MEDICAL PRACTICE

Style Matters

Peer review at work

In July 1984 Dr P B S Fowler and Dr J W Dean submitted a manuscript to the "BMJ" on "Borderline hypothyroidism—a risk factor in women with coronary artery disease," which was sent to a referee. As a result of the referee's comments we rejected the paper, but Dr Fowler asked us to reconsider it and we did. Two subsequent referees had reservations about the paper, and we eventually rejected it again. Nevertheless, stung partly by Dr Fowler's throwing back at us our own remarks about peer review being an inadequate mechanism for judging new and challenging ideas and because of our own interest in the process of peer review, we agreed to publish Dr Fowler's paper together with all the related correspondence and referees' reports, so that readers could make up their own minds and perhaps appreciate the editorial process better.

The paper published here is a revised version of the original manuscript, modified by the authors in the light of the referees' comments, and the correspondence is published with the agreement of all concerned.

Exaggerated responsiveness to thyrotrophin releasing hormone: a risk factor in women with coronary artery disease

J W DEAN, P B S FOWLER

Abstract

Thyroid function tests were performed and thyroid antibodies and serum cholesterol concentrations measured in 12 women aged 60 years or under with severe coronary artery disease proved by coronary angiography. This group was compared with 11 women with normal coronary angiography. Ten out of the 12 women with coronary artery disease had an exaggerated response of thyroid stimulating hormone to thyrotrophin releasing hormone compared with two out of 11 controls ($p < 0.008$). The mean serum cholesterol concentration was significantly higher in those with coronary artery disease than in the controls. Thyroid antibodies were present in four of those with coronary artery disease and one of the controls. There was no difference in the risk factors for coronary artery disease between the two groups except for cigarette smoking. Eleven out of 12 in the coronary artery disease group smoked cigarettes compared with four out of 11 in the control group ($p < 0.01$).

Minimal impairment of thyroid function is an important risk factor for coronary artery disease in women.

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Introduction

Autoimmune thyroiditis is not generally recognised as a risk factor for coronary artery disease. Yet in 1967 Bastenie *et al* found in a histopathological investigation that a fifth of men and nearly a half of women with fatal myocardial infarction had lymphocytic thyroiditis at necropsy whereas thyroiditis in men and women who died of other causes was present in only 10% of cases.[1] In the same year others pointed out the association of coronary artery disease to minimal impairment of thyroid function.[2] When thyroid stimulating hormone measurement became a routine clinical procedure and the thyrotrophin releasing hormone test was introduced, it was possible to measure minimal impairment of thyroid function. Tieche *et al* found in a cross sectional study that women with a

thyroid stimulating hormone value in the upper part of the normal range had double the incidence of ischaemic heart disease of women with thyroid stimulating hormone values in the lower part of the normal range.[3] A prospective study on Finnish subjects showed that the presence of thyroid antibodies doubled the incidence of coronary artery disease over a five year period.[4] The association of coronary artery disease with autoimmune thyroiditis has been noted especially in women, but cardiologists still do not list minimal impairment of thyroid function as an important risk factor in coronary artery disease. We therefore compared the thyroid function in women aged 60 years or under with coronary artery disease proved by angiography with that in women with normal coronary angiograms.

Patients and methods

Thyrotrophin releasing hormone tests were done on 12 consecutive women aged 60 years or under in whom severe coronary artery disease had been proved by coronary angiography and 11 consecutive women with normal coronary angiograms. Serum cholesterol and thyroid antibody determinations were also compared in the two groups. Ten out of 12 women with coronary artery disease were Caucasian and two were Asian. One of the 11 in the control group was Asian. Among those with coronary artery disease the least severe disease was 95% stenosis of a single vessel in one patient, and seven had triple artery disease.

The thyrotrophin releasing hormone test was performed as described by Ormston *et al.*[5] A maximum response of thyroid stimulating hormone to thyrotrophin releasing hormone of more than 15 mU/l was regarded as exaggerated. Thyroxine, triiodothyronine, and thyroid stimulating hormone were measured by double antibody radioimmunoassays. The thyroid stimulating hormone assay was standardised against the MRC 68/38 reference preparation; the interassay coefficient of variation was 9·5% at a level of 7·5 mU/l and 5·9% at 17·5 mU/l. Cholesterol was determined by a modified Liebermann-Burchard reaction (AutoAnalyser II, Technicon). Microsomal antibodies were shown by an immunofluorescent sandwich technique, being mixed IgG/M conjugate and sections of human thyroid, and also by haemagglutination using sheep red blood cells sensitised with thyroid microsomes. Antibodies to thyroglobulin were detected by haemagglutination using tanned red cells (Wellcome Reagents). This test is based on Boyden's passive haemagglutination system and used by Witebsy and Rose[6] for detecting thyroglobulin antibodies. No patient or control had been taking amiodarone or any other drug that might have interfered with thyroid function tests. The unmodified χ^2 test was used for statistical analysis.

