The *in vitro* binding of $T_3$ to the nucleus diminishes when cytosol is added, because the cytosol competes for the same fixed amount of hormone in the incubation mixtures[4]. But, *in vivo* that is not the case since both cytosol binding proteins and nuclear binding sites are in equilibrium with the same free hormone concentration outside the cell. This implies that the presence of more or less binding sites outside the nucleus probably has no effect on the degree of saturation of the nuclear binding sites with $T_3$.

As for the third point, the parallelism between the nuclear binding of thyroid hormone analogues and hormonal activity has been shown by Oppenheimer *et al.*[6] (not cited by Tata). Only Triac may be an exception. The completely different manners of binding of thyroid hormone analogues with cytosol and the nucleus[4,7,8], which implies a non-parallelism with biological activity, also suggests a physiological role for the $T_3$ binding components of the nucleus.

Finally Tata's fourth point presents no argument at all. For instance, does the fact that more than 60% of thyroxine in the human body is outside the cells imply that this compound has no intracellular action? On the contrary, it implies that the cell has a constant supply of the hormone, independent of variations in production. Perhaps a large binding capacity of $T_3$ outside the nucleus serves a similar purpose in the supply of $T_3$ to the nucleus.

We think that the arguments used by Tata are insufficient to reject the postulate that the binding of thyroid hormones to the nucleus is of physiological importance.

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Tata replies—I apologise for the errors (see corrigendum, this page) in my original article[1]. Nonetheless they do not in any way modify the essence of my arguments and conclusions, which Docter *et al.*[2] have misread.

The absolute value of $K_a$ for the interaction between the isolated nucleus and thyroid hormone is determined by the experimental conditions and is not relevant to my finding that in identical conditions all the subcellular fractions of rat liver exhibit rather similar $T_3$-binding constants and properties. Unless similar experiments comparing nuclei with extranuclear fractions are performed by others, I do not see how $K_a$ values of the order of $3 \times 10^{10}$ mol$^{-1}$ for isolated nuclei establish 'specificity'. Sterling and Milch have observed[3] $K_a$ values of $10^{11}$ mol$^{-1}$ for the binding of $T_3$ to mitochondrial extracts. Unpublished data from my own laboratory reveal that concentrations of $T_3$ lower than those reported in my article did not appreciably alter the result I reported there[1]. A study based on electron microscope autoradiography has also disclosed an ubiquitous intracellular distribution of thyroxine[4]. I agree with Docter *et al.* that it is important to consider the situation *in vivo*, but their reasoning (their second point) can equally well be reversed: that is, the number of $T_3$-binding sites within the nucleus may have little effect *in vivo* on the saturation of extranuclear sites.

As regards the parallelism between the relative binding affinities and physiological potencies of different hormone analogues (their third point), it would be desirable to observe it in any binding or receptor system. But such an analogy *per se* is of limited value since it is also observed in binding to inert materials like glass, paper, talc, and so on[5,6]. All of these considerations only highlight the difficulties of extrapolating from the results of interaction between isolated subcellular preparations and hormone 'receptors' *in vivo* of physiological significance.

Finally, as perhaps the first person to have pointed out the importance of the response of the target cell's nucleus to thyroid hormones, I would not like to rule out the possible location of hormone 'receptors' in that organelle. What I have, in fact, emphasised in my article[7] is the necessity for a more critical assessment of the current approaches based on the binding of thyroid hormones to isolated nuclei. As, and when, evidence is presented that such binding is related to a primary biochemical event leading to the physiological action of the hormone, then I shall be only too pleased to acknowledge that I am wrong in suggesting this note of caution and necessity for fresh thinking. Meanwhile, the past 50 years' history of thyroid hormone action has taught me not to be too dogmatic or 'fashionable'.

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## Matters arising

Matters Arising is meant as a vehicle for comment and discussion about papers that appear in *Nature*. The originator of a Matters Arising contribution should initially send his manuscript to the author of the original paper and both parties should, wherever possible, agree on what is to be submitted. Neither contribution nor reply (if one is necessary) should be longer than 300 words and the briefest of replies, to the effect that a point is taken, should be considered.

## Corrigendum

In the article "How specific are nuclear 'receptors' for thyroid hormones" by J. R. Tata (*Nature*, **257**, 18; 1975) the following corrections should be made.

On page 21, lines 22–26, the sentence should read . . . This is in agreement with recent reports from Baxter's laboratory[23,40], but whether or not the endogenous hormone–receptor complex is directly bound to DNA as concluded by these workers or merely to non-histone protein in intact chromatin, as proposed by others[14,15,20–22], is difficult to decide . . .

In Table 3 (page 22), the following corrections should be made:

The $K_a$ ($M^{-1}$) value for rat pituitary tumour cell line nuclei should read $3.3 \times 10^{10}$.

The no. of sites for rat liver and kidney cytosol should read 0.53 pmol mg$^{-1}$ liver and 2.9 pmol mg$^{-1}$ kidney, respectively.

References 28,29,30 should read 29,30,31.