined the fundi?
A Or visual fields.

Q Or visual fields.
A I could go on and say that with a patient with parasthesi, a tingling, there is not a record of the neurological examination. There are two particular types of parasthesi which may occur with the two conditions which have been postulated here. The tingling that you get in the hands with hypothyroidism does not involve the little finger; the tingling that you get with B12 deficiency would. So an examination might help to determine which type of neuropathy, if indeed there was a neuropathy, was occurring or indeed might have elicited the fact that there was no neuropathy at all on clinical examination at least.

Q Is there any sign of such an examination from these notes?
A No, there is not, but there are many causes of carpal tunnel syndrome, for instance.

Q Stop, carpal tunnel?
A As I explained a couple of days ago, this is where the ---

Q This where it was explained to the Panel too, but for their recall.

A This is compression of a nerve of the wrist and with that you get tingling in *these* four fingers but it spares the little finger. There are several causes of that besides hypothyroidism. So in this patient with normal thyroid function with one guesses normal B12 levels, although not tested, but if they were normal then one would seek an alternative cause and one would need to do nerve conduction studies to find out whether she truly had carpal tunnel syndrome.

Q Is there any indication that he did?
A No, because he did not do a neurological examination.

Q Alternatively, could he have referred her again, as it were, and arranged for her assessment elsewhere?
A Of course.

Q So far as the blood tests are concerned, I think your view (and I am dealing with the bottom paragraph at page 18 now) is that he misinterpreted the blood tests effectively as abnormal and you have made your comments already on secondary hypothyroidism and the dangers thereof.

THE CHAIRMAN: What page, 18?

MR KARK: Of the report.

THE CHAIRMAN: Of his report.

MR KARK: Professor Weetman's report. Sorry, I am jumping about a bit.

(To the witnesses) You finally say that if he suspected a diagnose of deficiency of B12 he should have performed appropriate investigations. Can we move on then, please, to patient B. He saw this patient, as we can see from tab 4 of our main bundle, on 20 March. This was done, as we know, I think without a referral, and we can see from page 6 that he writes to Dr Blair on 26 March and the letter I have described as the dog house letter: "I hope I will not be in the dog house" letter "with you".

Just dealing with that in passing, in normal circumstances if a doctor is purporting to act as a secondary referral, as I think Dr Skinner was, ought he to have a referral letter?
A It is best practice to have it. In the event of a patient turning up and forgetting a letter it would be appropriate to see the patient, but it would be appropriate then to wait for the GP letter before instituting investigations to make sure that these are not duplicated unnecessarily.

Q If we go back to the typewritten notes. 20 March 2003:

> "First consultation:
>
> Unwell since 1999. No enthusiasm, choking fits in the night, very low energy, insomnia for 12 years, low appetite, weight stable, no bowel problems, tired gritty eyes, asocial, poor memory and concentration, dry throat, tinglings in feet and arms, side vision hallucination of lights, no libido. [There is a] history of a legal dispute with decorator. Examinations …"

He sets out the temperatures there.

> "Eyes small and puffy, pulse 64 per minute then 58 per minute later in consultation. Tongue enlarged (++) sacculated."

Sacculated means?
A Irregular, I think. The little saccules around the edge of the tongue.

Q "Blood pressure 140/85." In fact, we need to go, I think, to the note at page 4 because right at the bottom of that note and just above the next date is actually the prescription which simply says "Thyroxine". So we need, I think, to add that to a typed explanation. There is no mention, I think, if we look at page 4, of the quantity or dosage. Now side vision hallucinations, if a patient comes to you complaining of that sort of problem what should you do?
A It is obvious to me that Dr Skinner has elicited the symptoms and recorded it in a way I am not familiar with. I would like to know more about exactly what the symptoms were that the patient described. As I have said, if the patient has got a disturbance of vision any physician would look in the eyes to make sure the fundi were normal, would check the visual field, this would take seconds to do and assure you that there was no significant threat to vision. If the patient had this as a significant problem one would want to get then an ophthalmological opinion.

Q Is there any indication in the note that he did do a peripheral field or a fundi examination?
A No. He seems to have related this to a symptom in hypothyroidism which I have not come across before which he says is due to mucopolysaccharide opacities in the eyes which move when the eyes move.

Q Stop for a moment. Let us just find that. It is at page 6 and it is in his letter to Dr Blair in the second paragraph. He talks about, "side vision hallucinations which I find to be quite common in hypothyroidism." Yes?
A Yes.

Q Have you seen that in hypothyroidism?
A I have not come across that. I think the description here of something moving when the eye moves, if this is what he is meaning, would sound to me most like what is called a floater and these are collections of dead cells mucopolysaccharides which lie between the jelly in the eye and the lining of the eye and move about when the eye moves. They are a natural feature of ageing and are certainly not related to hypothyroidism. That is one possibility for this set of symptoms, but let me again stress I did not take the history fully so it is only conjecture.

Q The patient also complaint of lack of enthusiasm and decreased energy and insomnia. Now may those be symptoms and signs of hypothyroidism?
A Yes.

Q What else?
A As I have said on page 19, two-thirds of the way down, even those sketchy symptoms as reported (and I am sure Dr Skinner took a more extensive history and only

recorded the key details which is again perfectly proper) but those details as laid down suggested to me the possibility of depression. Indeed, we heard from Dr Blair that he has undertaken a proper evaluation or rather a nurse, I believe, had gone out and undertaken a scoring scale to see whether this patient was depressed and indeed she scored within the range that signified depression.

Q From the notes there does not appear to be a record of the social family history and you say in your report the record of the examination is inadequate. Why do you say it is inadequate?
A When I mean social history I am talking about alcohol intake which may be associated with depression, other features we have got already a mention of a legal dispute which can precipitate depression, but the other things that I have mentioned with regard to the examination really relate to similar considerations as we had with patient A in that I think with a patient who is tired with these other features you have got a differential diagnosis clearly before you: she could be hypothyroid, she could have depression, but you want to rule out any other serious underlying illness. Some malignancy, chronic infections, neurological diseases, this lady had choking.

Q What would you be looking for with choking?
A Well there are many neurological disease that might present with choking as a phenomenon. Motor neurone disease would be one possibility, for instance. All I am saying here is that she has also got tingling in the arms and legs and we have been into tingling before in relation to B12 deficiency, hypothyroidism and the idea that this may be a peripheral neuropathy.

Q In your view, is the record of what happened sufficient? First of all, if it reflects what actually happened, was the examination sufficient?
A No.

Q Secondly, are the notes themselves sufficient?
A If this is all that was written – it is impossible to say since one was not present at the consultation to know exactly what history was elicited so I cannot say whether the notes are an accurate record, that would be impossible.

Q What we do appear to know is that Dr Skinner had some blood tests. If we go to pages 2 and 3 and these are from Dr Skinner's own notes.
A Yes, I have got it. It is the fourth page.

Q Page 2 at the bottom right-hand corner, it is dated 21 August 2002 and shows that this lady's T4 was 16.7 with a reference range of 11 to 23 and her TSH was 2.3 with a reference range between 0.4 and 4. Is there anything whatsoever unusual about those readings?
A These readings would exclude both primary and secondary hypothyroidism.

Q In particular the TSH level is once again below 2.5 which, even on the more extreme view, as it were, of where one should set the level, is below it?
A Yes.

Q Over the page, 15 January 2003, free T4 really has hardly moved, 16.8. In fact the blood was taken on 14 January 2003, I think. The TSH again has hardly moved, 2.4. On

A the basis of this examination and those blood tests, can you see any basis whatever for starting this patient on Thyroxine?
A No.

Q The letter that Dr Skinner writes at page 6 reveals this, if we go to the third paragraph:

B
> "I really thought there was a very good case for thyroid replacement and I have given her a prescription for Thyroxine sodium. I suggest that she does not begin this medication until perhaps ten to 14 days lest you did not wish her to come and see me and it would be discourteous to institute this without your knowledge."

Do you have any comment on that?
C A Of the patient truly had hypothyroidism I can see no reason why the patient should not start her treatment.

Q If we look at page 7, I think it is, there is a note there that there is to be an increase – if we look at the middle page – 100 µg till 17 June 2003, so that is the first three months following the appointment with Dr Skinner, and then 125 µg for three months. If that is what happened, any basis in your view for that increase?
D A No. In a typical patient with confirmed hypothyroidism, the dose of Thyroxine is increased based on blood test results, so one would start on a dose of Thyroxine which seems appropriate from one's experience and that dose depends on the initial blood tests. You then wait between two to three months and repeat the TSH level because it takes two to three months for the TSH levels to return to a stable level. If the TSH levels are within the reference range and the patient was well you would continue on the same dose. If the patient had a TSH which was elevated one would increase the dose of Thyroxine. If the
E TSH correspondingly was low, and your initial guess at the dose was therefore excessive you would lower the dose. Once you had a stable TSH level, you would then return to annual monitoring for that patient based on blood tests.

Q The last blood test that this doctor had, there was one for the blood taken on 21 August 2002 and one taken on 14 January 2003. It does not look as though he instituted his own blood tests. Doe that matter or did he have sufficient on what he had already
F seen?
A I have not seen the blood tests that you are referring to but in general I think someone who is changing the dose of Thyroxine should be the one who is undertaking the blood tests, otherwise it would end in confusion and unnecessary blood tests, for instance.

G Q The next blood test we see, I think, is at page 8, which is 9 December 2003, is the date of the report. This would be, of course, some nine months after the patient has started on Thyroxine and the blood level then is free T4 – do you have it?
A Yes.

Q Free T4 39, where the reference range was between 10 and 24, and the TSH level says "Less than 0.1". Does that mean…
H A Undetectable in that particular assay.

Q What does that say to you?

A This patient has thyrotoxicosis.

Q Which means what?
A Thyrotoxicosis is the state of having an excessive amount of thyroid hormone in the blood. Sometimes people call this state hyperthyroidism and several of our witnesses did, but that is strictly speaking incorrect, because hyperthyroidism means an overactive gland. This is not an overactive thyroid. This is simply excessive Thyroxine administration and so strictly speaking this is thyrotoxicosis.

Q We can see that the lab has reported, suggests, "slightly over-replaced with Thyroxine. I do not know if you agree with that comment?
A No, this is over-replaced without any qualification.

Q We also see in the box on the right-hand side where there are obviously, it would appear, instructions about what to do about this, that the box is ticked "Speak with doctor"?
A Yes.

Q So it seems that somebody in the laboratory thought that they ought to bring this to Dr Skinner's attention?
A Quite.

Q In fact it is the GP's attention, Dr Blair?
A Certainly our laboratory in Sheffield would do the same.

Q We know that Dr Skinner saw this patient again after that blood test and this blood test is within his notes so we can assume that he saw it. The typewritten notes appear at the very beginning of that bundle, dated 20 January. In fact I think it should be 21 January if we are looking at the bottom of page 4. This is the second consultation, very shortly after that blood test had been taken and his typed notes reveal:

> "Taking reduced dose of 200 µg Thyroxine per day on account of palpitations for a month."

What does that signify to you? Are you with me on the notes?
A I am. I just want to refer to my own notes. This was on 20 January and we knew at that stage that the month before, or five or six weeks before, the thyroid hormone levels were very raised and so I am not surprised.

Q Do you say is there a relevance to the fact that this lady was complaining about those palpitations? Is that relevant in your view to the Thyroxine that she was taking?
A I think if this lady had not had palpitations before, had developed them at a time that her thyroid hormone level was raised, as we know, then that would be by far the most likely explanation for that and if those palpitations then failed to recur with reduction in the dose of Thyroxine, that would prove the case.

Q At the bottom of that note it says:

> "Treatment. Thyroxine 150 µg, Tertroxine 20 µg."

We will find a note at page 5 and it is the very last entry above the word "Tesco's" – I think it is Tesco's, perhaps it is not – "Prescription 150 µg and 20 µg ." It does not actually say in the original note what that is. Do you agree with that?
A It does, but given the size of the tablets it can only be T4 and T3 in this context.

Q OK. The patient next saw Dr Skinner – the bottom of page 20 of your report now – on 18 March 2004 and again, in fact, she is complaining of her heart beating. I presume that does not mean a regular heart beat or she would not be complaining about it. "Three quarters of an hour heart beating during alcohol." Then Dr Skinner writes:

> "But excessive alcohol during the evening. No palpitations for five days on 75 µg Thyroxine and 20 µg Tertroxine"

So she is now on, as we know from the previous note, both T4 and T3. I appreciate you are going to say there was no justification for starting her on T4 in the first place, but was there any justification for starting her on T3 at any stage?
A No.

Q The relevance of the alcohol and the palpitations, if that is what they were; is there perhaps a relevance to alcohol?
A Unfortunately we do not have a blood test so we do not know what the thyroid function was at that particular stage, though I have mentioned to you that T3 levels can spike during the day because of the way that the tablet is absorbed. We also know that alcohol dilates blood vessels and renders people more likely to develop heart palpitations but then again one could also argue that she might not have experienced the palpitations had she only had alcohol alone. Perhaps it was the combination of alcohol plus thyroid hormone that led to palpitations in this case, the alcohol acting as one stressor on the heart and the thyroid hormone acting as a second.

Q Dr Skinner deals with that at page 24 of this section where he reveals to Dr Blair in the second paragraph:

> "As you know this lady is now taking 75 µg Thyroxine and 20 µg Tertroxine and she seems to be in reasonable shape although I still think she is hypothyroid."

Do you see any basis for that comment?
A It is back to the situation where Dr Skinner believes that symptoms are diagnostic of hypothyroidism but I think without a blood test one could not assert that. She has never been previously hypothyroid on the blood tests and there would be no reason to think, given this treatment, that she would suddenly have developed hypothyroidism.

Q

> "She had bradycardia of 52/ minute."

Bradycardia?
A Slow heart.