Results

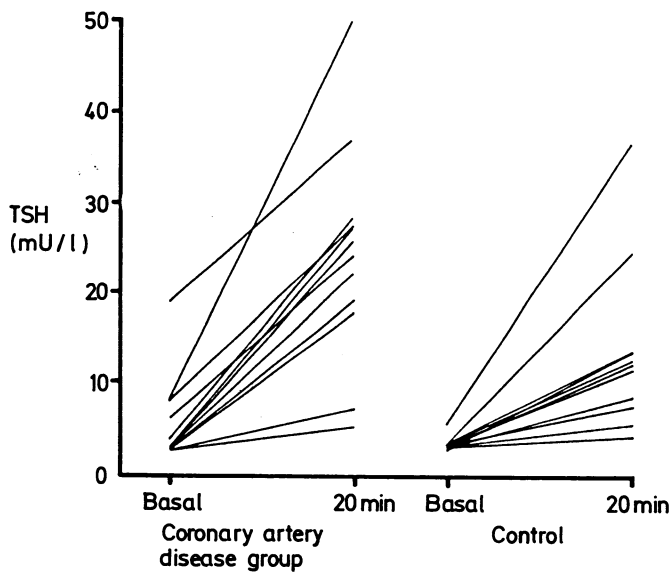
The mean age in the control group was 52 years (SD 8·9) and in patients with coronary artery disease 51 years (5·8). There was no difference in blood pressures between the two groups. One patient with coronary artery disease had diabetes. Oral contraception was used by three controls and two patients with coronary artery disease. Four of the 11 controls smoked cigarettes whereas 11 of the 12 women with coronary artery disease did so. The duration of smoking varied from 8 to 35 years and the average consumption was 15 to 60 cigarettes daily for the smokers in both groups.

Details of the thyroid function values and serum cholesterol concentrations are shown in the table. The serum thyroxine value was just below normal in one patient.

Ten out of the 12 patients with coronary artery disease had an exaggerated response of thyroid stimulating hormone to thyrotrophin releasing hormone compared with two patients in the control group ($p<0·008$) (figure). One of the two patients in the control group with an abnormal thyrotrophin releasing hormone test had previously undergone subtotal thyroidectomy. This patient had a basal thyroid stimulating hormone of 5 mU/l, which rose to 36 mU/l at 20 minutes. Thyroid antibodies were present in four (33%) of the group with coronary artery disease and in one (9%) of the controls ($p<0·2$). Three patients with coronary artery disease and exaggerated thyrotrophin releasing hormone responsiveness had strongly positive antibodies to thyroid epithelial cell cytoplasm and thyroid microsome haemagglutination titres of 40^2, 40^2, and 160^2. The other subject in this group had weakly positive antibodies to thyroid epithelial cell cytoplasm and a titre of 40^2, as did the only subject in the control group. None of the women in either group had antibodies to thyroglobulin.

Discussion

Our results show a close association in women between coronary artery disease and an exaggerated response of thyroid stimulating hormone to thyrotrophin releasing hormone. The risk factor of cigarette smoking is again confirmed. It has been shown that thyroxine given to subjects with normal serum thyroxine and triiodothyronine values but an exaggerated response of thyroid stimulating hormone to thyrotrophin releasing hormone causes a fall in the serum cholesterol concentration.[7] Since autoimmune thyroiditis is familial, screening tests have been done and thyroxine given to patients with impaired thyroid function and an ominous family history of early coronary artery disease,[8] but no prolonged double blind control trial of thyroxine has been done in such patients. The exaggerated response of thyroid stimulating hormone to thyrotrophin releasing hormone is such a well recognised indication of borderline hypothyroidism[5 9 10] that it can be accepted that this study again confirms that impaired thyroid function is a risk factor for coronary artery disease.



Comparison of TRH response of thyroid stimulating hormones to thyrotrophin releasing hormone in women with coronary artery disease and controls.

We thank Dr Alan Harris for allowing us to study patients under his care. We thank Dr Kenneth MacRae for his statistical analysis of our results, Dr Alaghband Zadeh and Mr Graham Carter for biochemical estimations, and Dr D Barrie for thyroid antibody tests.

Results of thyroid function tests in 12 women with coronary artery disease and 11 controls. Results are means (and SD)

	TSH (in U/l)					
	Basal	20 mins	T4 (nmol/l)	T3 (nmol/l)	Free T4 (pmol/l)	Cholesterol (mmol/l)
Women with coronary artery disease	5·4 (5·9)	24·1 (12·0)	91 (21·9)	2·7 (0·7)	15·3 (2·61)	6·98 (1·3)
Controls	3 (0·5)	13·1 (9·4)	109 (15·0)	2·7 (0·5)	18·2 (2·48)	5·52 (0·8)
Significance	NS	$p<0·02$	NS	NS	$p<0·05$	$p<0·005$

NS: Not significant.
Conversion: SI to traditional units—Cholesterol: 1 mmol≈38·7 mg/100 ml.

