Getting hooked on thyroid hormone action:  
A semi-autobiographical account

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1. Introduction

The main purpose of my writing this article is to illustrate the importance of how chance encounters and serendipitous events, early in one’s scientific research career, can have profound life-long effects on scientific thought, relationships with mentors and colleagues and the manner of conducting research. I illustrate these here with my work as a PhD student and first 10 or 12 years of postdoctoral life and research on several aspects of the physiology, biochemistry and developmental biology of thyroid hormone – work which led to a major pre-occupation of my scientific research life. Naturally, much, but not all, of what I say below is autobiographical as I illustrate it with some of the unforeseeable events, people and science that have shaped my own career, and I crave the reader’s indulgence with this personal account.

2. How it all began

After graduating at the relatively early age of 19 from the Royal Institute of Science, University of Bombay (now Institute of Science, Mumbai), I was fortunate in obtaining a scholarship to pursue postgraduate studies at the elite Indian Institute of Science in Bangalore, under the supervision of the Professor of Biochemistry, Dr K K Giri. Upon arriving at the Institute in the summer of 1949, I was surprised to be told that he had just left for one year on a sabbatical in Sweden! He had forgotten to inform the other members of his staff about me. After a frustrating week of unsuccessfully trying to persuade other professors and senior staff of the Biochemistry Department, I was advised to try other life sciences departments of the Institute. The head of the Microbiology Department, Professor M Sreenivasaya, offered to take me in his lab to work on a project on artificial diets for silkworms, silk being a major industry of Mysore state to which Bangalore then belonged. I did not think this was high-tech science and I was also quite terrified by the idea of working under this big bear-like man. Eventually, I was accepted by Dr N N De in the Pharmacology Department, whose main interest was malaria. The department had a total of only three or four very kind people, which included a local pathologist and a retired Indian army doctor with experience of clinical malaria. But there were no other graduate students or postdocs.

Thinking back, my decision to work on malaria may have been subconsciously influenced by a wonderful book called *Microbe Hunters* by Paul De Kruif that I had read two or three times when I was 12 or 13. In one of the chapters the author describes how a British army doctor, Ronald Ross stationed near Hyderabad, India, had worked out the complex life-cycle of the malarial parasite in man and mosquito, work rewarded by a Nobel prize. My first experimental task in De’s lab was a tedious one, namely to infect newly-hatched chicks with *Plasmodium gallinaceum* and determine the role of ascorbic acid in the progression of the disease through the different life stages of the parasite. When I asked him if I could embark on something more challenging, surprisingly his response was a most enthusiastic ‘Why not’. He suggested that I reproduce the recent work of William Trager, a distinguished malarialogist at The Rockefeller Institute of Medical Research in New York, who had succeeded in keeping malaria parasites progressing through the blood stages for several days in cultures of mouse red blood cells. Unlike mammalian erythrocytes, chicken cells are nucleated and therefore more difficult to maintain in culture for long periods. What’s more, neither I

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nor anyone else in the Department had any familiarity with or equipment to undertake tissue culture work. But, thanks to the excellent workshops at the Indian Institute of Science and advice from those more knowledgeable than us, after a few difficult weeks, it felt particularly good to see that the cultured parasites retained their infectivity to produce cerebral malaria in chickens. As I had not been registered for a PhD degree, it soon became clear that the most urgent task for me then was to take care of the backlog of unfinished experiments on avian malaria and to write up my thesis for Associateship of IISc (equivalent to a Master’s degree). This was submitted in great haste after two years and was to lead to a totally unforeseen life-changing event.

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In January 1950, soon after my arrival in Bangalore, the Indian Institute of Science was the venue for the annual Indian Science Congress where a number of foreign guests had been invited. Among them was a group of five or six French physicists and astronomers for whom I had to act as a volunteer guide. One of them, who turned out to be Le Prince-Ringuet, atomic physicist, Nobel Laureate and professor at the prestigious Collège de France in Paris, asked me what plans I had for my future. I replied something like ‘Sir, I would like to do research in biochemistry at Cambridge University’. He quipped: ‘Why do all you young Indians want to pursue further education in England? What’s wrong with France? I know the professor of Biochemistry at the Collège and can ask him if he will accept you to study under him’. It was just as well, as my application to work toward a PhD in biochemistry at Cambridge University was turned down on the grounds that I was too young and that there were very few places available anyway. Some months went by when, out of the blue, a letter arrived from a Professor Jean Roche, Head of the Department of Biochemistry at the Collège de France, in which he said ‘I have had students from all over the world but have not yet had one from India – I will have you, providing you could arrange the finance’. His offer sounded a bit like filling a stamp album. No cv was asked for, no questions asked about my capabilities, nor references from my mentors. On the strength of Roche’s letter I applied for an Indian scholarship and was quite surprised to get the award. Hence, the rush to submit my thesis in Bangalore and leave for France.

3. PhD student in Paris: the start of my love affair with thyroid hormone

Arriving at the Collège de France in the summer of 1951, I discovered that Jean Roche, director of “Laboratoire de Biochimie Générale et Comparée”, was a biochemist with a medical background who ran several unrelated projects, each with a small group. I was incorporated into a group working on the biosynthesis and metabolism of thyroid hormone (TH). The group consisted of my PhD supervisor Raymond Michel (figure 1a), along with his wife Odette, two mature graduate students, Serge Lissitzky (an ex-French military doctor; figure 1a) and Yasuo Yagi from Nagoya in Japan, my future wife Renée Zanetto, to be joined later by an Uruguyan, and a Frenchman from Tunisia. Roche’s department had people from about a dozen countries, which was a change from the mono-national lab in Bangalore. The thyroid group was a particularly friendly bunch – a crucial element for success in a research lab. I had arrived with little knowledge of the language and no contacts; my new friends told me later that at the beginning I found it safer to say ‘non’ rather than ‘oui’ when asked a question!