Q

"I thought perhaps the right approach here would be to alternate 75 µg and 100 µg Thyroxine but continue with 20 µg and I think it would be possible in a canny way as they say to increase her input of thyroid replacement as I personally doubt that the strange episode in the early hours of one morning was related to excessive Thyroxine replacement"

- I presume that is reference again to the heart. We do not know?
A I guess.

MR JENKINS: The first paragraph may help.

MR KARK: Yes, thank you very much. I just want to ask you about heart palpitations. You have told us that those may be related to the Thyroxine that patients take. Is there in fact any danger from a racing heart or heart palpitations?
A I think that if one was perfectly fit and health and had a healthy heart, then the short-term risks would be minimal to non-existent. The risks of atrial fibrillation that we have discussed earlier have been established over a period of years – ten years, let us say and particularly in the elderly, so I think that there is little evidence that a healthy heart would come to any harm given short doses of excessive thyroid hormone.

However, there are rare individuals who may have underlying cardiac defects in whom excessive doses of Thyroxine given inappropriately could conceivably be dangerous. There is, for instance, a condition called Wolffe Parkinson White syndrome, which is where the heart is pre-disposed to develop serious rhythm problems and it is conceivable – but no more than that – that any extra stress put on the heart, like excessive thyroid hormone, could have an adverse effect in such a situation. I know of no case reports and I would stress, therefore, that this is conjecture and is simply to point out that there are people who are predisposed to get dangerous heart problems and therefore one would be concerned.

This is, if you like, the theoretical concern which I have mentioned that endocrinologists have about T3 treatment.

Q Let us move away from theory for a moment and just concentrate on what we actually have. We have a patient on T4 and T3. They complain on two occasions of palpitations of the heart. In order to discover whether there are those underlying potential complications, what would you do?
A In this patient I would have done an ECG, an electrocardiogram, which is a tracing of the heart which will make sure there is no serious underlying problem and what I am saying here is that she could just be unfortunate and have a coincidental rhythm problem that could have been unmasked by either alcohol or thyroid hormones or both, but certainly she has presented with new episodes of palpitations and either one follows Dr Skinner's line of reasoning that this is not thyrotoxicosis, I which case an ECG should certainly be done because there is no other explanation, or one follows my line of reasoning saying that this is due to excessive thyroid hormone, in which case reduction of the thyroid hormone level to a normal biochemical level of TSH and complete cessation of palpitations on its own would be reassuring, but I think new palpitations in an other wise fit and healthy person do demand one of those two steps.

Q We know that the last consultation with Dr Skinner was on 18 March. If we could

go, please, to page 28 of this section, which is tab 4 of file 1. It does not look as thought there was any meeting, any consultation before this prescription. There were no blood tests and the last we heard from this patient was that she had on one occasion a thudding heart or palpitations, I should say.

I know you will say he should not have done it in the first place, but can we just deal, please, with this prescription at page 28, dated 14 July, further Thyroxine. Acceptable or not?
A I think that this represents a further change in thyroid hormone treatment because I believe that the previous treatment was Thyroxine plus Tertroxine.

Q Yes.
A Therefore any change in dosage or in medication – so from T3 and T4 to T4, or a change in overall dosage – should be preceded by a blood test to check what the TSH level is to make sure that such treatment is appropriate. Those are the recommendations of all the guidelines that I am aware on the management of thyroid hormone replacement.

Q At page 21 at the bottom of your report just summarising your views about Dr Skinner's management of this patient you say, first, he saw the patient initially without referral from a GP. You have made your comments about that. Secondly, his initial history and examination was inadequate. Three, I have put the numbers there, despite two normal tests for thyroid function Dr Skinner prescribed thyroid hormone. This was inappropriate. Four, excessively high doses of thyroxine were given, such that the patient became unequivocally thyrotoxic. Fifth, he invented a diagnosis of impaired conversion of T4 to T3 to explain abnormal test results. We have to go back think to a letter to the GP to deal with that. Page 11. He writes this to Dr Blair:

> "A note on [B] who has noticed some improvements but is clearly still hypothyroid notwithstanding the highish T4 reading."

You say, I will not go back to it, you say it was not just highish?
A That is right. It is unequivocally raised.

Q

> "I think the obvious hypothesis is that she is not converting T4 to T3 thus back stacking T4. I thought the solution was to reduce her thyroxine to 150 and supplement it with 20."

I should have dealt with this earlier. This explains why he added the T3 to the prescription. What do you say about evidence of back stacking, as he put it here?
A I am not aware of anyone who is otherwise healthy with normal biochemical tests prior to treatment who has any difficulty in converting T4 to T3. I have mentioned that there are drugs in very rare syndromes where there are conversion problems of T4 to T3 or changes in the way that that occurs and they are marked by abnormal blood tests. He also has not undertaken a free T3 investigation to support this diagnosis. If he really did believe that this was a unique circumstance then one would have seen a normal free T3, or a low free T3. We have no low fee T3 to start with and---

Q We do not know what the T3 was at all?

A No, but let me stress I am not suggesting that he should have measured the free T3 because there is no need to measure the T3 in diagnosing or treating hypothyroidism. I am simply saying that if he wished to conjecture that this was a unique circumstance not so far reported further investigation would have been necessary to substantiate that hypothesis.

Q Going back to page 21 you say:

> "He invented the diagnosis of impaired conversion of T4 to T3 to explain abnormal blood tests when the correct diagnosis was that he was over treating the patient with thyroid hormone. The patient subsequently describes symptoms which could well have been related to the thyroid hormone medication he was giving. Despite this he failed to check the thyroid function tests any further himself and he altered the medication without informing the GP or undertaking any blood tests."

Can we turn then, please, to Patient C and paragraph 8.3 of your report and we turn to tab 6 of our bundle. This patient saw Dr Skinner on 6 March. She had, I think, low blood pressure at 105 over 60. How low is that?
A That is low and I think there is a further record from the GP of 80 over 50 which is very low indeed.

Q The notes reveal that the patient was complaining that she was very tired and she had a poor memory; concentration jumping about; weight increased by a stone to nine stone; periods irregular; feels coldish; twitching legs; weepy; side vision hallucination of grey things; poor libido. As you say, she saw the GP who noted low blood pressure at 80 over 50. Family history: mum, uncle and gran diabetes. Examination: pulse 60 a minute; tongue indented; hair, skin and heel dry; thyroid nothing abnormal detected. So that presumably means on examination and palpation?
A Yes.

Q Blood pressure 105 over 60. Treatment: further tests. Then this:

> "Fasting blood glucose, urine glucose and T4 and TSH."

So in his note which we have at page 1, so we go two pages further forward, we can see right at the bottom that the notes "F14"?
A FT4, I think.

Q Sorry. "FT4 and TSH". There is no prescription but this patient seems to have started on thyroxine. If we go over to page 2 he writes to Dr Summers in relation to the consultation that he has just had. It is the dog house letter again. He says in the last line of the second paragraph:

> "I thought it quite likely he was hypothyroid although not seriously hypothyroid."

He does not seem then to have had any blood tests available to him?
A Well, he goes on to say have taken a blood sample.

Q I mean at the time that he writes that comment?
A As I understand it that is right.

Q

> "I have taken a blood sample for thyroid chemistry and should have the result in ten days and I will let you know what goes forward at that point in time."

He does not mention in that letter to the GP, if he did, putting her on thyroxine?
A I agree.

Q If he had put her on thyroxine should he have mentioned it?
A Yes.

Q Over the page we see the blood test that he received back dated 16 March, T4 11.6, reference range 9 to 20. TSH 2.2, reference range 0.4 to 5.5. Anything unusual about those thyroid tests?
A No, both are normal.

Q In your view, should you ever start a patient on thyroxine without a blood test?
A The only situation in which that would be indicated would be in the very rare situation of myxodoema coma which is an emergency situation where somebody has been so deprived of thyroid hormone that they are admitted to hospital as an emergency and the clinical features are such that you would give emergency treatment whilst awaiting the outcome of the blood test because this carries a 50 per cent mortality rate.

Q Any other circumstances where you would do it?
A No.

Q If, having started a patient on thyroxine for some good clinical reason, you then get this sort of blood test back, what ought you to do?
A Stop it.

Q Would you go to page 6, second letter to Dr Summers:

> "A note on [Patient C] who I think is already improving on thyroid replacement though she has recently, and off her own bat, put her dose up to 200 micrograms of thyroxine with (curiously) no thyrotoxicity."

Have you seen any blood tests relevant to that comment? The last blood test we had was back in March which, of course, was before she started on thyroxine.

A The only blood tests I was able to find in the notes were 10 March 2004 and then non until 10 August 2004.

Q So at the time that he writes curiously no thyrotoxicity, do you know what he is talking about?
A He can only mean that he cannot see any signs clinically either by taking history or

examination but exactly as with hypothyroidism, where the symptoms are not specific, so for thyrotoxicosis, the symptoms and signs are not specific and cannot be usaed to make a diagnosis.

Q He goes on:

> "Which made we wonder if perhaps there is a conversion problem here…",

We are back to the same issue as we had with the last patient here:

> "…so I thought we need rationalise and stabilise the situation and perhaps ad in some T3 if there is a conversion problem. I have set her dosage at 150 micrograms thyroxine per day with 20 micrograms of Tertroxin."

Is there anything scientific about any of this?
A No.

Q In his approach to this patient?
A Well, this is the same as the issue we had with Patient B talking about conversion problem. If you he wishes to postulate there is a conversion problem then the onus is on Dr Skinner to show that that is occurring using appropriate biochemical and genetic tests but I do not see any biochemical evidence that there is a conversion problem. I think what is particularly interesting here is that this is an example of a patient who has deliberately put up her own thyroid hormone dosage to derive benefit from it. You will see that Dr Skinner himself says that he pleaded with her that she stayed on this dose and that is clearly a recognition on his part that she was taking excessive dosages of thyroxine prior to that, I think, unless there is some other reason or this but that is how I would read this; that he wishes to see her on a different dose of thyroxine because he is sensitive because, indeed, he mentions in the first paragraph that 200 micrograms curiously has no thyrotoxicity. It is curious and he is clearly concerned about it.

Q If I take you back to his typewritten notes of this examination where he made that conclusion, it is at the very beginning of this section. He writes half way down the page:

> "Follow up consultation 8 May 2004.
>
> Feeling slightly better, marginally tired. Taking 200 micrograms thyroxin per day for three weeks. Patient put her own dose to this level. For three weeks if turns head quickly discomfort for 15 seconds. Some irregularity of bleeding."

Is there anything there to show again that he had specifically considered the issue of thyrotoxicity?
A No. As I have said, the way to make a diagnosis of thyrotoxicosis is based on blood tests. Certain signs however would be suggestive and would normally be elicited. So for instance he could have taken a pulse and found a tachycardia or atrial fibrillation indeed. He could have examine the hands to see if there was any tremor. He could have examined the hands to see if there was peripheral sweating. He could have inquired about weight loss which I do not believe he did.

Q The next time he sees this patient is in August, as we can see at the bottom of the page 1, this refers to his note at page 8 and I think with respect Dr Skinner has just actually forgotten to put into the typewritten notes what is on the right-hand side of the page, if I have got the date right, it is page 8, I think and I think that is the same note because we see can that the handwritten note starts of with "periods regular" and then "IOD fitted". So it is the same notes but in the far right-hand side we see "D 150mg" and "20mg" with a "T" next to both. May be it has been chopped off on the right-hand side and then "B12". I am not going to take you all the way back through the comments you have made about B12 but if this is a signal that he was either prescribing B12 or suspected B12 deficiency do your comments apply as before?

A Yes.

Q Now at that August consultation he did take a blood test and if we go to page 10 we can see the results of this lady having been on what she was on. It shows that her T4 level was now up at 25.5 and her TSH was immeasurable, the reference range for the T4 was between 9 and 20. What do you say about that result?

A Could you give me the page number please.

Q Page 10 of tab 6.

A These blood tests results show thyrotoxicosis and that is further supported by the free T3 level which is below the results you have just read out which is 8.9 and the reference range is 3.5 to 6.5.

Q You would say that this blood tests demonstrates that she is thyrotoxic?

A Yes.

Q Go to the page before because this is the letter that Dr Skinner wrote to this patient:

> "Here are your thyroid chemistry and cortisol which indicate that the level are a little on the high side but if you are not feeling adverse effect then I think you can should stay at the same dose until I see you next, or if you are planning any of your increasing strategies…",

Your, the patient, increasing strategies:

> "…then perhaps you would let me know."

Ignoring cortisol for the moment, is that an acceptable approach following this blood test?

A I do not think so. I think that again there is this equivocation which seems to attend many of the comments in blood tests in that it is a little high. It is unequivocally high, that is the T3 and the T4 levels specifically and the TSH is undetectable, meaning that the body has been exposed to a high level of thyroid hormone over a number of weeks. This is not simply that the patient took some tablets that morning. We have evidence from the TSH that this has been sustained. And an endocrinologist would decrease the thyroid hormone replacement to bring the TSH to within the reference range.

Q Finally just before we break for lunch, I am sorry I have not manage to finish you

by lunch, we have one patient to go effectively, he writes that:

> "The cortisol level is satisfactory but we should not entirely rule out the possibility of adrenal supplementation if we do not return you to optimal health."

What is he talking about there and what is the significance of it?

A As I mentioned the adrenal glands are two glands which lie above the kidneys and are responsible for the secretion of the hormone called cortisol amongst several other hormones. I will concentrate on cortisol because I think this is the most significant. Cortisol is responsible for the body's response to stress and without it a patient can succumb and die following any major stress such as an illness or infection. It is a very serious but rare condition. The commonest cause of adrenal failure is again autoimmunity. There is a link therefore between patients with thyroid disease and adrenal disease in that patients with adrenal failure are more likely to have autoimmune thyroid disease. Therefore, if this patient had had thyroid disease, which she did not, but if she had then it would be reasonable to think that if she continued to have symptoms she could have Addison's disease as a further cause. In addition this patient and an unexplained low blood pressure…

Q In addition, this patient had an unexplained low blood pressure and that is a very common feature in patients with Addison's disease. So it would be appropriate certainly to think of Addison's disease irrespective of the absence of any thyroid disease in this patient simply on the basis of the low blood pressure. However, a single random cortisol measurement such as this is not sufficient to exclude the diagnosis of Addison's disease.