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The Correspondence

Report of the first referee on the original manuscript 20 July 1984

The concept that women with minor degrees of thyroid failure may be at particular risk from developing coronary artery disease is, if it is correct, an exceedingly important one. The data provided in this paper do not, however, allow one to draw such a conclusion. There are a number of problems: the groups of individuals studied are far too small and the major distinguishing feature between the two groups is clearly the fact that most of the patients in the coronary artery disease group are cigarette smokers. It is difficult to conceive how 12 consecutive women aged 60 and under should have such severe coronary artery disease. Surely by chance there must have been women with less severe to trivial disease also undergoing coronary arteriography? In other words, how were these so called consecutive 12 patients chosen?

The interpretation of the TRH test is inappropriate as described. The use of the TRH test is well recognised in the diagnosis of hyperthyroidism and in the diagnosis of secondary hypothyroidism, usually due to hypothalamic pituitary disease. I am not aware of any benefit having been demonstrated of measuring a TSH response to TRH in primary hypothyroidism or in incipient thyroid dysfunction. Primary hypothyroidism is based on the basal resting TSH level without any indication or need to measure the TSH response to TRH. If the authors now claim that a TSH response to TRH is diagnostic of primary hypothyroidism, they need to provide evidence to demonstrate this; otherwise one might begin to conclude that a number of their so called hypothyroid patients have in fact pituitary hypothalamic disease rather than autoimmune thyroid disease. In the context of autoimmune thyroid disease they have been able to show positive antibodies in four of their patients. One needs to know exactly which antibody was measured and the titre of the antibody to know how significant the observation was. Furthermore, it is of interest that only two of the patients with positive antibodies had any abnormality of the basal TSH and in one of these, case 3, this was at borderline level.

Therefore it is difficult to draw any conclusions as to the significance of thyroid dysfunction since the criteria they describe for defining it are so imprecise and on the whole invalid.

Letter from the assistant editor, BMJ, 25 July 1984

Dear Dr Dean,

Thank you for giving us the opportunity to consider your paper entitled "Borderline hypothyroidism—a risk factor in women with coronary artery disease." I regret that we did not think your findings were suitable for publication in the *BMJ*. Our specialist referee has raised a number of critical points and I enclose his opinion. I am sorry to disappoint you.

Letter from Dr Fowler to the editor of the BMJ 31 July 1984

Dear Dr Lock,

Dr Dean and I were grateful to your assistant editor for considering our paper entitled "Borderline hypothyroidism—a risk factor in women with coronary artery disease" for publication in the *BMJ*. It was good of her to send the paper to your specialist referee and to allow us to see his comments. We agreed with his opening sentence. "The concept that women with minor degrees of thyroid failure may be at particular risk from developing coronary artery disease is, if it is correct, an exceedingly important one."

He goes on to state, "I am not aware of any benefit having been demonstrated of measuring a TSH response to TRH in primary hypothyroidism. . . . Primary hyothyroidism is based on the basal resting TSH level without any indication or need to measure the TSH response to TRH." These statements about the TRH test are in sharp contrast to what nearly all endocrinologists throughout the world believe. The list would include Besser and Hall in England, Toft in Scotland, Visscher in the USA, and Bastenie in Brussels. Sir Raymond Hoffenberg is the only authority I know who denies the value of the TRH test in borderline hypothyroidism.

Michael Besser and Reginald Hall, with their colleagues at Barts and Newcastle, state in their article in the *Lancet* of 3 July 1971: "It is suggested that, in the absence of pituitary or hypothalamic disease, the response of serum TSH to TRH provides a simple, safe, sensitive, and reliable test of thyroid function." Reginald Hall and Maurice F Scanlon in March 1979, after quoting my work of 1967, state that the diagnosis of subclinical hypothyroidism is best made by "demonstrating an elevated basal serum TSH level and/or a prolonged and exaggerated rise in serum TSH following administration of TRH. (*Clinical Endocrinology and Metabolism* 1979;**8**:31). *The Thyroid Gland*, edited by Michel de Visscher, contains the statement on page 191 "In primary hypothyroidism the TRH test is also most useful where the condition is mild or latent. . . ." In the same American textbook, on page 388, it is stated "The TRH stimulation test is very useful in borderline cases."

I appreciate that you will probably not go back on your decision to reject our work but feel that a protest is needed. If my guess at the identity of your referee is correct, it bears out the old adage that the greatness of a man can be judged by the length of time that he holds back progress. I enclose photostat copies of the quotations that I have mentioned. A stamped addressed envelope is also enclosed. Dr Dean and I would both be most grateful for your comments.

PS Since dictating the above, I have discovered that the columns of cholesterol results had been left out of the two tables [submitted with original manuscript; later removed in revised version]. If you reconsidered publishing our paper we would insert the cholesterol levels in the tables in place of the thyroid antibody results. The thyroid antibody results could be put in the text with more details, as suggested by your expert.

