To Val,
Hoping this will bring back some fond memories -
With love
Jan

ROSALIND VENETIA PITT-RIVERS
4 March 1907—14 January 1990

Rosalind Pitt Rivers

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Elected F.R.S. 1954

BY J.R. TATA, F.R.S.

ROSALIND PITT-RIVERS died on 14 January 1990 at her home in the village of Hinton St Mary, Dorset. She is best remembered for the discovery of the thyroid hormone triiodothyronine, which earned her worldwide recognition. Virtually all her scientific career, although twice interrupted by family events and the World War II, was dedicated to the Medical Research Council. Her attractive personality, wit and generosity meant that she left behind numerous friends and admirers. Despite her success as a scientist, Rosalind remained genuinely modest and retained continued interest in new developments in her area of work and in the careers and problems of those with whom she maintained a close contact until the end.

## FAMILY BACKGROUND

The eldest of four daughters, Rosalind Pitt-Rivers was born in London on 4 March 1907, to Brigadier-General the Hon. Anthony Henley and the Hon. Sylvia Stanley. Both parents were from old, established English families, and it is useful to consider their origins to appreciate fully Rosalind's background and upbringing.

The Henley peerage dates back to 1799, but without great estate or wealth. Although Anthony, Rosalind's father, became an heir after the death of his half brothers, he and his wife Sylvia had to move in 1924 to the rather modest family seat of Watford Court in Northamptonshire. He had graduated from Balliol College and was called to the bar, before joining his cavalry regiment and becoming a successful career soldier, reaching the rank of Brigadier-General during the First World War. Death came in 1925 at the early age of 52, it is said while playing cricket in Bucharest, to be succeeded as heir by his younger brother Francis, a chemist and Fellow of the Royal Society. Other than that, the Henleys do not particularly stand out in the academic or scientific world.

On her mother's side, the Stanleys of Alderley (near Manchester), an old Cheshire family, can possibly trace back their arrival to 1066. What is well established is that they have been baronets since 1660 and were raised to peerage in 1829, with estates both in Cheshire and Wales. Rosalind's grandfather, Lyulph Stanley (1839–1925), became fourth Baron Stanley of Alderley and also fourth Baron Sheffield in 1903, and whose son Arthur went back to being Lord Stanley of Alderley. Her mother had 169 first and second cousins, so it would be impossible to give even a brief genealogical account of her immediate ancestry and its ramifications. But some indication of the Stanley family, particularly the women, can be glimpsed from their 19th-century correspondence published by Nancy Mitford in 1938. A note, kindly provided by Rosalind Pitt-Rivers' son, Anthony, on Sylvia Stanley's aunts and sisters gives an idea of the character of the Stanley women. The eldest of five surviving aunts was Alice, who married a Pitt-Rivers (Colonel [later General] Augustus Lane-Fox Pitt-Rivers, 26 years later taking the name Pitt-Rivers upon inheriting the Estate from his second cousin Horace Pitt-Rivers, sixth Lord Rivers) despite strong opposition from Lord Stanley. Then followed Blanche, Countess of Airlie, Clementine Churchill's grandmother (hence Clementine Churchill was Rosalind's mother's first cousin once removed), followed by Maude who never married, and Kate who married Lord Amberley and who was mother of Bertrand Russell. Last, but not least, there was the formidable teetotal liberal Rosalind, Countess of Carlisle, who was left in possession of Castle Howard upon separation from her husband. Much has also been recently written about Sylvia Stanley's younger sister, Venetia, who had a long, and most likely platonic, relationship with H.H. Asquith, then Prime Minister, who later turned his attention to Sylvia herself.

The above brief description of the two liberal aristocratic families serves to illustrate the fact that whereas the Henleys were not particularly remarkable, the Stanleys moved in fashionable, intellectual and political circles. They were well known for their dual traits of eccentricity and genius in their women. Those who knew Rosalind well cannot help feeling that she had inherited these characteristics from the Stanleys. The Stanley inheritance was important to her not just because they were part of the Establishment, but also because so many of them made significant contributions. Not surprisingly, she often talked to her close friends about her mother and her Stanley ancestors, but she rarely mentioned her father's ancestors or, indeed, her father, though they also shared an aristocratic background. Clearly, her mother's was the more important influence in Rosalind's life.