Q I am sorry to interrupt you, where do we see the cortisol measurement?
A On page 10, tab 6. It is below the 3T3 result.

Q So cortisol 288 mmol/l?
A Millimols per litre.

Q Reference range 180 to 550. So it is within the reference range?
A Cortisol is unlike thyroid hormones in that the levels fluctuate far more. In addition, one is looking at the secretion of a hormone here which needs to rise very high very rapidly after stress. Therefore, secretion of cortisol can in some people with minor degrees of damage of the adrenal be within reference ranges during normal circumstances but under a stressful situation would not rise appropriately.

There are, therefore, two ways of approaching a potential adrenal problem. One way would be to do a nine o'clock cortisol, 9 am cortisol. It has to be specified because that is the time that the cortisol is at its highest. The cortisol level below 100 at nine o'clock would certainly diagnose adrenal failure. A cortisol above 400 at nine o'clock would reliably rule it out. A cortisol between 100 to 400 cannot be used to diagnose whether adrenal failure is present or not.

Q I do not think we know the time of day that this particular blood test was taken.
A If it was not a nine o'clock cortisol it cannot be interpreted.

Q If Dr Skinner was concerned at all about the possibility of adrenal supplementation

ought he to have taken steps?
A He should. This is a patient who afterall has a normal thyroid function, does not have hypothyroidism and has a number of symptoms and a cardinal sign of hypoadrenalism, namely low blood pressure. If he seriously suspected this potentially life-threatening illness, he should have either undertaken a *(inaudible)* test, having received this cortisol result, which is equivocal, or he should have referred it to an endocrinologist.

MR KARK: I wonder if that would be a convenient moment.

THE CHAIRMAN: Yes, I am certain it would. Thank you. We will reconvene at two o'clock.

(The Panel adjourned for lunch)

MR KARK: Professor Weetman, we are on page 24 of your report and we were just finishing off with patient C and you say in your report that the blood tests in September and October 2004 (this is the third paragraph) showed that the patient continued to receive excessive amounts of thyroid hormone. The patient notes are in fact at tab 5 of the main bundle at page 1 and we can see two thirds of the way down the page that on 24 September 2004 the TSH level was still being shown as 0.01. Is that the equivalent of unrecordable or is that 0.01?
A 0.01, but it is difficult to tell whether the surgery would have recorded the less than sign.

Q T4 level at 21.7. Then over the page we see that by 15 October she appears to have come down fairly dramatically on the T4, but the TSH was still showing at 0.01 and we heard the evidence that certainly at some time in October she came off Thyroxine.
A Yes, it is my recall in this patient C that she was also taking Tertroxine.

Q Yes. That is right.
A I think that it is important to point that out simply to explain to the Panel why the 3T4 is within the reference range and TSH is suppressed. When a patient takes T3 as well as T4 you can have this situation because, as I have mentioned, there are peaks during the day when the T3 level rises above normal and that will affect the pituitary and suppress the TSH.

Q In fact, at the time that she is on tertroxine or she is taking tertroxine, I think you told us earlier, the T4 is not necessarily a very good marker in any event because of that variance during the day.
A Indeed.

Q It would depend when she last took her pills?
A Indeed.

Q You summarised your conclusions in relation to patient C saying that you think the management of the patient by Dr Skinner was seriously below the standards of acceptable practice. He saw this patient without referral. He began inappropriate thyroid treatment without adequately informing the GP of this fact in his first letter. I think this was the one, he does not mention putting her on Thyroxine at all.

A

You say, "His initial history and examination were inadequate," his treatment resulted in thyrotoxicosis. Despite which he made a diagnosis of impaired conversion from T4 to T3 for which there was no basis. This was a backstacking point he made and he appears to have given the patient vitamin B12 although the details of this are sketchy and there is no record of any tests being performed to establish the diagnosis.

B

You could find no record that the GP was informed of the diagnosis. Yes, I do not think in this one that there is a mention to the GP of B12. Having heard the evidence that you have in this case, I should have asked you this earlier about your other comments about other patients, has your view changed in any way from when you wrote this report?
A No.

Q Could we turn please to patient D? If we could turn first of all in the report to
C page 25 and in the notes tab 7 and 8. This patient first saw Dr Skinner on 24 August 2004. She was complaining of a number of symptoms including weight gain. She was tired, poor sleep, but her appetite was very good.

"Aches all over especially lower back.
Poor concentration and memory.
Weepy.
D Asocial and irritable."

This, I think, was a patient we heard who cried during the course of the consultation.

"Pills make her aggressive.
Arms and leg paraesthesia.
Side vision hallucinations of wiggly lines, somebody there, regular hawking."

E

Hawking presumably refers to the cough. The side vision and hallucinations of wiggly lines of somebody there. Again in your view if that is what the patient was complaining about, what did he need to do?
A Again, it is difficult without a fuller history and no doubt there was a fuller history taken. Wiggly lines usually in my experience would come on preceding a migraine, but there is obviously no features of that here. So I simply cannot comment any further than
F to say that if somebody had disturbance of their vision, which is the best that I can make of this, I would want to look in their fundi and examine their visual field to check that they were normal and I would want a further more detailed history from the patient.

Q Then examination:

G

"Tongue chunky, feels too big in her mouth, rough, greyness, thyroid enlarged (++) nothing sinister, pulse 66 per minute, blood pressure 120/80."

The reference to nothing sinister, we will hear from Dr Skinner perhaps in due course. Can you explain that?
A When a thyroid is enlarged there is always a possibility that there could be thyroid
H cancer. The notes he has written do not help in that a thyroid cancer would present as a thyroid nodule and you would then want to check clinically to make sure there was no enlargement of the lymph nodes. If there was any suspicion you would go on to do

A further tests.

This is a patient who has normal thyroid function and has no reason, therefore, on the basis of a blood tests as we have them for the goitre and so I think that further investigation would have been warranted such as foreign antibodies and then I would like to know more about the goitre itself to know whether it was nodular and if there were nodules there I would have done something further about it.

B Let me just go on to add, if I may, that when I examine a patient and find a goitre, as with any endocrinologist, you record the goitre as being either diffuse or nodular and give more detail than is present here on a simple plus scoring system.

Q If we go to page 11 we find the original notes and we can see that there is something that I think Dr Skinner has missed in the translation, as it were. His typed note C ends, "FT4 and THS blood tests" and then "Thyroxine". If we go to the note at page 11 we can see on the left-hand side of the page that there seems to be a prescription of sorts. Can you help us with that?
A As far as I can make out (and the writing is not clear) it says: "Take 12.5 micrograms one week 25 micrograms three weeks." And that could only be for Thyroxine since they come in 25 microgram size tablets and therefore can be broken in half. You cannot get a prescription for T3 of those sorts of numbers.

D Q If we go over that page to page 12 we can see that his prescription did not in fact quite match up, if that is the correct translation of the note. The prescription does not quite match up to that.

> "Please supply Thyroxine 25 micrograms per day for seven days,
> followed by 50 micrograms for 21 days,
> E 75 micrograms 21 days
> 100 micrograms for 60 days."

MR JENKINS: I am sorry to interrupt. One really needs to look at the words "years ago" under the prescription on page 11.

MR KARK: Is that translated?

F MR JENKINS: I do not think the transcripts are entirely accurate, no, but I accept that. I think there are certainly a number of errors there and the Panel should use them as a guide, but not definitive.

G MR KARK: It is not meant as a criticism of Dr Skinner, it is not suggested that, we are just trying to glean what we can from the notes.

MR JENKINS: Of course.

MR KARK: *(To the witness)* Could we go back, please, to page 86 of the previous tab? This letter is also in Dr Skinner's notes at page 3 and here is a note dated 19 July 2004, so H just before this consultation where Dr Stewart writes to his patients saying,

> "I am pleased to tell you that your thyroid function tests, including free Thyroxine

A are completely normal indicating a good thyroid function at the present time."

Saying,

> "It would not be safe or wise for us, Dr Skinner, or anyone else to give you Thyroxine."

B On the page before we have those blood tests (pages 84 and 85 of tab 7) and we can see that the T4 is I think 13 with a reference range of 8 to 21 (that is page 84). The TSH is 0.67, reference range of 0.4 to 4. As I say, Dr Skinner seems to have had the letter from the GP and if we go to page 4 of Dr Skinner's notes whether he had the actual blood tests or not, he had the doctor's letter and he had this note from his patient saying, "My TSH result is 0.67."

C THE CHAIRMAN: I am sorry, give us the tab again.

MR KARK: Tab 8, page 4.

Q Where the patient writes:

> "Further to our telephone conversation on Wednesday 21 July please
D find enclosed a copy of the letter sent to me by Dr Stewart"

and revealing that the TSH result is 0.67. On the basis of that test result, if that is all that Dr Skinner had, any basis in your view for the prescription of Thyroxine?
A No, with the proviso that, as I have mentioned previously, there is the rare case of secondary hypothyroidism and if he had strongly suspected that then the free T4 would have been important.

E

Q Then you should do a blood test and look for secondary hypothyroidism?
A Yes.

Q You dealt with this much earlier on in your evidence. Your view was that this really meant a referral to an endocrinologist?
A No, as I have mentioned before, there is the rare case of hypothyroidism symptoms
F where the TSH can be normal but the free T4 is low because of an unsuspected pituitary problem and therefore for completeness one would do the free T4 estimation I mentioned right at the beginning of this morning that some laboratories offer both tests in order to prevent any patients with pituitary disease being missed. Other laboratories offer only a TSH and expect the doctor to elicit any other signs that suggest pituitary disease, so I am
G not saying any thing inconsistent to previous patients.

Q I understand that but perhaps I got it wrong. I thought you indicated that if there was a concern about pituitary disease that would indicate a referral to an endocrinologist. Am I wrong in that?
A Not at all but here we have no evidence of pituitary disease whatsoever. I am simply saying that in this situation Dr Skinner firmly believed the symptoms were those
H of hypothyroidism and only had a TSH, the next step would be to check the free T4. Were the free T4 to be normal, then that rules out pituitary disease so no such referral would be necessary. Had the free T4 been low then yes, at that stage you have clear

evidence of a potential pituitary problem and at that stage a referral to an endocrinologist would have been preferable.

Q I am with you. The letter that Dr Skinner writes to the surgery is at page 13 of tab 8, dated 25 August 2004. He writes this at the bottom of the page:

> "Her hair was rather thin and rough and she has a chunky tongue."

I ought to start at the paragraph above because he deals with some other signs and symptoms.

> "Patient D has a five year history of exhaustion and falls asleep most of the time with scattered aches and pains, associability, poor memory with interestingly side vision hallucinations which are very common in hypothyroidism and the poor soul was weeping during most of the consultation.
>
> Her hair was rather thin and rough and she has a chunky tongue and I thought an enlarged thyroid gland which seemed smooth and non sinister and moderate bradycardia of 65 per minute. Her TSH is perfectly normal but TSH levels are good servants but bad masters and I have taken a blood sample for FT4 and should have the results in a few days time."

Do you accept his comment there that TSH levels are good servants but bad masters and in what sense if you do?
A I do not accept that, but could I also add that just going back to this question of the goitre, we now have evidence that this was smooth, by which I take it Dr Skinner means diffuse and I take it when he says "non sinister" that there were no lymph nodes That may be his shorthand for this and therefore I am reassured that there was nothing in this goitre that needed further investigation except annual blood checks.

Q Over the page we see Dr Skinner writing again to Dr Blanchard:

> "I enclose [her] thyroid chemistry although we still await her FT3 reading. While her FT4 is a little low albeit within the 95% reference interval I would be quite prepared to institute a 4 month trial of thyroid replacement but will not proceed thus for ten days to allow you the opportunity to comment on this strategy."

Over the page, the T4 which he describes as "a little low" is seen to be 14.2 with a reference range of between 9 and 20 and the TSH is 1.9 with a reference range between 0.5 and 5.5. First of all at T4 do you regard that as low, high or what?
A It is normal and for the reasons reiterated again now but gone through this morning. Within the reference range I do not think it is profitable to talk about slightly low, slightly high. They are within the reference range so they are normal.

Q Again, any justification once that blood test was received back for continuing with the medication of Thyroxine?
A No, the possibility of secondary hypothyroidism has been ruled out by the free T4

level which is in the reference range and therefore hypothyroidism is not an explanation for this lady's symptoms.

Q You say at page 26 of your report:

"It is difficult to understand why Dr Skinner's letter of 25 August"

- which we have just looked at at page 13 of tab 8 –

"seems to imply the T4 level is critical for determining whether thyroid hormone treatment should be instituted while on 3 September he indicated the T3 measurement is awaited."

In the event the T3 level was also normal although that result was not reported until January 2005. We have that in the same section, I think, at page 26 where we can see that the T4 in January 2004 was 14.2, the TSH was 1.9 and the free T3 was 5.7.
A Mr Kark, may I stop you there? You will see that if you go to tab 8 page 15, this is a letter dated 3 September from Dr Skinner in which case, in the first line he says that he is awaiting the free T3 reading. That blood sample was taken at that time and you will see on page 26 of tab 8…

Q 26 August I think that it was received?
A Yes, so this is a specimen which is already long overdue.

Q Yes. Certainly if he had received this blood test in relation to the T3 back perhaps when he should have done – again I ought to ask you the same question, any justification on the basis of that of the medication that he gave?
A There is no justification for doing the free T3 in a patient suspected of having hypothyroidism if the TSH and free T4 are normal, so I do not know why this blood test was taken, but certainly it is normal and there is no justification there for Thyroxine treatment.