In regard to your expert's two criticisms in his first paragraph, we chose 12 patients with *severe* coronary artery disease to compare with the controls. TRH tests were done, as stated, on 12 consecutive patients with severe coronary artery disease. His criticism of the numbers studied is surely met by these statistics.

We would also like to mollify your expert by changing the title of the paper to "Exaggerated response of thyroid stimulating hormone to thyrotrophin releasing hormone—a risk factor in women with coronary artery disease." We would add a few key references in case other readers beside your expert are unaware of the importance of this test in borderline hypothyroidism.

Reply from the editor 6 August 1984

Dear Dr Fowler,

Many thanks for your letter. Obviously here we have no expertise in the matter under discussion, and I think the best thing therefore is to refer the original referee's opinion, together with your letter and your article, to a further referee asking for a judgment of Paris. I have done this and will let you know our decision as quickly as possible.

Letter from the editor to the second referee 6 August 1984

I should be extremely grateful for your opinion—and indeed a judgment of Paris—about the enclosed. As you will see, this concerns a paper from Dr Fowler, which was initially refereed and declined for publication with the referee's opinion enclosed (photostat A). Dr Fowler has now challenged this (photostat B), and I should be grateful for your opinion on the relevance of his claims. We have a feeling here, perhaps unjustified, that Dr Fowler's ideas are not necessarily mainstream, but he is always one to query decisions, and in any case we would like to ensure that we have been fair in this instance.

Report of the second refeee on the original manuscript 20 August 1984

Thank you very much for letting me see Dr Fowler's paper. After making my own assessment I was interested to see your referee's comments, with which I concurred in part, but I also enjoyed Bruce Fowler's reply and think his defence of the TRH test is valid.

I actually found this rather an interesting study; the pity of it is that the science is rather woolly and the authors' claim is therefore not validated. However, I am sure it should be pursued and, with improved data, published.

More detailed criticisms are as follows.

(1) A larger patient and control sample is required.

(2) More attention should be given to the methodology, particularly the TSH assay and the antibody tests. Since so much depends on the TRH test full details of the TSH assay should be given, and in particular it is essential that all samples from both groups should be measured in the same assay. What is the coefficient of variation of the assay? I am a little surprised at the method of thyroid antibody detection and think this should be looked at properly using one of the well validated quantitative tests; also they should do both thyroglobulin and microsomal antibody titres.

(3) Expression of results: a small point but, rather than giving tables of all the individual TRH tests, it would be more useful to see the means for each group plotted in a diagram. They do not quote the mean free thyroxine index for each group and clearly that should be given. A table to show the means (or medians) of all the measurements for each group might be helpful.

(4) Interpretation of results: one can dismiss apparent differences in antibody frequency because of the small numbers and the poor methodology. That leaves only the response of TRH to be explained. I have a suspicion that this may relate to cigarette smoking rather than indicate borderline hyothyroidism. The obvious way to look at this would be to do TRH tests in a group of cigarette smokers who do not have coronary artery disease, and, incidentally, some note should be made of the numbers of cigarettes smoked by the individuals in the study. It might also be interesting to assay all the samples for prolactin as it may be possible to show significant differences between groups in prolactin response to TRH also.

In conclusion I agree that the paper is too weak scientifically to be published as it stands, but I do think the authors should be encouraged to pursue this work and resubmit it.

Letter from the editor 28 August 1984

As you know, we asked another expert referee for a judgment of Paris on your recent article and you will see that he has come virtually half way. I am returning the article together with his comments.

Letter from Dr Fowler 18 September 1984

Dear Dr Lock,

John Dean and I are grateful for the comments made by your referee, which we feel are fair, valid, helpful, and encouraging. We are changing our paper to meet most of the criticisms that he has made and will then resubmit it as soon as possible.

An attempt was made in our last version to put over our message succinctly. We therefore left out much information that we have available but which did not seem completely relevant. We now appreciate that this has made the "science rather woolly," as your expert states. We have tackled the following matters that he has brought up under the headings listed below.

Thyroid antibodies

We did do acceptable thyroid antibody tests but left out details to shorten the paper. These will be included and more details inserted about methods.

Expression of results

(*a*) Diagram. We have replaced our cumbersome tables by a diagram as suggested. This certainly greatly adds to clarity and shortens the paper.

(*b*) Table. We have made a table giving the mean and standard deviations of T4, free T4, T3, and cholesterol in addition to the basal TSH and 20 minute TSH. Again we had left out the first four for brevity. Clearly your expert is right in asking for their insertion.

Cigarette smoking

We have made a note about the number of cigarettes smoked and duration for the two groups as requested.

Prolactin estimation

This was a very interesting suggestion and we wish that we had done the prolactin after TRH. I have done prolactin estimations in the past on many patients with coronary artery disease and exaggerated response of TSH to TRH, mainly in men, hoping that the association between the two conditions might be related to an exaggerated response of prolactin to TRH. We did not find this association, which is probably why we forgot to measure prolactin on this occasion. Although my data about prolactin concentrations and coronary artery disease are anecdotal, they are convincing. Unfortunately, three out of our 12 patients with severe coronary artery disease have died since we submitted this paper.