During my first year in Paris, Lissitzky and Raymond Michel had identified 3,3’, 5-triiodo-L-thyronine (T_3) in the hydrolysate of rat thyroglobulin and were able to establish its biosynthetic pathway in the thyroid gland (figure 2). This new compound was identified almost simultaneously by Gross and Pitt-Rivers (figure 1b) in London in human blood, later shown to be derived from L-thyroxine (T_4) in peripheral tissues (Pitt-Rivers and Tata 1959). All four were to remain my special friends for years to come, although Lissitzky and Gross died far too early. As iodinated biphenyl amino acids, T_3 and T_4 are unique signalling molecules, being found in the most primitive organisms as well as in man (Barrington 1964). Both are synthesized as constitutive amino acids of the large iodinated protein thyroglobulin within the thyroid gland (or its equivalent), from which they are released into the bloodstream. T_3 is now considered to be the physiologically active form of thyroid hormone and thyroxine a pro-hormone. It is however the multiplicity of the hormone’s actions which fascinated me above all and which was to influence a large part of my future thoughts. Its actions can be divided into two groups: (i) growth and developmental and (ii) regulation of metabolic functions (Pitt-Rivers and Tata 1959; Tata 2007). My own doctorate project concerned the metabolism of thyroid hormone, which culminated in the identification of several metabolites in the bile, principally their glucuronide and sulphated conjugates and their deaminated, acetic and propionic acid derivatives (figure 2). What concerned Raymond Michel most was to publish the results as quickly as possible, particularly in the light of competition with rival groups in 1952/53: that of Rosalind (Ros) Pitt-Rivers and Jack Gross at the National Institute for Medical Research (NIMR) in London regarding the identification of T_3, and that of Taurog and Chaikoff at the University of California in Berkeley who were also working on the metabolism of T_3 and T_4. To be present in the same lab during the discovery of T_3, and to participate in a race, was something quite exhilarating for a fresh graduate student. This, in spite of my being quite closely directed by my supervisor, such that there was only limited scope for me to use my initiative or to make mistakes – an important requirement for research. But the plus side of being closely
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Figure 1. Some of those who played an important role in the development of the early part of my career in scientific research. (a) The author as a graduate student in Paris in 1952 (even graduate students did their lab work wearing a tie in those days!), standing in the lab between his PhD supervisor Raymond Michel (left) and co-PhD student Serge Lissitzky (right) – two who discovered tri-iodothyronine (T3) in the thyroid gland. (b) Rosalind Pitt-Rivers (left) and Jack Gross at the National Institute for Medical Research (NIMR) in London, who discovered T3 in human blood. My early work on the action of TH on transcription and amphibian metamorphosis was carried out in the Pitt-Rivers laboratory. (c) Lars Ernster, in his office at the University of Stockholm and in whose laboratory I initiated my studies on the action of TH on oxidative phosphorylation and protein synthesis. (d) At a conference in Washington with Fritz Lipmann (right) who encouraged me to replace the hypothesis of uncoupling of oxidative phosphorylation by TH with that of regulation of protein synthesis. (e) Sir Peter Medawar who, as director of NIMR in the 1960s, encouraged me to initiate work on amphibian metamorphosis and later helped me set up my own laboratory. (f) The NIMR where I have spent most of my scientific research life.
directed was that I managed to write up my doctorate thesis very quickly, with invaluable help from Renée, during the summer vacation of 1954.

While I was busy with the thesis, I was also planning the next step in my scientific research career, i.e. where to begin my post-doctoral life. Although Roche had felt that it was too early for me to embark on a postdoctoral career elsewhere, and offered me a job in his lab, I decided to seek a postdoc position in the United States. The three years in the lab of Roche and Michel had attracted me to thyroid hormone and, indirectly, to the thyroid gland. Enthused by the idea of working on a more “socially relevant” problem concerning thyroid hormone, I decided to try my luck for my first postdoctoral training preferably at a centre with links to clinical science (no one talked about “translational research” in those days). Intrigued by a paper that I had come across on human thyroid cancer by Jacob (Jack) Robbins, Joseph (Ed) Rall and Rulon Rawson (all three clinicians) from the Memorial Sloan-Kettering Institute (MSKI) in New York, in which they described an unknown radioiodinated protein in the blood of a patient with a highly functional thyroid cancer and which they had called “Compound X”, I applied to come and work with them. Much to my surprise, Rall accepted me and sponsored me, successfully, for a Damon Runyon Post-doctoral Fellowship. To think that money from sports gossip and musicals like “Guys and Dolls” could keep a scientist and his family alive for the next two years! Of course, rushing into this venture without considering other options raised many doubts in my mind. Was this going to be a reckless risk? Should not I have waited and given some thought to other alternatives? Would I be as lucky with my next gamble as I had been with the hasty decision to come to France for my PhD? In any event, the decision had been made and it was final. The last three months in Paris were hectic, finishing last experiments (if ever there is such a thing as a last experiment) and getting married in the week before setting sail from Le Havre for New York on a cold November morning.

4. Postdoc stints in the US and UK

At Sloan-Kettering, I had to continue with the Compound X story where Jack Robbins had left off before moving to his new job at National Institute of Health (NIH) in Bethesda shortly before my arrival. He had analyzed the serum of a patient with a relatively rare thyroid cancer, which had metastasized in the lung and brain, and which had a high capacity to take up iodide and organify it. The major radioactive iodinated component, (Compound X), was not thyroid hormone, thyroglobulin or its constitutive iodo-amino acids. Repeating the biochemical and biophysical analysis on the same and other patients with similar thyroid cancer, I demonstrated that Compound X resembled iodinated human serum albumin (Tata et al 1956). To my great surprise, this work earned me the Van Meter Award of the American Thyroid Association. In Paris, as part of my project to identify and study the dynamics of the major metabolites of T₃ and T₄, I had shown that the major metabolites were conjugates of the phenolic hydroxyl group and their deaminated acetic and propionic acid derivatives. Knowing that the brain is a major target of thyroid hormone, I was curious to know the fate of the hormone in this organ. So when I mentioned to Ed Rall that I would like to take on this as my second project, he gave me the green signal, and even participated with me in some of the experiments (presumably to get away from some of his clinical and administrative chores). The result was that the major metabolites in the brain are the propionic acid derivatives of T₃ and T₄, whose significance as yet remains unknown, except that these compounds are biologically very active. Soon Ed Rall too left for the NIH to head the Clinical Endocrinology Branch of the Arthritis and Metabolic Diseases institute at the NIH (to end up many years later as

![Figure 2. A simplified scheme illustrating the synthesis and metabolism of 3,3',5-triiodo-L-thyronine (T₃) and L-thyroxine (T₄). T₁ and T₂ are synthesized within the thyroid gland by the coupling of MIT and DIT within the thyroglobulin molecule, and then released into the blood upon its hydrolysis. Much of the T₁ within the peripheral tissues is derived from the deiodination of T₂. Both of them are metabolized in many tissues to deaminated derivatives, some of which, such as Triac (shown), can be physiologically active.](image-url)
its director of intramural research). So many of my visits (as well as my family’s) to the United States included staying with the Ralls and Robbinses. It is such friendships born out of shared involvement in scientific research which are an invaluable perk not found in so many other professions. Sadly, both Ed Rall and Jack Robbins died weeks apart this year (2008).