Q We were looking earlier at the letter that he wrote to his patient on 3 September referring to the T4 as "a little low". Can we go to page 17? I am sorry to go back. We see more of his thinking in relation to this patient where he writes on 3 September:

"I enclose your thyroid chemistry and although it is not significantly abnormal I believe you may benefit from a trial of thyroid replacement based on your clinical features."

That perhaps encapsulates it?
A It does except that again there is equivocation over the results. The patient is not informed the results are normal. The patient is left in some doubt. I would be in doubt if someone said there is something significantly abnormal. I do not know what that means.

Q Indeed the results we see at page 18 we have looked at before I think elsewhere. The results are, you would say, well within the reference range?
A Yes. I think it would have been preferable to say in this letter, "Your results are normal."

Q As matters moved on the family practitioners, or the general practice that this lady was under clearly were concerned and we can see at pages 19 and 20 a letter written and signed by three doctors at the practice, Dr Stewart, Dr Blanchard and Dr Jackson, all of whom are effectively asking Dr Skinner to stop. They all write, at page 19, the third paragraph:

> "Consequently we do not see any medical reason for her to go on to Thyroxine in accordance with normal guidelines that we work to as approved by our local endocrinology Dr Newrick"

and we heard yesterday that Dr Stewart had consulted Dr Newrick and he seems to have been of the same view. Further down the page:

> "We do not feel it is safe or appropriate for her to have Thyroxine."

In fact we can see what happened thereafter. You will see at page 21 Dr Skinner's reaction, if any. That is not fair, there was a reaction. He writes in his second paragraph:

> "As you know I have been copied in the joint letter. I have been asked to discharge you from my care"

and saying:

> "quite frankly I do not know how to proceed in such a situation where your family practitioner have expressed the hope that I will be investigated by the GMC."

Over the page you can see that he certainly was not dissuaded, it would appear, and there is a prescription for 17 November 2004:

> "Please supply sodium Thyroxine",

etc. The consultation seems to have taken place the next day, the day after the prescription. If that is right and this prescription was written out the day before he saw the patient, do you have any comment on that?

A It is certainly not something that I would do. I would always evaluate a patient first and, as I have said this morning, undertaken a thyroid function test and adjust the thyroid hormone replacement when this is necessary based on the results of the blood test.

Q On 18 November he sees his patient. I think we can go back to the typewritten note if we go keep a finger in page 24. The first follow up:

> "Present dosage 100 micrograms per day, looking better but crying a problem still. Fewer side vision hallucinations, hawking less, still smoking ten to 15 a day, dosage 100 micrograms per day. Tongue and thyroid both smaller.
>
> Treatment.
>
> 125 micrograms Thyroxine for three weeks"

then 150, then 175. B12 1000 micrograms per day.

Dealing with the B12, you commented on that for the other patients. Do your comments apply here?
A Yes.

Q What about the increase or the apparent increase in dose of Thyroxine at that consultation? The next blood test he actually gets – I am not sure there is another blood test, in fact. January 2005. If he increased the dose in that way as he described, would you have any comment to make about that?
A As I have mentioned, this is an increase without any blood test results and I would get blood tests first and then make a single dosage adjustment. It is typical that you would increase by 25 or 50 µg of Thyroxine if the TSH was still elevated, you might decrease by the same sort of amounts if the TSH was suppressed. I would never increase in such a staggered way in an otherwise healthy person. There is no need to. One makes a single dosage adjustment, gets the patient back, as I have mentioned, within two to three months for a repeat TSH which gives the TSH level sufficient chance to stabilise, then one has an accurate reading of that and then makes further adjustments that are necessary. In my experience normally two or three visits are sufficient to get the TSH levels stable.

Q Then there is a further follow up on 23 February 2005. We see that from the typewritten notes?
A Yes.

Q

> "Present dosage 125 micrograms a day, definitely better but still a short fall in energy. Patient will not disclose weight, no more side vision hallucinations.
>
> Treatment.
>
> 125 micrograms a day for a month"

and then 125-150.

On that occasion again I think there was no blood test?
A To be clear, the only blood test I could find in 2005 was 18 November.

Q Which we have at page 42?
A Yes.

Q So he seems his patient again in August 2005. On this occasion he notes:

> "Weight increased by 2 stones --- tongue still biggish, thyroid +.
>
> Treatment
> 175 micrograms per day for 6 weeks, 200 micrograms Thyroxine per day for 6 weeks"

and so again he is increasing the dosage without any reference to blood tests?
A Yes.

Q The next attendance is 18 November and then we know that he does take a blood test because, as you point out, we have the result at page 42. His notes reveal:

"Present dosage 200 micrograms per day.

Feeling quite well. Improved on thyroid replacement."

We heard from the patient that she was certainly not sleeping during the day.

"Mentally better. Lost half stone in weight.

Libido improved"

and then there is the examination.

The blood test we find at page 42 revealed, I think T4 as up to 27.2 and TSH was unrecordable. What do you say about that reading?
A If you turn to tab 7 page 109 you will see not only those two results but also if you look below them you will see a free T3 result which is also outside of the reference range at 7.7 when the reference range is 3.5 to 6.5, so as in other patients we have discussed, these results show thyrotoxicosis.

Q Dr Skinner described that on 25 November when he wrote to the GP, page 43 of tab 8 – sorry to keep jumping around again – tab 8 file 1 page 43. He writes:

"I now enclose her thyroid chemistry wherein the readings are on the high side but I think quite acceptable in relation to her clinical status."

It almost does not need comment from you. You say that this was not just a reading on the high side, this was evidence of thyrotoxicosis?
A This is thyrotoxicosis, yes.

Q In summary, which you do at page 28, you say:

"The management of this patient was seriously below the standards of acceptable practice. He saw the patient without referral from the GP"

- we have seen the problems with that –

"Despite two requests from the general practice to discharge her he continued to treat her. His initial history and examination were inadequate. He initiated unnecessary Thyroxine treatment when the patient was clearly euthyroid and adjusted the dose without performing adequate blood tests to establish if it was safe to do so."

Q Effectively you say he made this lady thyrotoxic. Have your views changed since you wrote this report?

A No.

Q You finish saying:

> "In addition he prescribed B12 without establishing a diagnosis of vitamin B12 deficiency."

B your conclusions are at page 28. You say:

> "The prescription of thyroid hormone replace in each of the four cases above did not accord with the principles of *Good Medical Practice*. On two occasions pituitary and adrenal disease were apparently suspected and certainly should have led to endocrinological referral."

C You set out *Good Medical Practice* May 2001 which states that:

> "Drugs and treatment should only be prescribed when the practitioner has adequate knowledge of the patient's health and medical needs."

D On that point are you saying that this doctor did not have adequate knowledge of the patients' health and medical needs?
A I think there are examples where, as I have mentioned, there is insufficient detail in the history and examination to be sure that alternative diagnoses have been excluded and also adjustments made to the medication without appropriate blood test.

Q You say at the end:

E

> "His practice is completely out of step with normal matters of dealing with hypothyroidism. Dr Skinner is not trained as an endocrinologist."

You have now seen quite a lot of material produced by Dr Skinner, I think. Is that right?
A Yes.

F

Q Including a book that has been written by him?
A Yes.

Q Has your view changed about his training and expertise?
A No, but I think it would be helpful if I could expand for the Panel to say that by stating as I do I am not saying that hypothyroidism should only be treated by endocrinologists. Far from it. General practitioners are perfectly able to treat hypothyroidism in general practice, primary hypothyroidism. I think that the difference here is that Dr Skinner is working outside of accepted guidelines and we heard from GPs on this score and is treating patients inappropriately by endocrinological standards when a GP might have sought advice from an endocrinologist about this sort of dilemma, someone who is apparently hypothyroid yet the blood tests keep coming back normal. That would be the point at which a GP would seek alternative advice.

G

H

Q You say that:

> "Despite this he has developed his own theories in endocrinology which fall outside accepted national and international practice and has no support from within the endocrinology community."

Two final matters to ask you about. Patient D, by way of example, felt much better when she was on thyroxine. She has kept on thyroxine. She says that her quality of life is better. Just take that as read. First of all can you give an explanation, you may not be able to, as to why patients can when they are put on thyroxine feel more alive and in their own terms better?

A I think there are several reasons why this may occur. I think in Patient D we have one particular explanation which is that this patient was on excessive doses of thyroid hormone and she herself said yesterday that she has been told that her doses remain excessive and as a result has started to reduce the dose and feels worse on 100 micrograms of thyroxin at the moment. It is well established that high doses of thyroid hormone given to people who do not need it can lead to weight less loss and increased energy. Indeed, if one takes the situation of patients who have a thyroid gland which is overactive, a dangerous condition, but a truly overactive thyroid gland one of the complaints I frequently get is that when we restore them to normal they complain that their weight goes on and they complain that they have less energy but this is a highly dangerous state to have been in and there is no question about the need for treatment. So I think one of the GPs likened this to amphetamines, I would not go quite so far as to say that but the effects are somewhat similar in terms of giving people enhanced energy and helping with weight loss at excessive doses.

There are other reasons besides this. Two of the patients, I think possibly three had evidence of depression. Depression waxes and wanes. There could have been a spontaneous improvement. Then there is also the possibility that the patients have responded as we heard, again from Patient D, to the undoubted empathy and warmth shown by Dr Skinner to his patients. She said that he was the first doctor that had properly sat down and listened to her concerns. That in itself can produce a placebo response to medication which is given.

So I think there are a number of explanations but I think we have evidence in patient D and I think in other patients who were excessively treated that perhaps these benefits were the result of excessive treatment.

Q Finally I wanted to ask you about adverse effects on the four patients. I do not know if we need to put Patient D to one side, as it were, because she is still taking thyroxine and she is not apparently being monitored but so far as the first three patients certainly do you say that there is any long-term adverse effect in relation to them?

A I think Patient A continues on thyroid hormone at slightly excessive doses. I would be not overly concerned about this because her TSH is not particularly low. It is in that 0.1 to 0.4 range that I mentioned this morning where the evidence is inadequate so far to say there is harm. I think I would probably would want to get a bone mineral density performed on her. I would want to counsel her about possible risks of continuing and I would want to continue to monitor and try and persuade her to reduce the thyroxine dose slightly further. I would be perfectly prepared to all of those and to allow her to continue on the dose that she is on. The other two will not have suffered any long-term

consequences.

MR KARK: Thank you very much. Madam, that is what I want to ask Professor Weetman in chief. We do have Dr Prentice here and what I am going to ask to do, Mr Jenkins is aware, I am going to ask to interpose him. Provided I can find his statement.

MR JENKINS: Can I say I am entirely comfortable with that, as the Panel will anticipate. There is no way I am going to finish asking questions of Professor Weetman today. I would not even want to try and I suspect you may feel that at quarter to three it has already been quite a long day for people. I am in a similar position. So I am entirely comfortable that Dr Prentice gives evidence now and I start with Professor Weetman today but I can promise you I will not finish him.

MR KARK: Professor Weetman, if you can stand down for the moment, you can remain in the room but you cannot speak to anybody about your evidence.

THE CHAIRMAN: The suggestion is that we take a short break. The microphone does it keep cutting in and out? So perhaps someone could look at that and we can come back in twenty minutes, five past three.

(*The Panel adjourned for a short time*)

MR KARK: Can we have Dr Prentice, please?

MALCOLM PRENTICE, sworn
Examined by MR KARK

Q I think it is Dr Malcolm Prentice. Is that right?
A Yes, that is correct.

Q Can you tell us your qualifications?
A I qualified at Kings College Hospital in MB BS. I subsequently have MRCP and an FRCP and I am on the register of specialists for general internal medicine and for diabetes and endocrinology and I was appointed at Mayday University Hospital in 1988 as consultant physician internal medicine and endocrinology and diabetes and I am an honorary consultant at St George's Hospital, Tooting.

Q You have what you describe as a sub-specialty in thyroid disease. Is that right?
A Yes, that is correct.

Q You have previously been the Secretary and Treasurer of the British Thyroid Association?
A That is correct.

Q That was between 1997 to 2001?
A That is correct.

Q I am going to ask you about your involvement in this matter when you received a letter from somebody called Dr Ince in relation to a patient that we are referring to as

Patient C. So could I ask you please not to reveal her name but look at the list that is about to be put in front of you?
A (*Same handed*) Yes.

Q Can you confirm that that is the patient we are talking about?
A That is correct.

Q I think you received a letter dated 4 February 2005 and I am going to ask you to turn up the larger file. Could I ask you to turn up tab 5 and go to page 12. Do you have a letter dated 4 February 2005?
A Yes, that is on my page 12.

Q This was written to you in your position as a consultant endocrinologist at the Mayday University Hospital. It is written by Dr Ince. Did you know Dr Ince?
A No, I did not no.

Q I expect you are fairly used to receiving letters, perhaps not quite of this nature but asking for your assistance and advice by GPs who want specialist referrals and assistance?
A Yes, that is true and during my time with the British Thyroid Association subsequently I received them not only from my own area but nationwide.

Q We can see in the second paragraph Dr Ince is asking for your assistance:

> "Dr Skinner saw one of my patients, a 32 year old lady, prior to her registering with myself on 1 September 2004. She had been started on thyroxin by Dr Skinner after consulting him privately at Devonshire Place in London and he started the lady on 150 micrograms thyroxine when her blood results clearly show her to have been euthyroid at the time. She presented to him with symptoms of tiredness and general post viral fatigue. This was in March 2004.
>
> She carried on with thyroxine until I advised her to stop this in October 2004 when she showed me a copy of her original blood test results.
>
> I have written to Dr Skinner asking for more information regarding his diagnosis of hypothyroidism and also for him to send me a copy of the blood tests explaining exactly why he did what he did."

Over the page:

> "I would very much appreciate your expert opinion on this matter and if possible if you are willing to put this into writing."

She sent you the patient's initial blood test. I am afraid you are going to have to go to another part of the file, if you can turn over tab 6 and go to page 3?
A Yes, I have that.