Statistics

We went back to our statistician. He emphasises the significance of the difference in the TRH tests in our two groups and points out that greater numbers will give precision regarding the risk factor without changing the significance.

TSH assays

As requested, we have given further details regarding the TSH assay, in particular, the interassay coefficient of variation. We do appreciate that our samples from both groups would have been best done in the same assay. This defect is mitigated by the coefficient of variation, which has been given. It did seem to us that any alteration in the assays would balance out in the two groups but do appreciate that this is a very valid and fair criticism.

We do hope that when the above changes have been included in the paper that you and your expert will find it acceptable.

PS It is as difficult to guess the identity of your second expert as it was easy to guess the first. His criticisms are expressed so kindly that I suspect a friend. This widens the field enormously to at least three.

Letter from Dr Fowler, resubmitting the revised manuscript, 18 October 1984

Dear Dr Lock,

Exaggerated responsiveness to thyrotrophin releasing hormone: a risk factor in women with coronary artery disease

John Dean and I resubmit this paper as we threatened to do in our letter of 18 September 1984. We have now changed the text and the

table in the way he advised and have used a diagram as he recommended.

We have subjected three women members of the staff here who are heavy smokers to TRH tests. They demurred at the suggestion of coronary angiography. The results are as follows:

	T4	F T4	T3	Basal TSH	20 min TSH
Subject 1	94	15·4	1·6	<3	5
Subject 2	81	14·1	1·6	<3	13
Subject 3	135	19·2	1·6	<3	10

We know that even three swallows do not make a summer but have looked through the literature and have not found any evidence to suggest that smoking exaggerates a response of TSH to TRH.

We do hope that these changes will now make our paper acceptable to you and your expert.

Letter from the editor to the third referee 2 November 1984

I should be most grateful if you could give us a judgment of Paris on a particular problem we have been having. This concerns a paper by Dr Fowler and his colleagues, which I must admit we in the office do not understand. We submitted it to peer review and rejected it to a specialist journal on the basis of the first referee's report (photostat enclosed). Dr Fowler riposted and we then got another opinion, which, as you will see, fell half way between the two "sides"—as these things often do. Dr Fowler has now come up with yet another revised version and it is on this I am asking your opinion. Given the circumstances of this, I wonder whether you would care to read the revised paper "blind" and then open the enclosed envelope containing the two referees' reports and see whom you agree with.

While we are always willing—nay, anxious—to be fair, I must say that Dr Fowler and his team do seem slightly out on a limb, and for the readership of a general journal I am not sure how many people perceive the points at issue. I am may be being unfair about this, but it would be silly of me not to be entirely frank about my own view—though, of course, we shall be very intereted to have your advice.

Report of the third referee on the revised manuscript 9 November 1984

Dear Dr Lock,

I enjoyed this challenge but, although my task was no doubt simpler than that of Paris, if my memory serves me well, his was slightly more pleasurable. Having read the manuscript "blind," I am afraid that I agree with the opinion of your first referee for the following reasons.

(1) The control group is highly selected. It is likely that patients with normal coronary angiograms have presented with unusual chest pain and, no doubt, have had many other investigations performed including, perhaps, thyroid function tests.

(2) Although I know of no studies which have investigated the relation between TSH secretion and smoking, the two groups are ill matched in this respect. Patients who smoke heavily often also consume excess alcohol and there is no doubt that TRH tests may be abnormal in patients with alcoholic liver disease. In a similar vein, it is almost certain that the coronary artery disease group were taking a multiplicity of drugs including β blockers, calcium antagonists, nitrates, and possibly aspirin and persantin. In contrast, those with normal coronary angiograms were probably receiving no drug therapy. Although these drugs are not thought to influence thyroid function, some have not been adequately studied in this regard.

(3) Iodine affects thyroid function and therefore the TSH response to TRH. Assuming that the angiographic contrast medium contained iodine, it is extremely important to know when thyroid function was assessed in relation to angiography.

(4) The use of the χ^2 test demands that the normal range for TSH is known. How was this established? Was it, for example, derived from the control group or from previous laboratory studies.

The concept is attractive and Dr Fowler may be correct. However, the number of patients studied is so small and the criticisms so many that I do not consider that the paper should be published in the *British Medical Journal*. Dare I say that it might be more appropriate in the correspondence columns of the *Lancet*.

A copy of this report, together with a letter of rejection, was sent to Dr Fowler on 12 November.

Letter from Dr Fowler 16-19 November 1984

Dear Dr Lock,

Exaggerated responsiveness to thyrotrophin releasing hormone: a risk factor in women with coronary artery disease

I enclose copies of previous correspondence on the above in case the originals have already been through the shredder (*BMJ* 13 October, p 942).

You gave me the good news in your letter to me of 28 August 1984 that the new expert referee had "come virtually half way." John Dean and I complied with the suggestions which your referee made in order to make this paper acceptable. It is, therefore, a very great surprise to have a slip letting me know that you have rejected the paper. You have kindly sent a copy of the referee's second report. This brings up four entirely different objections from the ones previously mentioned. I should like to comment on the four new objections.