Several unconnected events during my second year at MSKI were to have another major impact on my future career and research. It began with a chance meeting with Ros Pitt-Rivers (figure 1b), who was spending a sabbatical year in Boston with Fritz Lipmann, and had come to give a seminar to our group. That was the year Lipmann was awarded the Nobel Prize (one of the rare scientists who won the prize before being elected to the US National Academy of Sciences). In her talk Ros suggested that Triac (figure 2) – a major topic of my PhD work – was likely to be the active form of thyroid hormone. When, during the discussion period I indicated that this was not likely to be the case, she suggested that perhaps one day I could work on this problem in her lab at the National Institute for Medical Research (NIMR) in London, where she was about to return. As the end of my second year at MSKI was approaching, my head of the department, Rulon Rawson, offered me a tenure-track appointment in his department with the possibility of building up a small group around me. But the catch was that I would first have to apply for a work permit from a country outside the US (no Green Cards in those days), whereupon I hit on the idea of asking Ros to come and work in her lab as a postdoc. I was successful in obtaining a Beit Fellowship – high in prestige but low on stipend. So within two years of my first postdoc stint I was embarking on a second one in another country. Was I being reckless again in venturing into the unknown? What was important for me was to keep intact my bond with thyroid hormone.

By the time I arrived at NIMR, Ros Pitt-Rivers had almost abandoned the idea that Triac was the active form of thyroid hormone and I was left to do more or less what I pleased. I spent a fair amount of my time studying a variety of physico-chemical properties of the hormone and its analogues, such as how these would be chemically altered when labelled with $^{131}\text{I}$ at a very high specific activity, their interactions with serum and tissue proteins, the biological half-lives of these compounds and new ways of separating them. But my most notable achievement at NIMR was co-authoring two books with Ros: “The Thyroid Hormones” and “The Chemistry of Thyroid Diseases” (Pitt-Rivers and Tata 1959, 1960). The arrangement was unique in that each of us wrote an equal number of different chapters and, except for minor modifications, left them as each of us had set them out. I consider that writing them in my late twenties taught me an immense amount of the history of the subjects and provided valuable insights which proved to be most useful for further development of my career. I was also enjoying the style and culture of scientific research in England, so that I decided not to take up my appointment at the MSKI (to Rulon Rawson’s great annoyance) and ended up spending four years on my second postdoctoral fellowship. Ros Pitt-Rivers was a popular figure at the NIMR, so that I got to know a large number of people there. For example, at our lunch table we were frequently joined by the director, Sir Charles Harington (he was her PhD supervisor), James Lovelock (inventor of gas chromatography and later to acquire greater fame as the author of the “Gaia Hypothesis”) and Rodney Porter who worked out the structure of antibody for which he was awarded the Nobel prize. Ros also had many varied connections outside the NIMR to many of whom she introduced me – family, cultural and social, with her aristocratic, intellectual background (related to Bertrand Russell, the Mitfords, Huxleys and Churchills).

In 1959 I attended a joint meeting of the British and Scandinavian Biochemical Societies in Finland. One of the principal speakers at the meeting was Lars Ernster from the Wenner-Gren Institute in Stockholm, a well-known figure in the subject of oxidative phosphorylation, one of the hottest topics of biochemical research in those days and of particular interest to those working on the mechanism of action of thyroid hormone. At that meeting Lars (Lasse) (figure 1c) presented a review of work from his own laboratory on oxidative phosphorylation, in which he mentioned the then generally accepted mechanism of action of thyroid hormone of uncoupling of oxidative phosphorylation in mitochondria. Although I had not previously worked on mechanism of action of TH or on oxidative phosphorylation, I was unconvinced by the uncoupling theory mainly on the grounds that effects were toxic, being only produced at high concentrations of L-thyroxine, the lack of tissue specificity and little correlation between the effects of biologically active and inactive analogues of the hormone. I argued these points with Ernster at that meeting, with what could only be described as chutzpah, adding that uncoupling of oxidative phosphorylation was unlikely to be the physiological mechanism of action of TH, whereupon he suggested that I go to his laboratory to disprove what was a widely accepted hypothesis. I decided to take up this offer and turned up in Stockholm the following year on one more postdoctoral adventure in a new country – an adventure that was to prove to be most rewarding, and perhaps the most important turning point in my research career.

5. Sweden and thyroid hormone action

As already mentioned, a major characteristic of thyroid hormone is the wide diversity of its physiological actions (see table 1). In young mammals it exerts a marked growth-promoting and developmental action, whereas...
in adult mammals it regulates many metabolic activities, the best known of which is Basal Metabolic Rate (BMR). The most spectacular action is that in initiating amphibian metamorphosis, as will be discussed later. Luckily, the very first set of experiments that I had designed in Stockholm worked beautifully. I found, as summarized in table 2, that in young rats thyroidectomy (to cut off the endogenous hormone supply) arrested their growth and lowered the BMR. A small replacement dose of T3, similar to that used in earlier work by others, raised BMR but caused a drastic loss of weight. When the mitochondria from different tissues were examined, it was clear that the enhanced O2 consumption at different concentrations of the hormone was produced via different mechanisms (Tata et al 1962). Low doses of T3 caused a slow elevation of mitochondrial respiration without any uncoupling of oxidative phosphorylation, but at high doses it rapidly elevated respiration by uncoupling oxidative phosphorylation, in the same way as was caused by uncoupling agents like dinitrophenol (Loomis and Lipmann 1948). Further experiments in which every variable was tested, led us to the conclusion that a new explanation had to be sought to explain the mechanism of action of thyroid hormone. We postulated that, under physiological conditions, T3 regulated BMR and energy production by controlling the amounts of different dehydrogenases and other components of the mitochondrial respiratory chain (Tata et al 1963). These findings were published in papers co-authored by Ernster, even though it went against his earlier ideas. This ability to reconsider one’s own (and a widely held) belief is to me the mark of a truly great scientific mind. To some extent, I was lucky and the risk I took was going to pay off handsomely.