Q We can see that the blood test reveals, which was received by the laboratory on 10

March, which was a few days after Dr Skinner had first seen her, that the T4 was at 11.6 when the reference range was between 9 and 20 and the TSH level was between 2.2 with a reference range between 0.4 and 5.5. Do you remember receiving that blood test?
A Yes, I do.

Q If you go over to page 6 of the same section, tab 6, file 1, we can see that following the March consultation Dr Skinner saw this patient again. He makes this comment:

> "I think she is already improving on thyroid replacement although she has recently, and off her own bat, put her dose up to 200 micrograms thyroxine with (curiously) no thyrotoxicity which made me wonder if there is a conversion problem here.
> I thought we needed to rationalise and stabilise the situation and perhaps add in some T3 if there is a conversion problem."

I think you have seen this letter in the past and noted that the dose had been increased apparently by the patient. Did you see any details of any examination which would have revealed why Dr Skinner was able to say no thyrotoxicity?
A No, I did not.

Q We know that this patient carried on with thyroxine and she was advised to stop in October 2004 and we know that she did actually stop in October 2004. I think you are able to confirm that she has not gone back on it to your knowledge. Is that right?
A That is correct.

Q We will not go through the later notes because we have all seen them and I think you have seen them as well. I am going to turn to the letter that you wrote to Dr Ince and if you take up the second file now which is open on the relevant page, file 2, tab 2, page 5. You wrote this to Dr Ince:

> "Thank you for kindly copying me with your letters and correspondence regarding this letter and Dr Gordon Skinner.
>
> As you say the patient does not appear to have been started on thyroxine in spite of normal blood tests and the repeat results on 16 August which you kindly forwarded showed that she was in the hyperthyroid range for both T4 and T3. The reason for this is apparent from Dr Skinner's letter of 10 May where he has given her thyroxine in addition to Tri-iodothyronine which appears to have put her into the thyrotoxic range therefore for both hormones. As far as clinical advice is concerned I would be concerned at this level of therapy especially as the patient had normal results to start with. She may even have had a sick euthyroid syndrome resulting in slightly normal low T4 for some other reason prior to starting therapy which of course is not an indication for treatment."

Can you help us with that, please?
A Patients who have some other medical condition, be it a post viral fatigue or any other illness such as pneumonia or a heart attack, are known in that situation to have

lower levels of free thyroid hormones on many occasions. Not everybody but quite a number of patients. That is not an indication for treatment. The TSH in that instance is most often normal and if the patient is re-tested when they have recovered from the illness is then found to be normal thereafter. So generally what we do is to re-test the patient when they are better.

Q We have also heard this morning and this afternoon from Professor Weetman that there is also a scenario where you may have a normal TSH level but a low T4 which can be a sign of secondary hypothyroidism?
A Yes, you can have a normal TSH and a low 3T4 in which case the 3T3 should be checked and if there is no doubt dynamic pituitary function tests can be carried out to ensure that the pituitary is not the cause of the underactive thyroid activity. If that occurs then the rest of the pituitary should be checked because to start on a patient on Thyroxine you may have a deficiency of cortisol could be extremely dangerous and lead to their collapse.

Q You carry on in your letter,

> "I think you did the correct thing by suggesting that they stop the therapy and have further blood tests to follow up in due course and for the underlying cause of the symptoms which may or may not be related to the thyroid."

You deal with the fact that Dr Skinner did not write to you as the patient's general practitioner.
A To Dr Ince.

Q Yes, I am sorry, of course, to Dr Ince. As the patient's general practitioner. I think that is something you say that you advised to take up with the appropriate authorities.

You finally says this:

> "Finally, as former secretary to the British Thyroid Association, I was involved with the British Thyroid Association in trying to counteract a number of private practitioners who called themselves endocrinologists but did not in fact have higher medical qualifications in endocrinology, who took it upon themselves to start patients on Thyroxine in spite of normal thyroid function tests.
>
> One of the practitioners took voluntary erasure from the medical register when he came before the GMC a year or two ago. I know that Dr Gordon Skinner has similar views and I think we are duty bound as medical practitioners to report to the GMC if we think that a patient has come to harm as a result of receiving treatment which we believe is inappropriate and against standard guidelines."

Having seen the blood tests that you saw, first of all could you see any basis upon which this patient should have been started on Thyroxine?
A No, none at all without further tests.

Q Having re-read this letter now is your mind, as it were, still in accordance with the advice that you gave Dr Ince then?
A Yes, it is.

Q One other matter, were you concerned in relation to the possibility that this patient had not been adequately investigated for other causes of her symptoms?
A I think that is one of the major concerns which I had, not only that she had been started on Thyroxine to no benefit and in fact to her detriment, I feel, but that she had not been investigated, from what I have read from the letters, to any degree for any other conditions. There are many other conditions which will give symptoms of tiredness and fatigue and unless these are looked for they will not be found.

Q Yes, thank you. Would you wait there, please?

MR JENKINS: I have no questions, thank you.

Questioned by THE PANEL

MRS WHITEHILL: Good afternoon, doctor. I am a lay member so some of my questions really are trying to understand a very complex disorder. Patient C, her blood results indicated to you thyrotoxicosis. Is that right?
A The initial blood test indicated normal thyroid function.

Q Yes.
A The second set of blood tests after she had been started on a combination of Thyroxine and T3 indicated thyrotoxic range of thyroid hormone levels both from the T4 and from the T3 treatments. So it is up to a level which we would normally start treating for an overactive thyroid and could lead to heart and other complications in the long and short term, which I am sure you have been told about.

Q With her blood results in that range, would she be experiencing any symptoms of thyrotoxicosis?
A Patients may not be feeling any symptoms of thyrotoxicosis because it is well-known by thyroidologists that quite often patients have a lot of symptoms of an underactive thyroid and do not have an underactive thyroid and in the same instance some patients who have thyrotoxic blood tests can actually become very tired and apathetic and as a form of apathetic thyrotoxicosis. So we know that you cannot rely on symptoms, you have to do a combination of the blood tests and see if that concurs with your symptoms and then you can feel justified that that is the cause of the symptoms and then you can go on to make the diagnosis and then give the patient the correct treatment and then see again if the patient returns to normal and recovers. But tiredness can be seen at the upper end of thyrotoxicosis and also with an underactive thyroid, so you have got to be sure you are dealing with the right condition.

Q Thank you very much, that has been very helpful.
A Thank you.

THE CHAIRMAN: Dr Prentice, could I just ask you one, I am sure you possibly elucidate it for me, but in your letter to Dr Ince at the first you say what was the expression, “she may even have had a sick euthyroid”.
A The sick euthyroid syndrome was a condition where the thyroid hormone tests changed when a patient becomes ill for some other reason other than for a thyroid condition and the thyroid hormones then drop. In fact, they may drop below the normal

reference ranges, but we do not treat that, we treat the underlying medical condition and then re-test the patient and the thyroid blood tests if the thyroid is normal, come back to normal.

Q Thank you. Are there any further questions?

MR JENKINS: No, thank you.

Re-examined by MR KARK

Q Only in relation to Mrs Whitehill's questions. just to get the document in front of you if you turn to tab 6, page 10.

THE CHAIRMAN: File 1?

MR KARK: Yes, file 1. *(To the witness)* If you have a finger in page 10 and a finger in page 3. At page 3 is where you started with the treatment.
A Yes.

Q Or, rather, just before the treatment …
A Yes.

Q … where her T4 is (we have looked at this so I will not go through it again) and then page 10 is that the result you are referring to at August 2004 where the T4 is then 25.5 with a reference range of 9 to 20. T3 is 8.9 with a reference range of 3.5 to 6.5 and there is also a cortisol figure given. Were those the readings that you were describing earlier?
A Yes, they were.

Q They are?
A Yes.

Q Is that evidence of, in your view, either hypothyroidism or thyrotoxicosis?
A Yes, that is correct.

MR KARK: Thank you.

Further questioned by THE PANEL

DR ELLIOT: Sorry to come back. I notice in your letter that in the ---
A Sorry, I cannot quite hear you.

Q I notice in your letter to Dr Ince in the last paragraph that you mention treatment which was inappropriate and against the standard guidelines. At that time in 2004/2005 what was the standard guidelines?
A They were that the patient should be treated for an underactive thyroid if the TSH was raised outside the normal range, usually on more than one occasion and usually with TSH greater than around ten. These were the Lancet guidelines from the early 1980s at that stage.

Q So they had been extant for a long period of time?
A Yes, they had.

Q Thank you.

THE CHAIRMAN: Thank you, Dr Prentice. There are no further questions so that completes your evidence. Thank you for taking the time to appear in front of us?

THE WITNESS: Thank you very much. *(The witness withdrew)*

MR KARK: Could we have Professor Weetman back, please.

ANTHONY WEETMAN, recalled
Cross-examined by MR JENKINS

Q Would you be able to give us a working definition of health or healthy?
A The absence of disease.

Q Does the patient's view or any symptoms they complain of, is that relevant to the question of their health?
A A patient complains of a number of symptoms to a doctor and seeks an explanation as to what those symptoms are due to. Doctors are aware of a large number of diseases that may cause symptoms. As I said this morning, there are a large number of patients who come and have no discernible cause for their symptoms. As I mentioned, between 25 to 35 per cent of outpatient consultations are from patients who have no obvious known at present explanation for their symptoms. As I said this morning, that is not to say that those symptoms are not real and indeed as research continues I am absolutely sure we will find causes for those symptoms. So those patients are unhealthy, but we do not have a satisfactory explanation as yet for those symptoms and the definition that we give to that group of symptoms complexes are the function of somatoform disorders.

Q You would say then that there is a lot more research that needs to be done?
A I would.

Q Are you familiar with the concept that when a patient meets the doctor it is a meeting of two experts?
A I am indeed.

Q Perhaps we can just explain that for those who may not be familiar with it?
A I think that when you meet a patient, particularly one with unexplained symptoms, in whom after extensive investigation there is no obvious cause for the symptoms, there are three sorts of consultation that may occur. One is dismissive where the doctor may simply say. "All of your tests are normal. Go away. There is nothing wrong." That is clearly unsatisfactory.

There is a collusive type of consultation where the doctor may go along with the patient's fixed beliefs and collude with them in an erroneous diagnosis or give them treatment they feel is necessary even when it is not necessary. The third (and to my mind the best type of consultation) is the empowering consultation where a doctor empowers a patient to

understand that at present we have no explanation for symptoms and tries to help the patient to adjust their lifestyle to those symptoms in order to feel better.

Q The patient is the expert about how they are feeling and what their symptoms are?
A As I have mentioned, an empowering consultation is exactly designed to help the patient, who is the expert about their symptoms, understand them better.

Q Can we come to what hypothyroidism is because it is important that we have a working definition so that we can discuss it. It is an underactive thyroid?
A Yes.

Q Can you tell us how we define hypothyroidism so far as tests, signs and symptoms are concerned? Is it just the blood chemistry?
A No, it is not the blood chemistry because we do not believe we should routinely test every single member of the population. So when a patient describes symptoms then one tries to get to the bottom of them and one uses a number of blood tests depending on the symptoms that the patient presents with. If a patient presents with symptoms that are suggestive of hypothyroidism, one would do, as I have mentioned, thyroid function tests. Laboratories differ in the thyroid function test combination that might be used, but provided that you check the TSH and that is normal and provided that you have established that there is no evidence of secondary hypothyroidism, then you can be sure the patient is not hypothyroid.

Q Can we come to the reference range and I know you have drawn a second line as part of the triangle towards the right-hand side superimposed on it. The reference range, what is it, a modified Poisson distribution?
A No, I think it is a modified normal distribution and, as I said, it was a log transformed to make it into a normal distribution.

Q You have shown us how it is that 95 per cent of the patients within that reference range, 95 per cent of the patients that are looked at fall within the reference range?
A No, these are not patients; they are healthy subjects

Q Of the people who are tested?
A Yes, but a patient is someone who complains of disease. The point I made this morning very clearly is that one takes either a group of people who are otherwise healthy, have no complaints, laboratory staff, samples that are the sent in for screening, a variety of ways that one might collect such a sample of normal or one can go the whole hog, as it were, and screen individuals to make sure there is not the slightest evidence whatever of any thyroid abnormality and use those in your reference range and you will still get two reference ranges which overlap in iodine sufficient populations. They are not patients.

Q You are getting result for specific individuals?
A Yes.

Q You are putting them on a chart?
A Yes, and they range from one part of the reference range to another exactly as height varies in a general population.

Q I understand. Let us take height. Is there any problem, is there any difficulty with

those who are right at the bottom two and a half per cent?
A Well of course height charts are produced and when somebody lies outside of three standard deviations that is when one gets worried about their height.

Q Here we are dealing with two.
A Here we have two. As a conservative measure and, I mentioned this morning, that means that if you are lying just outside the reference range you are very likely to be normal and you are very likely to be normal because we have got that conservative element built in. We are not taking three standard deviations which would include 99 per cent of healthy individuals, we are taking 95 per cent.

Q Of any given patient, let us take a patient this time, do they have a normal TSH reading? Do they have one which is specific to them?
A Individuals do have set points for their TSH and these are healthy individuals we are talking about, not patients again, but healthy individuals' TSH is determined by their age, by their sex, by their body mass and one can show variations at that level. There are genetic differences between individuals and there are differences due to nutrition. As I mentioned, iodine deficient populations will give a different TSH range, but all of these factors are accommodated within the reference range which is why there is more than a single value which is normal.

Q I understand, but if you take one individual and you measure their TSH, is that going to tell you, that reading whatever it is, is that going to be their normal TSH reading?
A I am afraid I do not understand the question.

Q How can you tell if that individual, given one reading for them, whether that is a healthy TSH reading for them?
A Well we know that if you repeatedly test individuals over a period of months the TSH level will vary very little. Indeed, you have seen in some of the cases that we have looked at that the GP has repeated the TSH level and it has varied little.

Q Could there be people outside the reference range who are perfectly healthy? I think you have said they could.
A Of course.