(1) It is stated that the control group is highly selected and that these patients might have had other investigations including thyroid function tests done. In fact thyroid function tests were not done on these patients before the present study (it would not matter if they had been done).

(2) As stated in the paper, we made absolutely certain that none of these patients had amiodarone, which interferes with thyroid function. I challenge your referee to produce any evidence to support his statement that β blockers, calcium antagonists, nitrate, aspirin, or persantin might affect the TRH test. The only known effect of any of these drugs on thyroid function is a possible blocking of conversion of T4 to T3 by propranolol. This would not have altered the TRH test. Your expert goes on to say "patients who smoke heavily often also consume excess alcohol. . . ." Our patients did not take excess alcohol and did not develop alcoholic liver disease as he suggests. We cannot conceive how such a ludicrous statement could have been seriously made, and neither can those who have seen this correspondence.

There can be no serious thyroidologist who has done less laboratory work than myself. There is no UK thyroidologist other than myself who has been following personally over 2000 patients with impaired thyroid function. I have been criticised for doing TRH tests too often, again more often probably than any other thyroidologist, and therefore have the greatest clinical experience in its use. This has produced a sort of Matthew effect. The more often you do the test, the more you find impaired thyroid function when clinically the diagnosis might be unsuspected.

(3) Iodine does affect thyroid function and therefore the response of TSH to TRH. We were, of course, aware of this and checked that the relation of angiography to the thyroid function tests was similar in the two groups.

(4) Your expert brings up the subject of the χ^2 test and we have seen our statistician about this again. The normal range was derived from a paper in the *Lancet* of 12 November 1977, pages 998-1000, entitled "Association between exaggerated responsiveness to thyrotrophin releasing hormone and hypercholesterolaemia." We could certainly include this in our list of references, which already seemed rather top heavy with our own work.

It is clear that we cannot win against the "endocrine mafia," and the article that you wrote on the 30 October 1982, page 1224 [Peer review weighed in the balance] is very apposite. Your referee suggests that we should send our data to the correspondence columns of the *Lancet*. This was how Deborah Doniach first reported her discovery of antibodies after her work had been dismissed by the "experts." Krebs had the same trouble with his

cycle. I have always been an optimist, and reading your superb paper "Peer review weighed in the balance" again gives us a glimmer of hope. If you read our correspondence again, you may decide to call a plague on all your experts and accept it. When you suggest that the peer review is adequate for the middle of the road, unadventurous article, but hopeless for the one with new and challenging ideas you seem to hit the nail on the head.

19 November 1984

I have had a weekend to reflect on your expert's suggestion, "Dare I say that it might be more appropriate for the correspondence columns of the *Lancet*." It might be more sensible to submit the letter to the *BMJ* correspondence columns since your journal was our first choice with this article. We now have 12 controls, whereas in the article submitted to you there were only 11 controls for the 12 patients. Your referee failed to realise the great problem of getting controls since it is unethical to submit patients for coronary angiography unless there is good reason for suspecting coronary artery disease. When our paper is published it will be only the second that has ever compared thyroid function in two groups where the presence or absence of coronary artery disease has been confirmed by coronary angiography. There are 10 out of our 12 patients with coronary artery disease who had an abnormal TRH test and only two in the controls, of whom one had previously had a thyroidectomy. For the statistically illiterate this means that the findings could have occurred by chance once in 125 times. If the subject who had had a thyroidectomy is excluded the chance is one in 250 times. We would offer to send the data to anyone interested, hoping that they would do similar studies to confirm or refute our findings. Confirmation would be a major breakthrough in the aetiology and prevention of coronary artery disease in women. None of the patients in our study attended my clinics since this would have produced a bias because of my known interest in the association of coronary artery disease to the thyroid, dating back to my first paper on the subject in the *Lancet* in 1967. If this information is to be published as a letter it would be tempting to point out why it has not been accepted as an article. The identity of the first referee was obvious since there is only one "expert" who could state "I am not aware of any benefit having been demonstrated of measuring a TSH response to TRH in primary hypothyroidism or in incipient thyroid dysfunction." It could be pointed out that you kindly referred the article to a second referee, who suggested alterations with which we complied. He rejected the revised article on the grounds that, inter alia, "patients who smoke heavily often also consume excess alcohol, and there is no doubt that TRH tests may be abnormal in patients with alcoholic liver disease" (incidentally, this statement is incorrect).

At this stage the revised manuscript was sent to the *BMJ*'s statistical adviser.

Report of the statistical referee on the revised manuscript 30 November 1984

This is a small study, with insufficient explanation given of the source and nature of the "control" group. These should be presented together with their justification—why, for example, was age matching not considered when such factors as serum cholesterol and blood pressure were to be considered? Why was the coronary artery disease group restricted to be aged 60 years or under but apparently not the "control" group (see means and standard deviations in results section)?