A series of events and encounters in the summer of 1961 turned out to be most timely and productive. In July of that year at the International Congress of Biochemistry in Moscow, Marshall Nirenberg described for the first time how a trinucleotide coded for an amino acid in a simple in vitro protein synthesis system while Asher Korner described how treatment of rats with growth hormone caused the stimulation of incorporation of amino acids into protein by isolated liver polysomes and microsomes. Soon after the Moscow Congress I undertook an extensive tour of North America, visiting a number of research groups interested in thyroid hormone action and oxidative phosphorylation to argue that the idea of uncoupling oxidative phosphorylation as the mechanism of the physiological action of the hormone was flawed and that some other mechanism of its action had to be sought. I had not met earlier several of the renowned groups working on oxidative phosphorylation in the US, such as those of Lardy in Wisconsin, Lehninger at Johns Hopkins and Racker in New York, most of whom simply did not accept my conclusions (Tata 2005). However, my last

![Table 2.](image-url)

<table>
<thead>
<tr>
<th>Growth and developmental actions</th>
<th>Metabolic actions</th>
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<tbody>
<tr>
<td>Rate of postnatal growth of many mammalian and avian tissues</td>
<td>Regulation of basal metabolic rate in homeotherms</td>
</tr>
<tr>
<td>Functional and biochemical maturation of fetal brain and bone</td>
<td>Movement of water and Na+ ions across cell membranes</td>
</tr>
<tr>
<td>Morphogenesis, gene switching and cell death in amphibian larval metamorphosis</td>
<td>Regulation of metabolism of cholesterol and other lipids</td>
</tr>
<tr>
<td>Control of molting in birds</td>
<td>Nitrogen (urea, creatine) metabolism</td>
</tr>
<tr>
<td>Regulation of synthesis of mitochondrial respiratory enzymes and membranes</td>
<td>Control of oxidative phosphorylation and energy metabolism</td>
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Table 2. (A) The effect of a small and a large single dose of triiodothyronine (T3) on the basal metabolic rate (BMR), liver mitochondrial respiration (Q02) and P : O ratio and the latent period of action in normal and thyroidectomized (Thyrex) rats. (B) The effect of adding a high dose of T3, directly to thyroidectomized rat liver mitochondria

<table>
<thead>
<tr>
<th>(A) In vivo Rats</th>
<th>Dose of T3 (μg/100g)</th>
<th>BMR (Δ ± % over normal at 48 h)</th>
<th>Mitochondria</th>
<th>Latent period (h)</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.8</td>
</tr>
<tr>
<td>Thyrex</td>
<td>-</td>
<td>-21</td>
<td>-28</td>
<td>2.7</td>
</tr>
<tr>
<td>Thyrex 20</td>
<td>+31</td>
<td>+87</td>
<td>2.7</td>
<td>35</td>
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<tr>
<td>Thyrex 1700</td>
<td>+59</td>
<td>+133</td>
<td>0.7</td>
<td>2</td>
</tr>
<tr>
<td>(B) In vitro Thyrex</td>
<td>10^{-3}M</td>
<td>+195</td>
<td>0.4</td>
<td>&lt;0.1</td>
</tr>
</tbody>
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Mitochondrial Q02 and P : O measured with pyruvate + malate as substrate.

visit on that trip was to Fritz Lipmann’s lab at the Rockefeller Institute. Although Lipmann (figure 1d) was the first to demonstrate the uncoupling action of high concentrations of thyroxine to be similar to that of dinitrophenol (Loomis and Lipmann 1948), he showed me some old unpublished data from his lab in which, at lower doses, it stimulated protein synthesis in vivo, and encouraged me further to pursue my idea of looking at protein synthesis in detail — encouragement which I value greatly, as until that visit I was so discouraged that I had contemplated abandoning my work on thyroid hormone action.

Back in Stockholm, I teamed up with Erik Arrhenius’s group to isolate mitochondria and microsomes (or polysomes) simultaneously from the same tissue and follow various biochemical activities and components associated with oxidative phosphorylation and protein synthesis as a function of time after replacing TH in thyroidectomized rats. The results were quite clear-cut. The protein synthetic capacities of both microsomes and mitochondria from liver, heart and skeletal muscle (all major targets of the hormone) were tightly coupled and were enhanced after a fairly long period following hormone administration. This was accompanied by a selective rise in cytochrome oxidase, as an index of mitochondrial respiration. Later, when the same experiments were repeated in London it was found that indeed additional mitochondrial enzymes and structural proteins were selectively increased, anticipating the acute hormonal stimulation of oxidative phosphorylation activity (Roodyn et al 1965 and figure 5).

A chance meeting in Stockholm was to change once again the course of my future scientific career. In December 1961, at a reception at the Karolinska Institute on the day after he received his Nobel Prize, I met Peter Medawar (figure 1e) for the first time. He came up to me and said that he was aware of the work I was doing in Stockholm on oxidative phosphorylation, described in our Nature paper (Tata et al 1961), and suggested, along with Harington, that I return to NIMR where he was soon to be the new director. It is difficult to describe the feeling of pride and flattery at being approached by such a great figure of twentieth century biology. I accepted his offer of a junior Medical Research Council (MRC) appointment and left for London in early 1962. Undoubtedly, 1961 and my 31st year will always remain among the most memorable years.

