PE1463/K

John E Midgley Letter of 19 February 2013

I have been in contact with Mrs L Cleaver who was one of the two petitioners to a Scottish committee examining present protocols for the diagnosis of adrenal and thyroid function as currently carried out in Scotland and elsewhere. From the discussion and submissions to the Committee it is clear that there is currently a significant shortfall in the quality, thoroughness and appropriateness of diagnostic procedures in this area, leading to unnecessary suffering by some patients and also to expensive secondary testing which is often not relevant to the underlying problems. During the submission, Mrs Cleaver mentioned my name in the light of recent research I have carried out in this area together with Professor Rudolf Hoermann (formerly head of thyroidology diagnosis and treatment in Luedenschied Hospital, Germany, now semi-retired to Australia). On examining what was said I am in full agreement with the petitioners and would like to add my own name to the list.

My Background and Credentials.

First I will state that I am not formally medically qualified. My career is summarized as follows: 1) B.Sc in Biochemistry (Leeds University) 1958; 2) Ph.D in Physical Chemistry (University of Oxford) 1961; 3) Postdoctoral Fellow in Molecular Biology, Carnegie Institution of Washington 1960-1962; 4) University Lecturer in Biochemistry, Leeds University 1962-1967 ; 5) University Lecturer and Research Fellow in Biochemistry and Molecular Biology, Newcastle University 1967-1975; 6) Clinical Trials Coordinator for development and clinical validation of blood tests and injectable diagnostic radiopharmaceuticals,The Radiochemical Centre (later Amersham International plc) 1975-1988; 7) Inventor and copatentor, one-step blood test for free thyroxine (FT4) and free triiodothyronine (FT3), Amersham 1980 (this won the Prince of Wales Award for Industrial Innovation and Production, 1985); 8) Inventor and copatentor for a new improved test for these substances, Amersham 1988; 9) Independent Consultant on Medical Diagnostic devices 1988-1998; 10) Clinical Trial Abstractor for the Cochrane Collaboration on Gastroenterology 1998-2005. Also from 1980 to the present day, author of many peer reviewed scientific papers and reviews on bacterial molecular biology (antibiotic action) and thyroid function especially as regards the performance and interpretation of thyroid based diagnostic tests.

The perceived problem.

In the petitioners meeting of February 5th, Ms's Whyte and Cleaver clearly demonstrated that, in the situation of hypothyroidism secondary to adrenal insufficiency, the current diagnostic strategy for clarification of the problem and suitable treatment was significantly lacking, leading to the expense of unnecessary testing, misapprehension of the real underlying problems, and prolonged adverse experiences for the patients as regards quality of life (QOL). However, I also believe that for a significant minority of patients with severe primary hypothyroidism, under thyroxine (T4) therapy, the current diagnostic procedures similarly fall short. This leads similarly to added expense of frequent patient visits to the doctor, unnecessary testing and dismissal of symptoms as irrelevant to the thyroid problem with again a

significant reduction in QOL. I believe that this problem arises principally from the modern over-reliance of diagnosis on the test for thyrotropin (TSH) often used as sole determinant for thyroid function diagnosis. A philosophy of "tick-box" diagnosis has therefore developed because of the large numbers of results needed to be scrutinized (see below).

History of thyroid diagnostic protocols.

Before about 1985, the diagnostic test for TSH was relatively insensitive. It was only capable of distinguishing between the hypothyroid (underfunctioning) state and normality. It could not detect and diagnose hyperthyroidism (overfunctioning of the thyroid gland). Accordingly in the period 1980-1985, when simple, accurate direct tests for measuring FT4 and FT3 (see above) had become available, all tests were used to gain a complete diagnostic picture of the patient. When the TSH test was sensitized sufficiently to discriminate hyperthyroidism from normality, this test then became paramount as the preferred screening method for thyroid function diagnosis. The reasons for this were several-fold. First, the perceived cost of diagnostic testing could be cut significantly if only one overarching test was used as a screen. Secondly, the simultaneous development of automated platforms for high throughput testing schedules meant that, because of the steady progress of "defensive medicine", many more tests could be done in a given time, without significant "hands on" influence from the clinical chemist and a concomitant reduction in their required level of expertise. Thirdly, the predominance of TSH testing disincentivized the commercial producers of FT4/FT3 tests from improving their products, a problem that persists to this day. Fourthly, unfortunate myths and legends disparaging the FT4/FT3 assays were propagated by certain researchers both in the UK and abroad who did not understand the scientific basis of the methods, and performed irrelevant and misleading experiments to disparage them as suitable and robust measurements. The misconceptions arising from such studies also persist to the present day. The outcome of all these events has been that TSH as a cheap, infallible, and rapid diagnostic test has gained credence at the expense of other, more informative diagnostics, whose reputation has been unfairly traduced.

The facts.

It has become increasingly clear that the "TSH only" diagnostic screening strategy is neither infallible nor "cost-free" from the consequences of using this strategy. Ms's Whyte and Cleaver highlighted its failure in situations where adrenal insufficiency (or pituitary insufficiency) secondarily causes profound disturbances in thyroid function. Recent evidence, including papers of mine, has shown that this problem can extend to patients with primary hypothyroidism, on T4 monotherapy. This is especially true where a patient has little or no functioning natural thyroid residual action (eg ablation of gland after cancer, Hashimoto's thyroidits etc). The TSH strategy merely applies to the interplay between the thyroid gland and the pituitary, but has nothing to contribute to measuring the production of T3 from T4 to maintain health in the peripheral tissues (i.e. those outside the thyroid-pituitary axis). It is this latter parameter which is the true indicator of overall health and patient satisfaction with their therapy. It appears that in many cases, total suppression of the pituitary (i.e. undetectable TSH) has to be achieved before the T3 level in the tissues becomes adequate. In the current strategy of TSH-only screening, such patients would be

considered overdosed and the unhappy result of reducing their T4 dose to give a detectable TSH would result in the return of hypothyroid-like symptoms, as the T3 levels in the body would be inadequate. Thus, the use of TSH-only screening and diagnosis has unwelcome effects in that it promotes more frequent visits to the doctor, unsatisfactory diagnosis and advice, poorer QOL, and in some cases inability to work because of ill health. Diagnoses of fibromyalgia, chronic fatigue syndrome or depression often substitute for a failure to realise the true underlying problem of thyroid insufficiency. Counted against the narrowly budget-based perceived savings from the "TSH-only" approach are therefore what I would call the opposing "costs of the general social audit" of this misjudged approach.

I therefore add my name to the petition for the return to "intelligent" diagnosis in thyroid function testing, using all available tests where appropriate, as was the position before 1985 and a retreat from the simplistic "TSH-only" philosophy and diagnostic strategy at present recommended.

John E Midgley