The unmodified χ^2 test, if this implies without the continuity correction, is unsatisfactory for these data on such small numbers. It would be preferable to use the exact test for 2×2 tables. There is no statement given of the statistical test used for quantitative measurements in, for example, the table. In the results section, "There was no difference in blood pressure levels in these two groups" presumably is intended to read ". . . no statistically significant difference. . . ." What is the reader meant to make of $p<0{\cdot}2$ in relation to the relative presence of thyroid antibodies in the two groups?

This paper is of dubious quality.

Letter from the editor 4 December 1984

Dear Dr Fowler,

I have now had time to reflect on your paper of 16 November, talking to my colleagues and seeking advice from a statistical expert (not that his verdict was all that much different from those in earlier referees' reports, but I thought you might like to see it and it is enclosed herewith). First of all, I do not think your paper should be published as a letter to the editor in our correspondence columns: for one thing it is far too long, for another we tend to reserve these almost exclusively for items of great topical importance or for comment on matters that have recently appeared in the journal, which is why we have created new forms such as Short Reports and Unreviewed Reports, where, appropriately peer reviewed, items of scientific importance can be printed.

All this means that I have to make up my own mind, and, given the good humoured nature of our exchange, I wonder whether you would accept the following offer—that is, to print your paper together with all the correspondence and the referees' reports. In this way a number of purposes might be served: firstly, the non-expert reader will be left in no doubt that your article is not holy writ, so to speak; secondly, there is the point which you cogently raise—and my researches tend to agree with—that the "system" favours unadventurous nibblings at the margin of truth rather than quantum leaps; and, thirdly, that for the reader who could not care less there would at least be the fascination (?) of seeing the almighty peer review process at work.

What do you think of all this, please? Such an offer would, of course, depend on the willingness of all the expert assessors to have their reports quoted—but knowing them I do not think they would object.

Letter from Dr Fowler 5 December 1984

Dear Dr Lock,

I was delighted to get your letter today enclosing the third referee's comment, which is in agreement with those of the two previous referees, ending "This paper is of dubious quality." John Dean and I accept your offer without reservation.

Your last referee brings out a point about controls which is really about honesty. The one patient (which he mentions) in the control group who was over 60 was one of only two controls who had an abnormal TRH test. The other was the patient who had had a thyroidectomy, which is known to alter the response to the TRH test. None of the coronary artery disease group had had a thyroidectomy, so we could quite fairly have left out the one patient because she was over 60 and the other patient because a thyroidectomy had been done. It may well be that our honesty has been stretched to the point of stupidity. My statistical knowledge is abysmal but John Dean and the statistician who always helps me both reassure me that 10 out of 12 is very different from nil out of 12.

What fun! Can you get it out for Christmas?

Letter from Dr Fowler 11 December 1984

Dear Dr Lock,

John Dean took your statistical referee's report of our paper to our adviser on statistics. His comments on your referee's criticisms seem apposite, as does the article by Upton that he refers to.

Comment from Dr Fowler's statistical adviser 10 December 1984

The statistical referee is too dogmatic. There is a controversy about the version of χ^2 (χ^2_i=uncorrected χ^2; χ^2_y=Yates's correction to χ^2) to use (see Upton GJG. A comparison of alternative tests for the 2×2

comparative trial. *Journal of the Royal Statistical Society* 1982;**145**, part 1:86-105).

TSH to TRH	10	2	$\chi^2_1=9{\cdot}76$ p=0·002	"exact" p=0·0056*
	2	9	$\chi^2_y=7{\cdot}33$ p=0·007	
	12	11		
Thyroid antibodies	4	1	$\chi^2_1=1{\cdot}98$ p=0·16	"exact" p=0·372*
	8	10	$\chi^2_y=0{\cdot}81$ p=0·37	
	12	11		
Cigarettes	11	4	$\chi^2_1=7{\cdot}74$ p=0·005	"exact" p=0·022
	1	7	$\chi^2_y=5{\cdot}49$ p=0·025	
	12	11		

*Fisher's exact test usually agrees very closely with χ^2_y (Yates's corrected χ^2), and it is not worth the trouble of calculating.

You, of course, compared means with an unpaired *t* test. "Peer review" is what it says: the reviewers are "peers," not absolute authorities!

The editor wrote to the referees asking permission to publish their comments and guaranteeing anonymity. All agreed, and two made further comments.

Letter from the second referee 13 December 1984

On looking again at my own comments I think I was unduly polite and really should have emphasised more that the science is bad. Could Dr Fowler and colleagues not be persuaded to provide the necessary additional data: in fact in the time since he submitted it he could easily have done the study properly. In particular, I think it is important that he checks up on the question of cigarette smoking and the TRH test, since, as I recollect, the groups were different in their smoking habits. It seems clear from other studies that smoking is associated with long term alterations in thyroid regulatory function and there are now quite a few papers in the literature relating to this.