6. Transcription: more good luck

When I arrived back at NIMR in 1962, actinomycin D had become commercially available and I carried out a “crazy” experiment with this inhibitor of transcription in vivo. At the lowest possible dose, actinomycin D prevented the calorigenic (measured as stimulation of BMR) and growth-promoting actions of T3 (Tata 1963), and abolished the stimulation of mitochondrial and cytoplasmic protein synthesis and mitochondrial respiration, also caused by T3. Near that time, when Chris Widnell joined me as my first graduate student, it was decided to look directly at transcription in vivo and in vitro. After establishing methods for isolating nuclei from various tissues such that they would be reasonably active in synthesizing RNA in vitro, almost the first assays of RNA polymerase activity of isolated rat-liver nuclei gave novel and unexpected results. When the activity was measured by varying time-course, substrate concentrations, pH, anions, cations and ion strength, it appeared that there had to be more than one RNA polymerase activity, in contrast to a single enzyme previously described in bacteria. Would the RNA products synthesized under different conditions be different? This question was not that easy to resolve in the early1960s in the absence of high-specific activity α-32P-labelled nucleotides, techniques of DNA-RNA hybridization, PCR-based analysis or nucleic acid sequencing, techniques that beginners now take for granted. Relying on the laborious and “primitive” nearest neighbour base frequency analysis using low specific activity 14C-labelled ATP and paper chromatography, based on Chargaff’s AU:GC ratios, we were able to show (figure 3) that in the presence of Mg2+ and at low ionic strength, the product was more GC-rich, i.e. mostly ribosomal RNA, whereas with Mn2+ at high ionic strength it was more AU-rich, i.e. messenger RNA-like (Widnell and Tata 1964).
The idea of multiple RNA polymerases in eukaryotes was quite novel then, which meant that we lost considerable time trying to satisfy the serial demands of the referees and editors of the journals where Widnell and I wished to publish our findings. We also lost time in attempting to resolve and isolate the two activities and from the failure to have access to inhibitors that would selectively inactivate one or the other enzyme. A letter from F. Stirpe from Milan that he wished to spend a few months in my lab to demonstrate that a fungal toxin, α-amanitin, could selectively inhibit the enzyme catalyzing the synthesis of mRNA and not that synthesizing rRNA, filled me with joy. But my thoughts were dashed when I discovered that I was refused a small amount of extra space and a supplementary budget for Stirpe by the head of my division. A few months later, Roeder in Seattle and Chambon in Strasbourg succeeded in separating the three RNA polymerases, thanks to the selective action of α-amanitin (see Tata 2005).

My frustration at not having the smallest amount of additional lab space and an independent budget was not lost on Medawar. He was also aware of the offers of jobs that I was receiving from universities and research institutions. I remember him saying to me once that he wished ‘to see me “institutionalized” at NIMR’, whose meaning only became clear when I discovered that, near the end of my 3-year contract as junior staff, I had been granted unlimited tenure. I also remember Medawar suggesting that he wished to see me made a Fellow of the Royal Society. He was a bit taken aback when I said ‘I don’t much care for the Fellowship as I am so enjoying the work I am doing’. Needless to add, both the MRC tenure and being a candidate for the Royal Society took care of my space and independent lab finance when he offered me very generous space in a newly furbished lab, new equipment and the possibility of more staff and visiting workers. The new lab was to become the Division of Developmental Biochemistry which I headed (with several long and short sabbaticals) until my retirement. Sadly, Peter Medawar was struck down by a cruel illness and had to give up his position as director of NIMR, but the brilliance of the mind of this extraordinary person survived till his last days.

Important as it was to demonstrate the multiplicity of eukaryotic RNA polymerases, our real goal was to understand how thyroid hormone regulates nuclear and mitochondrial transcription in its target cells, both in vivo and in vitro. The first major conclusion to emerge from these studies was that the dynamics of the effect of the hormone varied according to the RNA product and the method of assaying RNA polymerase activity, which further confirmed the concept of the multiplicity of enzymes (Tata and Widnell 1966; see figure 4). The second major finding was that the action of T₃ on oxidative phosphorylation and BMR, mitochondrial and cytoplasmic protein synthesis, and mitochondrial RNA synthesis, were all tightly coupled to nuclear transcriptional activity (see table 1, figure 5). In the early 1970s, Oppenheimer, using our data on the kinetics of stimulation of transcription by T₃, was able to superimpose on them those of the intra-nuclear accumulation of labelled hormone, and suggested a close link between nuclear receptor for TH and the regulation of transcription. A decade later, the advent of gene cloning technology confirmed this principle, not only for thyroid hormone but also steroid hormones, retinoic acid, vitamin D₃ and all those signalling molecules that act via nuclear receptors. This is now a ‘central dogma’ for explaining the hormonal regulation of gene expression (Mangelsdorf et al 1995). However, it was already clear to many of us in the early 1960s that measuring overall protein and RNA synthesis to express the action of thyroid hormone (or any other growth and developmental hormone) would be of limited value and that one had to study clearly identifiable, specific gene products as hormonal targets. What better model to exploit for this purpose than the well-known obligatory control of amphibian metamorphosis by thyroid hormone.

7. From human to frog: Thyroid hormone and amphibian metamorphosis

In 1912, Gudernatsch had made the chance discovery that feeding thyroid extracts to tadpoles induced metamorphosis. Several studies in the 1930s established that removal of the thyroid gland or treatment of tadpoles with anti-thyroid drugs abolished their metamorphosis, inhibition which...
liver and tail and of haemoglobin switching in bullfrog (studies in P Cohen’s and E Frieden’s laboratories, establishing been laid down in the 1940s and 1950s, particularly from the 1998; Shi 1999). Much valuable biochemical background had to analyze the biochemical responses to the molecular and to exogenous TH has provided a convenient experimental tool The early developmental competence of tadpoles to respond beyond the time of natural metamorphosis. Conversely, can be reversed by the administration of TH, even well beyond the time of natural metamorphosis. During natural metamorphosis, the first detection and rate of appearance of morphological (and biochemical) changes characteristic of metamorphosis match the appearance and rapid increase in those of circulating hormone (see figure 7). The early developmental competence of tadpoles to respond to exogenous TH has provided a convenient experimental tool to analyze the biochemical responses to the molecular and cellular actions of the hormone (see Gilbert et al 1996; Tata 1998; Shi 1999). Much valuable biochemical background had been laid down in the 1940s and 1950s, particularly from the studies in P Cohen’s and E Frieden’s laboratories, establishing the induction of urea cycle and hydrolytic enzymes in the liver and tail and of haemoglobin switching in bullfrog (Rana catesbeiana) tadpoles undergoing natural or TH-induced

metamorphosis. Some of the well-studied, wide-ranging biochemical and physiological actions of TH in regulating amphibian metamorphosis are summarized in table 3 (Weber 1967; Gilbert et al 1996; Shi 1999; Brown and Cai 2007). There was little work on developmental biology at the NIMR in the 1960s, but, thanks to the encouragement I received from Peter Medawar, I embarked on research in this most intriguing post-embryonic developmental and signalling system. The African clawed frog, Xenopus laevis, is an organism of choice of embryologists and developmental biologists who had already obtained important molecular biological information during early embryogenesis; so in 1964 I switched from the bullfrog Rana catesbeiana to lab-bred Xenopus tadpoles for our work on thyroid hormone-induced metamorphosis. A major characteristic of metamorphosis, as illustrated by the diverse, and seemingly, contradictory, responses to TH, summarized in table 3, is an indication of the acquisition of the adult phenotype. Administration of TH to early tadpoles leads to the premature activation of the developmental programme. The initiation of the process is preceded by an early burst of RNA synthesis which is essential for the later biochemical and morphological changes, as was demonstrated by experiments with transcriptional inhibitors. Another important feature of hormonally regulated metamorphosis is that no two tissues, or groups of cells, exhibit the same hormonal response, which ranges as widely as de novo morphogenesis, functional reprogramming and total tissue regression.