Q There will be people within the reference range who are not healthy?
A As I mentioned to you this morning (and this is where my line rises up) we know that from the Wickham Survey, which looked at a group of people over 20 years, that if you followed those who had TSHs above two, there was a slight increased risk of future hypothyroidism. That is the vast majority ---

Q Can I interrupt you? You have turned the X axis into an axis over time, have you not, by plotting that in that way?
A No, it was meant to give you the idea that if you took a snap shot of somebody's TSH 20 years ago that would be a distribution of population who later became hypothyroid.

Q Let me come back to my question. Could you have an individual with a reading within the reference range for their TSH, but who was not healthy?
A In general terms, of course, you can, as you have heard from Dr Prentice, there are

many non-specific illnesses that can affect TSH.

Q I would suggest there may well be individuals who have an underactive thyroid who would appear within the normal chemistry range.
A I have not seen any such evidence.

Q Well that is because you defined hypothyroidism as reflecting the chemistry or abnormal chemistry. Is that not right? Your definition of hypothyroid requires that the chemistry is abnormal that is why you cannot contemplate a patient who is hypothyroid and who falls within the normal reference range?
A Well that is right. I am sorry, I may have misunderstood something here, but if a patient has a normal TSH and a normal 3T4 then we do not regard that as hypothyroidism.

Q The suggestion I make is that there may be patients who have an underactive thyroid but whose TSH falls within the reference range.
A I made the point to you this morning (and I think the Panel probably understood it) that the TSH is incredibly sensitive to changes within the thyroid hormone range and it is as T4 falls slightly there is a logarithmic, an amplified TSH response and we use that because that helps us to determine that the TSH is very sensitive to minor perturbations of T4.

I also described to you this morning the reservoir effect of thyroid hormones and the regulation that occurs at the tissue level for the distribution of T3 at the tissue level and that is why that even when you take individuals whose TSHs lie above the reference range, unequivocally above on repeat, so these are patients with subclinical hypothyroidism, most of the recommendations recently have been that treatment is not necessary until the TSH rises above ten. There are very few patients who have symptoms it is thought within that group that will respond to treatment. So if you like that is a further line of reasoning that even if one takes people whose TSHs are just above the reference range, many recommendations, not all, but many recommendations are that you will not need to treat even those until their TSH became ten.

Q I will come back to the point I made and I suggest that there will be patients who have signs and symptoms of underactive thyroid and who nonetheless fall within the normal reference range, the 95%?
A Except in the situation of secondary hypothyroidism where the T4 will be abnormal, I disagree.

Q I suggest the reason why you disagree is because you define hypothyroidism as meaning someone who falls outside the reference range for TSH?
A That would be the same as saying someone who has short stature if their height is five foot six. That lies within the reference range. You would not say someone who is five foot six was short stature. You have to lie outside of a good reference range in order to be considered abnormal and warrant investigation.

Q Let me agree that the blood tests for TSH and T4 and T3 are very accurate in that they do indeed measure what they purport to measure, components of blood and various chemicals within the blood. The question is what the correct interpretation to be placed on those levels is. Would you agree? To say that they are accurate and reliable means that they may accurately reflect what is in them but I suggest the important thing is the

interpretation that can be placed upon them. The question that arises is whether someone where the TSH is within the reference range, whether that actually means that the patient is not hypothyroid?

A All the evidence that we have so far is that that does not exist. I have mentioned the need for further research. If a trial were to be done which were to show that those individuals who had a free T4 of 3.5 truly benefited from treatment and a test was devised which could show that, then endocrinologists would of course shift their practice as they continually do, but so far no such information or evidence exists.

Q Would you agree that there is a need for large scale trials and many more? There have been many, many trials done but there is a certainly a need for many more to be done?

A I do not think – there is no need at the moment, I believe, for treatment of patients who have unexplained symptoms with normal TSH. I think that if we had the resources we would put that into answering questions more with regard to sub-clinical hypothyroidism where there is still some uncertainty because if one were able to show definitively the treatment of TSH at levels between, let us say, 4 and 10 was useless – and I think the evidence is on balance that it is not necessary but if one was able to show that definitively – then further investigation in those whose TSH levels were lower would be clearly futile.

Q Can I come back to the 95% reference range? We looked the other day with Dr Stewart at bundle 1 tab 8 page 15. It is Dr Skinner's letter to him. Dr Skinner is talking about Patient D's FT4 is a little low albeit it within the 95% reference interval. That is the section of the curve which you have shown us. Do not worry about the result. It is not the result I am interested in. It is Dr Stewart's understanding of what that meant that I am concerned with. I am going to ask you to keep a finger in there and turn to the previous tab, tab 7, page 99.

A Which page?

Q This is Dr Stewart's letter to the General Medical Council complaining about Dr Skinner and his treatment of this patient, Patient D. It is the bottom paragraph on page 99. Do you have it?

A Yes.

Q

> "I am concerned that this may have been an inappropriate use of Thyroxine and secondly by Dr Skinner's own admission (see correspondence) Mrs D's untreated thyroid function was on the 95th percentile."

I take that to be a reference to the correspondence that we have just looked at, the letter at tab 8 page 15?

A And it is a clear error by Dr Stewart.

Q Does it mean anything to you, "on the 95th percentile"?

A It means that it is an error because the free T4 on that occasion was 14.2 and the reference range is 9 to 20 and therefore it is well within the reference range and around the mean.

Q What does 95th percentile mean? If you are looking at the growth of a baby and there are charts, are there not, to show whereabouts it falls?
A As we have agreed.

Q As against other babies of a similar age?
A Precisely.

Q Dr Stewart goes on to say:

> "This means to me that if it is justified to treat her on the basis of her biochemistry, we will have to be thinking about treating 94% of the population with Thyroxine."

Does that make sense to you?
A As I have said, that is an error by Dr Stewart. I think he has misread Dr Skinner's letter. Dr Skinner says that the T4 is a little low albeit within the 95% reference interval and I think – but again I cannot speak for Dr Stewart – that that has been transformed into saying it is on the 95th centile. To be on the 95th centile you would have to be down here *(demonstrated on C6)* which is within the reference range. This is the 97.5% percentile and this is 95 centile. This free T4, if we were drawing up the reference range, is down *here*. It is neither.

Q If you are talking about FT4s or TSHs, do you ever talk about being on a certain percentile?
A I personally do not.

Q What you have told us is that reference range can vary from lab to lab?
A Because they use different assays and different machines.

Q We have seen, I think, in the course of the case, one lab changing the reference range for one of the readings?
A As the manufacturers do change their kit.

Q Your inference from that is they have changed that assay that they are using?
A Yes.

Q Or their testing process? I understand. I do not need to go back to the documents. Is it right that reference ranges may change or may differ from country to country as well?
A They differ depending on the iodine intake and so on.

Q You have seen, I think, a report from Dr Hartog, who is Belgian and I think you have seen included in his documentation some German readings - this is appendix 72 – where a German laboratory, the reference range for TSH range from 0.3 to 2.0?
A Indeed you remember this morning I mentioned to you the idea of getting a constrained reference range and I pointed out that there were four studies which had been undertaken, three of which showed that the constrained reference range - that is the range taking into account individuals who had absolutely no evidence of thyroid dysfunction as based on extensive testing, ultrasound examination of their thyroids, were exactly the same as the ordinary reference range taken from random individuals. However, I

A mentioned that a fourth study gave a much narrower reference range. That study came from Germany, form an area of prior iodine deficiency. I explained to you this morning that that was irrelevant to the UK population, which has been iodine sufficient for many years now.

Q The range of the TSH changed in the United States, or the guidance changed quite recently, did it not?

B A Not the universal guidance. Individuals have claimed that the TSH range should be narrowed, as indeed I have put in my report.

Q You have. Can I just take you back to it?
A Yes.

Q It is your page 7, I think. You talk about the United States National Academy of

C Clinical Biochemistry gives a reference range of 0.5 to 2.00 or 2.5 mU/L?
A No, I do not state that. What I say is that the National Academy of Clinical Biochemistry has indicated that ideal treatment may consist of maintaining the TSH level. That is not the same as the reference range with regard to diagnosis.

Q Forgive me. Was there not a recommendation in 2003 by the NACB that the upper limit of reference range should be reduced to 3 mU/L?

D A I happen to have the guidelines with me. The NACB guidelines state..

Q Can you tell us the year, please?
A 2004. It might be 2003 but I think it is 2004:

"In the future it is likely"

E - likely -

"that the upper limit of the serum TSH euthyroid reference range will be reduced to 2.5mU/L because greater than 95% rigorously screened normal euthyroid volunteers have TSH values between 0.4 and 2.5."

F It was based on that postulate that these studies that I have just alluded to and discussed this morning were undertaken and the three studies which are most relevant to the UK have shown that a constrained reference range, as indicated by the NACB, give reference ranges which are virtually the same as the unselected healthy population. This is written as it clearly states something which needs to be explored and research has established that in fact the narrowing of the reference range does not accord to what the NACB thought it

G might do.

Q I am suggesting that what they were saying is that the upper limit of the reference range should be reduced t 3 mU/L?
A Please can you show me where it says that?

Q Yes. Have you seen Dr Hammond's report?

H A Dr…

Q Peter Hammond's report?

A I have a copy here.

Q It quotes a reference Beloc(?), the guidelines committee of the National Academy of Clinical Biochemistry 2003, reported in 2003. Do you have his report?
A Yes, I do. I read the guidelines extensively and, as I say to you, the guidelines say – and I have got the paragraph in front of me, TSH upper reference limits, NACB guidelines page 34, there is no mention of the figure 3. The figure of 2.5 is mentioned and I have given you the statement which is the conclusion of that paragraph but I can certainly give you the whole page if that would help you.

Q I do not think I need to see it today. It may be I will want to look at it overnight and we can talk about it tomorrow. What he suggests and what I suggest to you, is that the range, reducing the upper limit to three units is the range quoted by the American Military Hospitals in the UK and endorsed by the American Association of Clinical Endocrinologists?
A Indeed, I cover that in my report, as you will see, and the largest protagonist of those is Professor Wartofsky and even if you take that upper limit of the reference range, none of the four patients under consideration came within that reference range.

Q I understand that but that means there is still a debate as to what the reference ranges should be. You are on one side of the debate but there are plenty on the other side?
A I think Mr Kark was clear at the beginning of this case but it is up to him to press the case that we are talking about four specific patients, those are the ones that I have commented on and in none of those, even by the most constrained reference range, even going down to 2.5 was their TSH outside that reference.

Q The point I have just put to you is that there is a debate, a wide-ranging debate, and you are very much on one side of it. There are plenty on the other side of the debate?
A No, there are not plenty within the United Kingdom. I have mentioned clearly in my report that there is a debate. I do not shy away from the debate, I think the debate is important. My appendix 2 is a publication which you will see I am an author on but there are many other authors from other countries within Europe and I think that shows that there is a European consensus and many of those names on those papers will be regarded as key thyroid experts in their own individual countries. They have all been members of the European Thyroid Association Executive Committee, for instance.

Q What would the consequence be if the upper limit of the range of TSH were to be reduced?
A The consequences would be that there would be much greater testing, much greater follow-up, much greater cost to the National Health Service. There is the possibility that treatment might be instituted in these patients unnecessarily. We know that when Thyroxine treatment is given to patients between 20-30% of patients, no matter how carefully treatment is monitored, tend to be over treated and it is the balanced view represented in appendix 2 that the dangers that would accrue even from lowering that on a theoretical basis, the risk would outweigh the benefits.

Q Can I shorten that answer and suggest this, that one consequence if the upper limit of the TSH reference range was reduced is that it would seem that more people, many more patients have an underactive thyroid than is presently the case? It would bring

more people into the definition of being hypothyroid?
A Obviously if you narrow the reference range you will have more people with sub-clinical hypothyroidism. The question is whether any of those patients need treatment and whether the treatment would have any benefit and whether there would be any risks.

Q Who is it that should treat thyroid problems, or patients with hypothyroidism? You were at pains earlier on today to say that it is not just endocrinologists who would be treating patients with thyroid problems but that other medical practitioners will do so as well quite routinely?
A Yes, this is something a general practitioner would be expected to treat.

Q What about other specialities of medicine?
A Again, provided they are following guidelines then I see no problem about treating it as long as they feel comfortable. It is something we treat our medical students about very early on in their careers.

Q Tell us what other fields of medical practice may come across patients with an underactive thyroid and may need to treat them? Psychiatrists?
A I cannot recall the last time I saw a patient referred by a psychiatrist but I am sure they occur there.

Q Is that because the psychiatrist is treating them and they do not refer them to you?
A No, I see plenty of patients with thyrotoxicosis and I get plenty of phone calls from individuals but yes, it is possible. The one situation where we do see it from psychiatry a lot is that the treatment that is often given for manic depression, lithium, causes hypothyroidism and since I see a lot of lithium-induced hypothyroidism referred by psychiatrists, I guess that there is not a lot due to other diseases that they are treating and then they are not able to treat lithium-induced hypothyroidism, so I do not think that your hypothesis is correct.

Q But it is not just endocrinologists is the point?
A Absolutely.

Q There are a number of other doctors?
A For sure.

Q A fair range of other doctors who treat such patients?
A For sure.

Q For a hypothyroidism patient, what should treatment involve? Let us assume for these purposes that the patient is hypothyroidism. What is the range of treatment that might be appropriate?
A Standard treatment would be with Thyroxine which is instituted, as I said this morning, in a dose which is appropriate based on one's experience, looking at the thyroid function tests. You then bring the patient back at eight to twelve weeks, check the TSH and adjust the Thyroxine based on the blood test.

Q What sort of dose would you start on?
A As I say, that depends on the test result, so if one had a TSH which was greater than 50 and a free T4 which was undetectable in a young, otherwise fit person with no

other medical complications, one might start at a dose of 100 to 15o micrograms because the dose of Thyroxine is related to body weight and therefore assuming they were normal body weight one might do that.