Letter from the first referee 20 December 1984

Regarding Dr Fowler's publication on "Exaggerated responsive ness to thyrotrophin releasing hormone—a risk factor in women with coronary artery disease," I find it interesting that Dr Fowler has been so persistent with his request that this should be published. It seemed to me from memory that there were two problems with the study. One was that it was performed inadequately and the other was that the hypothesis seemed unlikely. Whereas I can understand that on the latter grounds you might be accused of undue bias and unwillingness to take a risk, it did seem to me that the study was inadequately performed and the criticisms that I raised regarding the performance of the study still remain unaltered unless, of course, in the continuing correspondence with you some of these have been met by extending the numbers used or by removing some of the other biases that seemed to be associated with the selection of patients.

Letter from Dr Fowler and Dr Dean 20 March 1985: the authors' last word on returning the proof

Dr Dr Lock,

We have now seen your referees' further comments. One states that he was "unduly polite"—a creditable trait, we think. The other finds it "interesting that Dr Fowler has been so persistent . . . that it should be published." This innuendo does him little credit. We are trying to put over a simple message which others can confirm or refute. If the work is confirmed the implications for preventing coronary artery disease are obvious. Our work has continued since the paper was accepted. If we exclude the patient over 60 initially included in error and the patient with thyroidectomy, we have 12 out of 15 patients with proved severe coronary artery disease who have an exaggerated thyrotrophin responsiveness compared with one among the controls.

A 2 year old girl developed pronounced swelling of her mouth and difficulty in swallowing on first eating fish, a reaction that recurred. She also has a tendency to mild asthma. What advice should the parent be given?

The most practical step to be taken in preventing a young child from experiencing what was a mild but definitely anaphylactic reaction to eating fish is obviously to exclude fish and fish products from the diet. It would be wise to exclude both fully cooked and shell fish. It is not possible to predict how long an allergic child will remain sensitive, but I suspect that with fish, unlike allergy to milk which usually resolves in the second year, this may be a long standing problem. The coexistence of mild asthma confirms that the child is atopic—that is, likely to be easily sensitised to ordinary environmental anotypes. Dietary control may be difficult during the early toddler years when the child is not necessarily open to persuasion. It will therefore be necessary to have powerful antihistamines on hand, such as chlorpheniramine or clemastine, if, for example, dietary exclusion cannot be maintained. An alert warning bracelet may be considered useful. No aspects of this problem depend on general health.—C B S WOOD, professor of child health, London.

What is the Steele-Richardson-Olszewski syndrome and what are the aetiological or genetic factors?

The syndrome is a rare variant of parkinsonism, resistant to all conventional treatment with unrelenting progression of death, usually within eight years of the onset. The deeper grey matter of basal ganglia, tectal region, brainstem, and cerebellum is enveloped in neurofibrillary tangles (without senile plaques) with nerve cell loss, gliosis, and granulovacuolar degeneration. Men are particularly affected (ratio 5:2). The onset is typically in the early 50s with unsteady gait, abrupt falls (often backwards), altered vision, slurred speech, and dysphagia. In the early stages it is not unusual for one symptom to predominate. Characteristically there is a fixed, wide eyed stare, mask like facies, and fixed forward flexion of the neck with increased tone. The head moves rather than the eyes. There is a spastic dysarthria, pseudobulbar palsy, extreme rigidity, and bilateral extensor plantar responses. The end stage is of total rigidity, anarthria, aphagia, and inanition. All patients develop voluntary paralysis of downward gaze with a progressive paralysis of voluntary and later pursuit eye movements (synonym: progressive supranuclear palsy) until the eyes are fixed centrally, even in sleep, with bilateral ptosis. It is the severity of the ophthalmoplegia, rather than its presence, which separates the syndrome from Parkinson's disease, vascular disease, or senility. Mental activity is appreciably slow in timing and activation but, although the term "subcortical dementia" is used, verbal and perceptuomotor capacities are often strikingly preserved. There is no response to dopaminergic drugs. Temporary improvements with shunt procedures and methysergide have been claimed. The aetiology is unknown. There is no evidence for a toxin or slow virus. There are no familial cases unless one considers the syndrome of Mata *et al.*[1]—E M R CRITCHLEY, consultant neurologist, Preston.

1 Mata M, Dorovini-Zis K, Wilson M, Young AB. New form of familial Parkinson-dementia syndrome: clinical and pathological findings. *Neurology* 1983;**33**:1439-43.
Steele JC. Progressive supranuclear palsy. *Brain* 1972;**95**:693-704.
Albert ML, Feldman RG, Willis AL. The subcortical dementia of progressive supranuclear palsy. *J Neurol Neurosurg Psychiat* 1974;37:121-30.
Morariu MA. Progressive supranuclear palsy and normal-pressure hydrocephalus. *Neurology* 1979;**29**:1544-6.
Rafal RD, Grimm RJ. Progressive supranuclear palsy: functional analysis of the response to methysergide and anti-parkinsonian agents. *Neurology* 1981;**31**:1507-18.