The dramatic changes induced by TH are not determined by information in the hormonal signal but by that in the programme laid down earlier during postembryonic development. The amphibian larval brain is a major TH target with a wide variety of changes taking place during metamorphosis in both the anatomical and functional characteristics ranging from morphogenesis to cell loss in its different regions. Similarly, genetic reprogramming leads to the acquisition of new morphological and biochemical characteristics, such as the appearance of “adult” type of digestive enzymes in the pancreas, urea cycle enzymes and serum albumin in the liver and the keratinisation of the larval skin. Perhaps the most dramatic morphological and biochemical changes are the almost simultaneous emergence of limbs and total, or almost total, loss of larval tails, gills and the digestive system. Indeed, there are few, if any, larval cells that escape the impact of thyroid hormone. Thus, tissue-specific gene switching is central to hormonal signalling and postembryonic development.

8. Thyroid hormone and developmentally programmed cell death (apoptosis)

Earlier studies to explain thyroid hormonal induction of tissue regression during metamorphosis were based on such
processes as macrophage infiltration, lysosomal expansion or activation of lytic enzymes (reviewed by Weber 1969; Tata 1994; Yoshizato 1996). These ideas were not fully verified experimentally and raised the possibility that the hormonal elevation of lytic enzyme activity in larval tissue programmed for regression was caused by a selective enhancement of the synthesis of some or all of them. In the mid-1960s some laboratories were able to maintain *Xenopus* tadpole tails in organ cultures for sufficiently long periods such that it was possible to induce tissue regression by the simple addition of TH to the culture medium (Weber 1965; Tata 1966), with the resultant induction of several lytic enzymes such as cathepsins and nucleases. The increase in lytic enzyme activity and tissue regression following the addition of T₃ to organ cultures of *Xenopus* tadpole tails was accompanied by a burst of RNA and protein synthesizing activity. This finding raised two important questions. Is the enhanced protein synthetic activity necessary for cell death? Are any new proteins synthesized at the onset of tissue loss and, if so, what is their nature? When inhibitors of RNA and protein synthesis, such as actinomycin D, puromycin and cycloheximide, were added to organ cultures of tadpole tails, along with or after T₃, a paradoxical result was obtained (Tata 1966; Weber 1965). These cytotoxic agents, which normally kill cells, were found to protect cells programmed to die during postembryonic development. When the kinetics of tail regression was measured, actinomycin D not only blocked tail regression if added along with T₃ at the beginning of the culture, but also when administered after T₃ had initiated regression, as shown in figure 6. What my studies revealed was that ongoing protein synthesis is necessary for programmed cell death (PCD) to be initiated as well as for it to continue.

Seem several years later, genetic and molecular biological studies from the laboratories of Horvitz and others on the worm *Caenorhabditis* and cultures of normal and cancerous mammalian cells established without any doubt that cell death or apoptosis required the activation

**Figure 6.** Effect of inhibition of RNA synthesis by actinomycin D on T₃-induced regression of *Xenopus* tadpole tails in organ culture. Kinetics of *Xenopus* tadpole tail regression in culture following the addition of T₃ (5 × 10⁻⁸ M) at the beginning of culture period (day 0) and actinomycin D (5 μg/ml) added at day 0 or day 3. The reduction in the length of the tail is a good index of tissue regression and corresponds to the loss of total DNA during culture (adapted from Tata 1966).

| Table 3. Morphological and biochemical responses to thyroid hormone during amphibian metamorphosis |
|---------------------------------|---------------------------------|---------------------------------|
| **Tissue**                      | **Morphological**               | **Biochemical**                 |
| Brain                           | Re-structuring, axon guidance, axon growth, cell proliferation and death | Cell division, apoptosis and new protein synthesis |
| Liver                           | Re-structuring, functional differentiation | Induction of urea cycle enzymes and albumin; Larval to adult haemoglobin gene switching |
| Eye                             | Re-positioning; new retinal neurones and connections; lens structure | Visual pigment transformation (porphyropsin rhodopsin); -crystallin induction |
| Skin                            | Re-structuring; skin granular gland formation; keratinization and hardening; apoptosis | Induction of collagen, 63 kDa (adult) keratin and magainin; induction of collagenase |
| Limb bud, lung                  | *De novo* formation of bone, skin, muscle, nerves, etc. | Cell proliferation and differentiation; chondrogenesis |
| Tail, gills                     | Complete regression             | Programmed cell death; induction and activation of lytic, enzymes(collagenase, nucleases, phosphatases, matrix metalloproteinases); lysosome proliferation |
| Pancreas, intestine             | Major tissue re-structuring     | Reprogramming of phenotype, induction of proteases, fatty acid binding protein, stromelysin. |

*See* Tata (1998) and Shi (1999) for details.
of well-defined genes. Some of these belong to the now classical bcl-2 family of proteins that may either induce or inhibit apoptosis (Korsmeyer 1995). In our laboratory we investigated the possibility that the genes whose activities are responsible for cell survival, rather than death may be differentially regulated in tissues programmed for growth and regression during Xenopus metamorphosis (Cruz-Reyes and Tata 1995). For this purpose Xenopus bcl-2-like genes were cloned and two members of this family (xR11 and xR1), closely related to mammalian bcl-X\textsubscript{L}, were studied in detail, as it is considered to be a major gene conferring survival function on cells (Korsmeyer 1995). Both xR11 and xR1 exhibited all the criteria of protecting heterologous cells against the apoptotic action of cytotoxic agents. However, both xR1 and xR11 continued to be expressed in regressing as well as non-regressing tissues during natural and TH-induced metamorphosis. XR11 is indeed up-regulated in the brain during metamorphosis. It is therefore most significant that in a later study in collaboration with groups in France, over-expression of xR11 in transgenic Xenopus enhanced the survival of Mauthner’s and Rohon-Beard neurons in froglets that had just completed natural metamorphosis (Coen \textit{et al} 2001). Normally, these neurones undergo total or partial regression during natural or precociously hormone-induced metamorphosis.