If one had an elderly patient who had a history of heart problems and even if her thyroid failure was very profound, one would start very much more cautiously at a dose of 12.5 or 25 micrograms of Thyroxine.

Q Can I show you what the BNF would say? I appreciate it is just a snapshot but I wonder if we could distribute copies? It is a BNF from March 2006l so that people know where it comes from. I think this is D4.

THE CHAIRMAN: D5. (*Same handed*)

MR JENKINS: I do not imagine you look at the BNF terribly often for thyroxine?
A No.

Q This is what was in the March 2006 documents:

> "Thyroid hormones are used in hypothyroidism and also in diffuse non-toxic goitre, Hashimoto's thyroiditis and thyroid carcinoma."

There is mention of neonatal hypothyroidism but I do not think we need trouble ourselves with that here:

> "Levothyroxine sodium is the treatment of choice for maintenance therapy. The initial does should not exceed 100 micrograms daily, preferably before breakfast or 25 to 50 micrograms in elderly patients or those with cardiac disease, increased by 25 to 50 micrograms at intervals of 4 weeks. The usual maintenance dose to relieve hypothyroidism is 100 to 200 micrograms daily which can be administered as a single dose."

I do not deal with children or infants:

> "Liothyronine sodium has a similar action to levothyroxine but is more rapidly metabolised…",

This is T3:

> "…and has a more rapid effect; 20 micrograms is equivalent to 100 micrograms of levothyroxine. Its effects develop after a few hours and disappear within 24 to 48 of discontinuing treatment. It may be used in severe hypothyroid states when a rapid response is desired."

I think you told us that in severe hypothyroid states you would use T4 rather than T3?
A I do not think I did. I think I said that in a condition of myxodoema coma, I cannot really remember but there is no trial of any one treatment in severe hypothyroid, myxoedema coma, people use T3, T4 or combinations.

Q Let us come onto the levothyroxine sodium:

"Indications hypothyroidism."

The Panel can read the cautions and if we need look at any particularly please tell us which. I was going to go on to the contraindications:

"Side effects usually at excessive dosage (see initial dosage above) include anginal pain, arrhythmias, palpitation, skeletal muscle cramps, tachycardia, diarrhoea, vomiting, tremors, restlessness, excitability, insomnia, headache, flushing, sweating, fever, heat intolerance, excessive loss of weight and muscular weakness.

Dose
ADULT initially 50 - 100 micrograms (50 micrograms for those over 50 years) daily, preferably before breakfast adjusted in steps of 50 micrograms every 3 - 4 weeks until metabolism is normalised (usually 100 to 200 micrograms daily)."

Deals with cardiac disease and talks about changing the dose, initially 25 daily or 50 micrograms on alternative days adjusted in steps of 25 micrograms every 4 weeks. It deals with congenital hypothyroidism and juvenile myxoedema. I do not need read about neonates and children. It tells us the cost of non-proprietary levothyroxine. I am not going to read the liothyronine sodium.

On the basis that Dr Skinner is starting patients off when he did prescribe thyroxine at 25 micrograms for seven days and then increasing the dose to 50 micrograms for several weeks and then increasing the dose a number of weeks later, would you agree that his prescribing regime falls in with the suggested in the BNF as appropriate?
A Except that the patients were not hypothyroid, yes.

Q We will come back to that. I am talking about the prescribing regime. Dr Prentice may have be misinformed about starting a patient at 100 or 150 micrograms but we will come that when we hear Dr Skinner's evidence. What Dr Skinner was doing by way of prescribing; going up in stages, falls very much in line with what is proposed here?
A It is.

Q Can we talk about the risks of treatment with thyroxine or other types of thyroid replacement. You have talked about atrial fibrillation?
A Yes.

Q And you mentioned osteoporosis and bone marrow density?
A Bone density, not bone marrow.

A Bone mineral density, it is my own note I cannot read. What is the evidence that patients who may be over replaced with thyroid replacement stand a risk of bone density problems or osteoporosis?
A As I mentioned this morning the evidence was collected and summarised in JAMA, a large number of references were looked at. Studies have been confusing over

time but I think a clear pattern has emerged now and that is that in those individuals who are pre-menopausal or men there is insufficient evidence to conclude that there is long-term harm. That is not the same as saying there is no evidence but there is insufficient evidence. However, in individuals who are post-menopausal, that is women who are already at risk of developing osteoporosis, there is evidence that, fair evidence that bone density can be affected. We also have the evidence from the trials of T4 at T3 of bone markers that I mentioned this morning. In those there was an increase in bone markers which are a surrogate for an increase in bone turn over. That I fully appreciate is not the same as saying that this is osteoporosis or an increased risk fracture but it is an indication that the excessive doses of thyroid hormone are having an effect on the bone.

Q Would you agree there are a significant number of trials and papers which suggest that there is no effect?
A There are a number but I think increasingly as we look with more sensitive markers we are seeing evidence of an effect and I think the evidence was weighed fairly by the experts in the JAMA paper who considered all of the trials.

Q What I would suggest is this is part of a controversy. There is debate on both sides as to whether there is any effect on the bone density?
A That is precisely why where there was equivocal evidence the Panel concluded that there was insufficient evidence, and I pointed that out in the range of 0.1 to 0.4 for the TSH, they claimed there was insufficient evidence. So the evidence was equal on both sides but where there was fair or good evidence in favour of an effect then they stated that.

Q Let us come to the aim of treatment or goal of treatment. You deal with this in your report at paragraph 6.2 on page 6. What you say at the bottom of page 6 is that a UK consensus statement published in 1996:

> "…stated that the correct dose was one which relieved symptoms and would in most patients result in a normal or raised serum thyroxin concentration."

That is a T4 figure. Yes?
A Yes, but not a free T4 figure.

Q And normal T3 concentration?
A But, again, not a normal free T3.

Q And a normal or below normal serum?
A Based on assays in use at that time.

Q What you then go on to say is that practice has developed since that publication and you go on to talk about JAMA, the Journal of the American Medical Association, publishing a summary in 2004. Is it a British journal?
A No, it is the journal of the American Endocrine Society.

Q Published in 2005 is the one you give a reference to?
A Yes.

Q Can we remind ourselves that Dr Skinner was treating these patients between 2002, 2003, 2004 and 2005?
A I think the risks with regard to the heart were recognised as far back as 1994.

Q I understand but you are not suggesting that Dr Skinner should be following guidelines and suggestions published in the journals after his treatment of the patients, are you?
A I think that between the guidelines that I mentioned here in 1996 and some of the patients being treated there were a number of developments which would have led endocrinologists over that time to be far more cautious about suppressing the TSH.

Q Dr Skinner's expressed aim was to treat the symptoms of these patients. Would you agree? That was why he was prescribing?
A Apparently so.

Q That follows what you have said at the bottom of page 6; the correct dose was one which relieved symptoms?
A But these guidelines concern those patients with *bona fide* hypothyroidism.

Q Which you define as having abnormal biochemistry?
A Thyroid function.

Q I suggest that that is just one definition of hypothyroidism and that there can be patients who are hypothyroid but whose blood chemistry falls within the reference range?
A We will have to differ on that.

Q I agree we differ on that but I suggest what was happening with some of these patients was that Dr Skinner was treating them which may have resulted in a normal or raised T4 concentration - and I am looking again at the bottom of page 6 - and that there was for some of them a normal or below normal TSH concentration. Those are the results that we have looked at?
A No. You have also missed out the fact that it says clearly a normal Tri-idothyronine concentration.

Q That is for T3
A Yes, and we have evidence that the patients did not have a normal T3 concentration, they had elevated T3 concentrations. These guidelines were based on practice in treating patients with thyroid cancer and this is still the case in treating thyroid cancer. One can give patients with thyroid cancer a dose of thyroxine which is sufficient to deliberately suppress the TSH which is known to drive tumour remnants.

Q Do you say that in the report? These guidelines were set up to treat cancer patients?
A If you let me finish, the principles, I am saying, are based on the concept that has been derived in treating patients with thyroid cancer and it is a complex area so please bear with me. You can if you are treating patients with thyroid cancer give a dose of thyroxine which is sufficient to suppress the TSH which is of benefit to any residual tumour. The T4 levels can be high in the blood, the TSH levels can be low but the principles of treatment there are to keep the T3 levels normal. We know that the T3 levels are the active hormone and by doing that one thereby minimises the risk of

thyrotoxicosis. That is why that was written in such a way at that time but we see with the patients that Dr Skinner has treated that where this has been measured on occasion the T3 is elevated. Patient D. We did not get measurements in Patient B but I am convinced based on that T4 level the T3 would have been elevated and in Patient C. So they fell outside even those guidelines.

Q Forgive me. We will come to the specific patients later on but again and again you speculated, have you not? You have speculated as to whether this may have been depression, I think it probably was depression in the case of some of the patients which is what led to her condition and her symptoms. You are speculating there again that in respect of one of the patients the T3 reading would have been abnormal?
A I think with a T4 of 39 in my experience it is highly likely it would. Where I have speculated today I have been very clear to point out to the Panel that it is speculation.

Q Let us come to atrial fibrillation. What you said a few minutes ago was that the risk of that was known for some time?
A Yes.

Q Known for a number of years?
A Yes.

Q When a doctor prescribes a drug to a patient would you anticipate that the doctor would quite routinely say to the patient: if you experience this, or if you have that problem, or if you are not feeling well on the drug then either stop taking it or get in touch with a doctor. Phone me up?
A Yes.

Q Come and see us. That is what you would expect a doctor to do if they were prescribing almost any drug?
A Yes.

Q Particularly drugs that could have serious side effects. If it were the case that Dr Skinner were cautioning patients as to possible side effects that is what you would want to happen. I accept you would not have wanted to see the patients prescribed at all but, again, if Dr Skinner had advised the patients about possible side effects and what they should do, you would agree, I suspect, that that would be appropriate practice?
A Yes.

Q So far as patients taking medication we have an example or two here of patients taking more than was prescribed for them. Taking at a higher level. Would you agree that it is not uncommon for patients of any kind of doctor to either not take the drug that was prescribed or to take more than was prescribed for them?
A Indeed it is common.

Q You do not blame the doctor if that is what happens?
A I do blame the doctor if the treatment was unnecessary in the first place because that exposes the patient to the potential to acquire the drug in order to overdose in the first place.

Q But if the patient was being treated appropriately - I agree we differ on that, we

will come to that. If the patient was being treated in a way which was not inappropriate and the patient took more than had been prescribed you would wish to know that the doctor had cautioned about it?
A Yes.

Q Asked them not to or pleaded with them, whatever the language is?
A For sure.

Q That, it would appear, would you agree, is what happened in this case?
A Yes.

Q Can I ask about note keeping. You work in a hospital. For patients that you see in clinics there would be other doctors that will see those patients either on the same day or on different days from when you saw them. There will be other doctors that treat the same patients that you do?
A No.

Q You are the only person who makes a record?
A Yes.

Q Generally in hospital medicine then, moving away from your practice, is it the case that for most patients they may be treated by a number of doctors over time?
A There was a time when I had a registrar, that is right.

Q I understand. Cuts have been forced on you like others in medicine but it is certainly the case, is it not, that those who make records about patients can anticipate that other doctors, other healthcare staff will look at those records at some future date?
A Sure.

Q For that reason it is important that every relevant part of the consultation is recorded in the notes?
A Yes.

Q For those who are the only person who ever see the patients would you accept that sometimes the doctor may not record everything that they have done with the patient or every piece of advice because that is their invariable practice and they take a slight short cut?
A No, I would not accept that as good practice. The reason for that is that the Medical Defence Societies are very clear that if one does not record oneself as having done something then to all intents and purposes it never took place. I have been an expert at sufficient numbers of cases now to realise that doctors can often do things but they are not recorded and unfortunately that invariably counts against them and therefore all of our medical students have it hammered into them from the outset that notes must be kept as completely as possible.

Q Well I understand that as a statement of good practice. My question of you is what doctors actually do and you have told us you have been in enough cases to know that it has happened on a number of occasions?
A Yes, and then the doctor has suffered the consequences.

Q That may be right, but that has happened because the doctor has not recorded everything that took place in the consultation.
A I think that if one is seeing a patient for a consultation which lasts half an hour to an hour, as we have heard some of these consultations, I cannot see how any doctor does not have sufficient time to record accurate and full notes.

Q I am just trying to deal with the real world, Professor Weetman, and look at what doctors may actually do.
A I work in the NHS, I run a medical school and I keep full notes.

Q You have indicated that your experience is such that you practise defensively; you practise with a view to the possibility that there might be a claim being brought against you and you are concerned to ensure that you should be properly protected should such a claim be brought?
A No, I said that that is one reason for keeping complete notes. You, yourself, have said another reason is that others may wish to look at the notes at a future date and I have indicated to you, this is not just my practice, it is the practice we teach our medical students.

Q I understand. Plainly medical students should be taught the best thinking and taught best practice as they may not learn it later on.
A If I could go on ---

Q Please do.
A When we have senior house officers or we have registrars, it is our practice to vet the notes during the first few weeks of that SHO or registrar's experience with us to make sure that the notes are up to the standard that we wish.

Q Can I come onto private doctors?. We saw in Dr Prentice's letter the suspicion that there may be concerns by those in the NHS or others about private doctors. There are concerns, are there not, about those who may prescribe privately for patients? I am talking in general terms.
A I see patients myself privately, I am not aware that anyone has expressed concern about that.

Q What is important, I am sure that you would agree then, is that the doctor should be well intentioned and should have an appropriate approach to patient care?
A Yes, and I think should also make clear to the GP what their level of expertise is. The GP should be aware when they refer a patient for a second opinion what sort of opinion it is that they are getting.

Q You have seen but the Panel have not, you have seen a lot of letters from doctors who have referred, GPs, who have referred patients to Dr Skinner. Is that right?
A Yes.