9. Sequel

Since this perspective mainly deals with the first 10–12 years of my early scientific research career, I shall only briefly mention the direction in which our studies on metamorphosis evolved in later years. In the 1980s, while some members of my laboratory were studying the activation of egg protein genes by oestrogen in the liver and oviduct of male and female Xenopus, respectively, we observed the induction of vitellogenin (egg yolk protein precursor) genes de novo in primary cultures of hepatocytes from adult males was preceded by a marked elevation of oestrogen receptor following the addition of the hormone. Furthermore, in an attempt to determine at what developmental stage the tadpoles became competent to respond to the steroid hormone, we observed that this competence was acquired during metamorphosis. Induction of metamorphosis precociously by treatment of early Xenopus larvae with T\textsubscript{3} advanced the activation of the silent vitellogenin genes and, at the same time, the auto-induction of estrogen receptor. These findings, and the advent of gene cloning, led us to embark on exploring the expression of thyroid hormone receptors during natural and hormone–induced metamorphosis.

About 50 genes encoding a large multigene family of nuclear receptors, which are cellular homologues of the oncogene erbA (c-erbA), have been cloned and characterized. Their products are often tightly bound to DNA as chromatin proteins and function as ligand-activated transcription factors (Mangelsdorf \textit{et al} 1995; Laudet and Gronemeyer 2002; Tata 2002; Benoit \textit{et al} 2004). Two distinctive characteristics of the sub-group of nuclear receptors to which the two thyroid hormone receptors belong are (i) they form heterodimers with a member of the same sub-group, namely retinoid X receptor (RXR), and (ii) the high degree of target gene specificity for a given hormone which is determined by the hormone response element (HRE) of the promoter of the target gene and the DNA-binding domain (DBD) of
the receptor which recognises it (Mangelsdorf et al 1995). A number of large proteins termed CBP (CREB binding protein) and p300, p160 nuclear receptor co-activators and the 270 kDa nuclear receptor co-repressor (N-CoR) form complexes with nuclear receptors. Such complexes are thought to integrate multiple signalling pathways in the cell nucleus, being themselves regulated by protein phosphorylation (Brivanlou and Darnell 2002). The binding of the hormone to its nuclear receptor is thought to lead to an alteration in the chromatin structure such that it will induce the binding of non-receptor transcription factors to allow the transcription of the hormone-regulated gene promoter. Wolfe's group has suggested that both the silencing and activation of the Xenopus TRβ gene is determined by processes controlling nucleosome assembly (Wolffe 2000).

The expression of TRα and TRβ genes in Xenopus tadpoles is under developmental and hormonal control. Very small amounts of both TR transcripts can be detected in unfertilized eggs and early embryos. A substantial increase, particularly of TRα mRNA, occurs when the tadpole first exhibits competence to respond to exogenous thyroid hormone (see Tata 1968). At this stage of development, several tissues which are programmed to undergo major changes later during metamorphosis show high concentrations of TR mRNA, such as brain, liver, limb buds, small intestine and tail, as seen from both biochemical and in situ hybridisation analyses (Yaoita and Brown 1990; Kawahara et al 1991). At the onset and through completion of metamorphosis there is good correlation between the accumulation of TR transcripts and the circulating level of thyroid hormone in Xenopus tadpoles (figure 7). The functional receptor must therefore be in place well before the hormonal signal impinges on the tissues during normal development and that TH induces its own receptor. Several studies, based on a variety of molecular and cellular techniques, have established that administration of exogenous T3 to pre-metamorphic stages of Xenopus tadpoles, and organ and cell cultures causes a substantial induction of both TR mRNA and protein (Machuca and Tata 1992; Kanamori and Brown 1993; Eliceiri and Brown 1994; Fairclough and Tata 1997; Shi 1999; Tata 2006; Brown and Cai 2007). Administration of T3 augmented the amount of both receptors in tadpole tissues, irrespective of whether the tissue is programmed for extensive gene switching and functional maturation (liver, brain) or substantial cell death (tail) following metamorphosis.

Analysis of gene switching has been extended to the characterization of genes that are activated or down-regulated in limbs (de novo morphogenesis), intestine (partial regression) and tail (total cell death) during natural metamorphosis or by TH administered to pre-metamorphic Xenopus tadpoles (Shi, 1999; Brown and Cai 2007). Of particular interest are genes that can be classified as 'direct response' genes (activated in the absence of protein synthesis) since it is likely that their products may play a causal role in the cascade of regulatory elements leading to tissue-specific biochemical and morphological changes listed in table 3. Many transcription factor genes have been identified as direct response genes, particularly noteworthy being TRβ gene itself. Thyroid response elements that interact with thyroid hormone receptors have been identified in the promoters of some direct response genes. Whereas both TR isoforms are auto-induced by TH during metamorphosis, only the TRβ gene in amphibians has been shown to be a "direct-response" gene with a functional thyroid response element in its promoter (Machuca et al 1995), which could account for the phenomenon of auto-induction of receptor.

The wider significance of the phenomenon of auto-induction, described above, may lie in the fact that it is not restricted to up-regulation of TR by TH during amphibian metamorphosis but is also seen with the expression of other nuclear receptors under the control of their own hormonal ligands (Tata 2002). It is likely that the gene encoding a given receptor is constitutively expressed to produce a very low level of functional receptor in the target tissue at early stages of development, and that low concentrations of the liganded receptor would only suffice to activate its own receptor gene, but not of its target genes which would require a significantly higher concentration of the hormone and receptor. An intriguing question for the future is whether unliganded receptors have some, as yet unknown, functions other than mediators of signalling by their ligands? One recent study hints that it may be so (Havis et al 2007). Meanwhile, it is clear that amphibian metamorphosis has served as a most fruitful model for advancing our knowledge of signalling and the regulation of post-embryonic development by thyroid hormone.

10. Will we ever discover the mechanism of action of hormones?

Ever since the discovery of signalling molecules, scientists have speculated and advanced hypotheses on the mechanism of action of hormones. What has been accomplished over the last several decades is an ever-growing catalogue of effects, and not the mechanisms of their action. This fact emerges from the time-line in table 4 in which I have indicated some important milestones in the study of most hormones in general, but thyroid hormone in particular. With the rapid growth of biochemistry in the 1930s and 1940s, and advances in techniques for working with isolated tissue and cell preparations, it became possible to define the physiological actions of hormones at the whole body level in terms of individual enzymes and cellular constituents. The availability of radioactive hormones of high specific activity in the early 1960s made it possible to locate the primary site of interaction of a given hormone which gave

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a rough indication of the location of its receptor. A major breakthrough, both at the technical and conceptual levels, has been the molecular cloning of membrane and nuclear hormone receptors and the realization that they are cellular homologues of erb A and B oncogenes. More recently, thanks to the information accumulating on structural and functional characteristics of chromosomal proteins, the emphasis has shifted to the interactions between nuclear receptors and co-receptors and how these modify the higher order organization of chromosomal elements. Newly emerging technologies, such as chromatin immunoprecipitation (ChIP) to follow targeted chromatin binding and histone acetylation in vivo, and the introduction of RNA interference, are now beginning to offer new insights into the complexity of chromatin organisation of genes in the context of signalling mechanisms involved in the regulation of their expression. Finally, the current emergence of concepts of systems biology, bioinformatics and networking advances in all aspects of regulatory biology – starting with physiological processes in vivo to biochemical analysis in cell free-systems to molecular and cell biology and, finally, to structural biology – and will continue to do so. This does not mean that the enormous effort devoted to explain the mechanism of hormone action has been futile. Far from it. Attempts to understand how a hormone works has often led to uncovering some fundamental regulatory biological principles of wider and greater importance beyond that of hormone action. There is no better example than the discovery of cyclic AMP by Sutherland and Rall in 1956 as a consequence of their work on the action of the hormones adrenaline and glucagon. The same is true for nitric oxide-mediated regulation and protein phosphorylation, processes in which cyclic nucleotides are intimately linked.

11. Personal perspectives

Looking back over fifty decades of my life as a scientist, I am struck by the unpredictability in science and the importance of willingness to take risks. Both have played an important role in moulding my career. If Professor Giri had not left the Biochemistry Department in Bangalore when I arrived there as a graduate student, it is most likely that I would not have developed my life-long love for thyroid hormone, but
become involved in a different branch of biochemistry. It is simply the risk I took to leave at short notice for France for my 
doctorate that brought me face to face with thyroid hormone. 
Being present during discovery of tri-iodothyronine in the 
thyroid gland by my PhD supervisor Raymond Michel and 
co-graduate student Serge Lissitzky was a rare and thrilling 
experience. My next three moves to different parts of the 
world as a postdoctoral scientist could also be considered 
as hasty and risky for my career. The first was to work on 
human thyroid cancer in New York, followed by moving to 
London, largely dictated by bureaucratic requirements of 
a work permit, and then to Sweden to work on the action 
of thyroid hormone. Besides being lucky in ventures of 
common scientific pursuits which have led to my life-long 
love for thyroid hormone, it is the enduring friendships – 
with Raymond Michel in France, Jack Robbins and Ed 
Rall in the United States, Ros Pitt-Rivers in England and 
Lars Ernster in Stockholm – that I treasure deeply. There is 
no better joy in one’s scientific research endeavours than the 
comradeship and trust of colleagues that one develops.

As regards my own contributions to understanding 
thyroid hormone action, serendipitous findings have played 
a major role in my early career. On three separate occasions I 
have “stumbled” on to some very basic regulatory processes 
of biology. The first is the idea that basal metabolic rate 
is determined by the selective synthesis of respiratory 
enzymes and proteins in mitochondria, rather than by the 
efficiency of coupling of oxidative phosphorylation (section 
5). The second is the chance discovery of multiplicity of 
eukaryotic RNA polymerases when attempting to follow 
the transcriptional responses of isolated nuclei following 
treatment of animals with T3 (section 6). And finally, studies 
on the regression of isolated tadpole tails induced by T3 
in organ cultures led me to propose that developmentally 
programmed cell death (apoptosis) is initiated by the \textit{de novo} 
synthesis of specific RNAs and proteins rather than by the 
activation of pre-formed hydrolases in lysosomes (section 
8). These serendipitous findings have in themselves not 
elucidated the mechanism of action of thyroid hormone, but 
have underlined the importance of some very fundamental 
regulatory biological processes of living organisms.

What major lessons have I learnt from the few successes and 
failures (of which there were many, not mentioned here) 
of my first 10–12 years as a postdoctoral scientist? First is not 
the risk of taking risks at an early stage in one’s career – 
a time when none or very few are adversely affected by 
decisions that may turn out to be wrong (except perhaps one’s 
family). For example, moving from London to Stockholm 
following a chance meeting with someone I did not know to 
work on a biochemical problem with which I was unfamiliar 
and adapting to life in one more new country, paid off for 
me handsomely. The generosity of Ernster in co-authoring 
papers with me, in which we were demolishing the dogma of 
uncoupling of oxidative phosphorylation as the mechanism 
of action of thyroid hormone – initially supported by him 
and others – revealed to me that he placed scientific thought 
above his personal opinions. This work led me to venture into 
the uncharted territory of protein synthesis and transcription 
and which, eventually, secured a permanent career position 
for me at the National Institute for Medical Research in 
London, where I have enjoyed the generosity and support of 
so many (especially Ros Pitt-Revers and Peter Medawar) 
and spent much of my working life. It is at the NIMR that a 
“hunch”, based on a relatively primitive technology of 
transcription in the early 1960s, led Widnell and myself to 
suggest that eukaryotic RNAs were synthesised by multiple 
RNA polymerases (even though we were not able to pursue 
this concept in greater depth) and turned out to be a most 
exciting development. A little later, also at the NIMR, working 
with tissue regression during amphibian metamorphosis, 
I suggested that programmed cell death necessitated the 
expression of new genes – also an equally thrilling experience. 
These last three diverse ventures within a period of six years 
of my postdoctoral life, proved to me that “sticking my neck 
out” turned out to be the right move. Nothing else that I have 
done since then has given me the same satisfaction. I accept 
the criticism that I did not delve into any of these new directions 
in depth to lay down more solid foundations. But then the way 
research is conducted is a highly personal matter. There is also 
the important element of luck, timing and support from your 
elders. I have been most fortunate in all these respects. What I 
do know is that scientific research has always been my passion 
– and thyroid hormone action the object of my fascination. No 
wonder that I have never managed to fall out of love with this 
unique regulatory signal.

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