Q What the Panel have heard from is a handful of GPs who have complained about him, but you have seen a significant number of GP letters praising Dr Skinner's approach and the success he has had with their patients?
A Are you referring to bundle 20 in my original set of ---

Q I do not know which bundle it is.
A Well I cannot remember how many patient letters or GP letters I have read at this stage, I am afraid.

Q On the question you have just raised that the GPs should know who they are dealing with it is absolutely clear from the letters that you have looked at that GPs do know. I see someone about to rise.

MR KARK: I am sorry, this area that Mr Jenkins really wants to examine we had discussions about.

MR JENKINS: Well I am going to move on. I will move on. *(To the witness)* I am going to ask about patients. Can you tell us why the patients like Dr Skinner?
A I cannot tell you, I can speculate but you do not seem to like speculation.

Q You have seen patient letters as well?
A Again I would be speculating from the letters, would I not? If you wish me to speculate, I am happy to.

Q I would encourage you to – you have indicated some reviews in your report which have been redacted, the Panel have not seen those views as to why it is that patients should have such a high regard for him.
A As I have said earlier I think this morning, I have no doubt that Dr Skinner is a very empathic doctor. He spends a lot of time with his patients. We heard from a patient yesterday who said very clearly that her relationship with the GP was such that she only had ten minute consultations and he did not listen to her symptoms and Dr Skinner was able sit down and spend a long time going through those symptoms with her.

I have mentioned also another possibility or an additional possibility rather than an alternative possibility in the different styles of consultation and I have indicated the three types of consultation which may occur and instead of being rejected I think this was evidence perhaps – well evidence certainly in fact that in some of these cases Dr Skinner was colluding with the patient's own beliefs that their symptoms could only be due to thyroid disease and, of course, if someone feels that they have been battering away trying to get a doctor to understand and the doctor has rebutted them and has not empowered them, the third type of consultation that I mentioned to you, then of course one may end up feeling very, very sure that at long last one has found the answer to one's concerns and I have no doubt from many other bits of evidence that I have had from patients themselves that they feel very strongly that this diagnosis of hypothyroidism is being missed by conventional testing.

Q Is this the placebo then? Patients are deluded into thinking that they are getting better?
A No.

Q As a result they do get better?
A No, I did not say that. What I have said clearly is that there are several possibilities for the therapeutic benefit which has been seen in one or two of these patients, that is that they may be getting a benefit from the excessive doses of thyroid

A hormone which have been given to them and we know that and we have been through that.

I have mentioned also that just having an empathic consultation itself and reinforcement of one's ideas can act as help. We know that cognitive behavioural therapy is one the best treatments for chronic fatigue syndrome. If these people were suffering chronic fatigue that could have helped. If they were suffering from depression, that could have helped.
B Cognitive behavioural therapy does not have to be sophisticated, it can be simple support at the kind of level that Dr Skinner was giving.

Q Can you explain ---
A Then, of course, there could be a placebo effect and then, of course, they could have had conditions which remit and relapse. Do not forget that one of these patients said that she felt better once treatment had stopped.

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Q That is patient C.
A Patient C. Patient B, as I understand it, she has stopped treatment and has not, we are not able to determine whether she felt better or worse from stopping treatment. Patient A, when she gave her evidence, she was uncertain of the current benefit of continuing treatment and has not tried stopping it.

D We only have one patient in whom there is clear evidence of benefit and that is patient D. With Patient D we have evidence that she is thyrotoxic and she told us that now that she has reduced the dose then she started to feel worse and so my first hypothesis that I have just given you, which is that this is an effect of excessive thyroid hormone, seems to be borne out in the case of patient D.

Q You do talk about placebo effect in the parts of your report that have been redacted
E and it is the bottom of page 30 and over to page 31 which the Panel do not have.
A I do not shy away from the fact that part of the response in some of these patients could be a placebo response enforced by the empathic attitude of the doctor acting as a kind of cognitive behavioural therapy in collusion with their beliefs, but I have also given you alternative explanations.

Q Mrs A's constipation was alleviated once she was placed on treatment. Is that a
F placebo effect or because the doctor is empathic?
A Patient A, from what I recall, had seen a consultant gastroenterologist and had extensive investigations including endoscopy of all of which was negative. Ninety-five per cent of outpatient consultations – sorry, 95 per cent of consultations to general practitioners for abdominal symptoms turn out to be either irritable bowel syndrome or
G non-specific dyspepsia. Irritable bowel syndrome is a function of somatoform disorder and just like autoimmune diseases, functional somatoform disorders tend to cluster together so patients with chronic fatigue are more likely to have irritable bowel syndrome. I think this patient had irritable bowel syndrome of which constipation is one cause.

Q Again you have not examined any of these patients.
A Yes, but I have read Dr Veitch's letter.

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Q You saw one of them on the video link, that was patient A, and you saw patient D the other day.

A I have read Dr Veitch's letter.

Q Are you suggesting that patient A had depression and was part of the problem?
A I am suggesting it is a possibility.

Q You have read the letters from the two consultants saying that she does not suffer from depression in December 2003? The month before Dr Skinner saw her. You are suggesting without having seen the patient, that depression may well be part of the problem?
A No, that is not what I said. I did not say it may well be part of the problem. I said it is a possibility.

Q Can you tell us why patient D's life should have changed in the way that it did? She told us she would still be on the sofa if it were not for Dr Skinner and a prescription of treatment for her?
A She was given excessive doses of Thyroxine and she started to feel unwell again now that she is no longer thyrotoxic.

Q We know she had been, her final six years, imprisoned in her own home being - and I am sorry for upsetting her but it was upsetting when she reflected on how active she was able to be as a mother to her children. We know that she was sleeping all the time and part of that period, I think in 2002, a couple of years before she was treated by Dr Skinner, she was on antidepressants for a year and she described herself as a zombie. For the rest of the five or six years, she had no quality of life whatsoever. Are you saying that the reason why her life should have been completely turned around was because Dr Skinner was empathic and talked to her and that the drug had nothing to do with it?
A You are continuing to try and force me into making a single diagnosis in these patients which, as you rightly say, I have not examined. I am simply discussing possibilities and I have said, I think, specifically in the case of patient D, we have good evidence, both from her testimony and from the blood results, that when she felt better she was thyrotoxic and when her thyroid hormone has been reduced recently she has felt less well, therefore a likely possibility is that part of the benefit that she has derived has been the period of time when she was thyrotoxic. Of course, time will tell. That is one possibility. There are other possibilities which I have already elicited for you.

Q Well again, you have seen many letters from patients whose experience of life has been very similar to that of patient D.
A Mr Jenkins, I see plenty of patients with chronic fatigue syndrome and I see many of them get better without help of Thyroxine as well. You may find this very difficult to understand, given my extensive experience, I do not.

Q I wonder if we could just look at Dr Skinner's position. The Panel have the material in the bundles in front of them but I do not think they have been referred to just yet. If we turn to bundle 2. I think the Panel have tab 4. If you turn, please, to page 78 there is a document which sets out a little bit about Dr Skinner?

THE CHAIRMAN: I am sorry, what is that page?

MR JENKINS: Page 78. I am sorry, madam.

THE CHAIRMAN: Thank you.

MR JENKINS: You will see his background ---

MR KARK: Could Mr Jenkins just establish what this is because the Panel do not know.

MR JENKINS: Yes, of course. The Panel should know - well perhaps we should go to page 2 of this bundle. This is material arising out of a request that Dr Skinner undergo a performance assessment and the Panel should find at page 2 a letter to Dr Skinner from a representative of the General Medical Council. It is actually Eversheds, the solicitors to the GMC, enclosing, you will see, from the fifth paragraph, enclosing a document called an Assessment Portfolio:

> "The Assessment Panel require you to complete this in advance of the assessment to provide information for them about yourself and your practice."

There then follows over many, many pages an assessment and attached to that, if you turn to section 9.

THE CHAIRMAN: Section 9?

MR JENKINS: Page 73, I am sorry. There are additional comments referring to Good Medical Practice and over then, please, to page 76, some appendices attached by Dr Skinner to the documents that he was asked to complete.

The second of those is the document I have asked you to look at page 78, setting out in the first paragraph in very short form Dr Skinner's experience and qualifications and then goes on to talk about the management and diagnosis of hypothyroidism.

He talks about increasing nervousness among colleagues in family practice due in some measure to difficulty and uncertainty in managing patients who are clinically hypothyroid but whose thyroid chemistry lies within the 95 per cent confidence intervals.

Can I take you on in that bundle, please, to page 128? This is a paper, Dr Skinner is the lead author, published in 2000, and sets out the results of a small study that he was engaged in. Can I read the purpose of the study which was:

> "To examine clinical response to thyroid replacement therapy in patients considered to be clinically hypothyroid but with normal thyroid biochemistry."

I do not set out the design or the materials or methods, but I imagine you would say it is a relatively small study with 139 patients.

A The size of the study does not concern me.

Q The conclusions are that:

> "Clinically hypothyroid but biochemically euthyroid patients have favourable clinical response to thyroid replacement which correlated with the level of thyroid replacement. It is suggested that these findings be examined in a prospective and placebo controlled clinical trial."

A

I am not going to go through the paper, but I give you the opportunity to comment on it if you wish.

A Yes, the paper is published in the Journal of Nutritionally and Environmental Medicine. I tried to look up this journal on the ISI web of knowledge. This is a ranking system for journals within the science fields. It includes the most important journals in each scientific field and the selection for journals for inclusion in the ISI list was based on

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peer review by scientists within those respective fields.

The paper, as I say, is in a journal which does not appear in this web of knowledge and therefore has a poor standing in the field. The paper, for instance, cannot be accessed through AdMeD which is the standard way, this is the access to the National Institute of Health library of clinical papers. This is the standard way in which scientific papers in medicine would be accessed by clinicians.

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It is not an endocrinology journal and I do not believe it would have been accepted for publication in any endocrinology journal that I am aware of and I doubt that it has been refereed by endocrinologists.

Turning to the paper itself you will see that in 7.1 of my report which you have (this is page 11) I have commented on this study. I mention there that the data (this is on page 12

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now) so it starts at the foot of page 11 and goes on on page 12, is that I find it difficult (and I speak with considerable editorial experience) to interpret this paper scientifically. There is no control group, that is there was no group that were not given treatment and whose symptoms were then compared to those that were treated. The survey is a retrospective one, that is patients were treated and then examined after treatment was initiated, whereas an ideal trial would be one which is prospective and the assessment is subjective, there is no symptom score, for instance, employed and it is not blinded by

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which I mean that the people doing the assessment were not aware of what treatment was being given. Therefore, I cannot make any conclusions from this paper had it been submitted to a journal that I have been involved in either as an editor or an editorial board member, it would not have been accepted for publication.

Q I understand. Page 135, tab 4. It is pages 122 of the journal, if one looks at the

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top left-hand corner, it is absolutely clear that what the authors of the paper, including Dr Skinner, are recognising is that there is no control group, they cannot exclude a placebo effect – I am looking at the bottom part of that written part of the page – and if one goes over what they are seeking, if one goes to the final paragraphs at page 137, in Summary:

> "We feel that the results of this study should be subjected to the

G

> scrutiny of a formal clinical trial."

I think they recognise that this is perhaps a start, that they are seeking, are they not, further trials?

A Speaking with my experience as an editor and editorial board member of many endocrine journals, this would not have been accepted simply because it is a hypothesis which they should have been tested properly. You will, however, see if you turn to page

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135 again, right at the foot that the authors welcome the trial which has been instituted, they say, at Stobhill Hospital, Glasgow, so they were producing this at the same time they were aware that a formal trial, a properly conducted trial, was under way and indeed if

you go to my report you will see that I mention that trial too and so whilst welcoming the report in this paper, they do not appear to welcome the conclusion of that trial when it was finally concluded, which was that there was no benefit objectively from thyroid hormone treatment in euthyroid individuals when given in a prospective placebo controlled fashion.

Q Let me take you to the next document, page 138. This is as letter in the BMJ in 1997. We can see the Thyroxine letter:

> "Thyroxine should be tried in clinically hypothyroid but biochemically euthyroid patients"

and the authors, of which Dr Skinner is the lead author, write as follows:

> "We wish to question present medical practice which considers abnormal serum concentrations of free thyroid and thyroid stimulating hormone, those outside the 95% reference interval to indicate hypothyroidism but incorrectly considers 'normal' free Thyroxine and thyroid stimulating hormone concentrations to negate this diagnosis. It is unusual for doctors to start Thyroxine replacement in clinically hypothyroid but biochemically euthyroid patients."

They then go on to refer to 80 patients. I do not need to read anything on that column except the bottom four lines:

> "We contend that an incremental three month trial of Thyroxine treatment in clinically hypothyroidism but biochemically euthyroid patients is a safe and reasonable strategy. The dangers of osteoporosis and cardiac catastrophe, particularly during a three month trial, are sometimes quoted but these worries are unfounded and condemn many patients to years of hypothyroidism with its pathological complications and poor quality of life. We urge that the question of clinical hypothyroidism in biochemically euthyroid patients should be subjected to a formal clinical trial."

What do you say about a trial of Thyroxine in patients who are exhibiting signs and symptoms which may indicate hypothyroidism?

A I would agree that it is safe for three months provided the TSH is kept within the reference range. I would not agree it is reasonable because I do not think that this constitutes hypothyroidism and we know that because the trial that they urge be performed has been performed and the results have shown no benefit, so based on current evidence I do not think that there is a need to do this but I would agree with the contention that giving Thyroxine for three months, keeping the TSH normal, would have no ill effect.

MR JENKINS: Madam, I wonder if you would allow me to stop there? I have got a lot of other material that I would like to look at again before I keep going and, if I may express my own view, it has been a long day. It may be a view you share.

THE CHAIRMAN: Yes, I do share that and I think that is acceptable. We will meet tomorrow at 9.30. Could I also say that on Monday we will be finishing at three o'clock.

Thank you very much.

(The Panel adjourned until 9.30 am on
Friday 6 July 2007)