## CHILDHOOD

Relatively little is known about Rosalind's* childhood. She was born two years after Anthony married Sylvia in 1906, her early years being largely spent following her father to his various postings. The family moved as his army career progressed to such places as Salisbury Plain and Camberley, culminating in a staff appointment at the War Office in London. The years of the World War II were spent with her Stanley grandparents at Alderley, a large and rambling but otherwise 'unbeautiful' house. The life-style was that of the twilight of the Victorian and Edwardian ages, complete with French governess and ponies in a large park surrounding the house. There must have been some happy moments shared with her Stanley (and, occasionally, Mitford) cousins in the schoolroom of this house. Her father visited Alderley only infrequently on leave. Rosalind's sister Juliet recalls a cousin, returning to England in 1919 after five years in Australia, telling her how amazed she was

* Rosalind was known to her family, friends and colleagues at work as Ros, a name that will henceforth be used for the most part in this memoir.

at the extent of the terror the Henley children displayed in the presence of their parents and grandparents, and one can only wonder how Ros overcame this terror.

Even less is known about the critical period of Rosalind's later development, the teenage years. However, her sister Juliet writes:

> My chief recollection of Ros during her teenage years is that she was always working; the child was father to the man. Everything not work was of relatively little importance. To her passion for work and her view of its importance, I partly attribute the fact of her indifference to the fact of its being a man's world. The subject was what mattered, never mind the people. Far too much has been written about the Stanleys, by writers from Nancy Mitford to Bertrand Russell, but there was, in the family, a strong trait of determination, single-mindedness and self-confidence; good characteristics for those embarking on a career.
>
> Beatrice Webb, in early life, wrote, that, before any daunting social occasion, she urged herself to remember that 'you are one of the cleverest members of one of the cleverest families in England, and have no need to be bashful about anything to anybody'. Whatever sphere she wanted to get into, that was her world, let the others be who they may or think what they liked.

She concludes:

> I wouldn't press the comparison too far, but I think Ros had something of the same attitudes to life and work.

Those who knew Ros well will agree that this is a most perceptive and incisive analysis of her critical and formative years, especially made by a sister ten years her junior.

There is, however, no doubt that it was her mother who had the greatest influence on Ros' formative years. In fact this strong influence persisted through much of her life. Her father contributed much less to her development and career. One may also ask to what extent her being the eldest of the children and the absence of a brother meant that she assumed the dominant role expected of the eldest son. Could this partly explain her self-confidence and complete ease later in life in what was a male-dominated world of science?

### Early education

Ros was first educated at home by a French governess, not altogether surprising from the above account of her Victorian/Edwardian background and upbringing, until the age of 13. There followed a period of four years of formal schooling in London at Notting Hill High School. Nothing very remarkable can be gleaned about her education at home or in school, except that she grew up to be fluent in French and showed a broad interest in literature, arts and science.

When she was about 12, Ros was given a chemistry set by an uncle. This present proved to be such a great success that she, along with her cousin Ed, the future Lord Stanley at Alderley, was given the stables (presumably part of Alderley) to be used as a laboratory. The inhabitants of the estate were not only alarmed by the smells that emanated from there but remember at least one explosion that came quite close to a disaster. Later in life, she told her sister Juliet that this present lay at the origin of her interest in, and life-long love for, chemistry. She had to wait until the end of the World War I and formal school education in London to satisfy her curiosity and to absorb knowledge about this subject. Ironically, and not atypically, the science mistress at Notting Hill High School wrote in one of her reports 'I fear Rosalind will never make a chemist', something that Ros recounted often with great relish. How many Fellows of the Royal Society must have had such reports from their science teachers at school?!

## UNIVERSITY EDUCATION

After completing school, Ros joined Bedford College, then a women's college of London University, to read for the degree of Bachelor of Science. She graduated in 1930 with a First Class Honours Degree, being top of the University. Naturally, her mind was fully tuned to pursuing a career in chemistry. Fortunately for her, E.E. Turner and Margaret M. Murray taught the subject at that time and greatly augmented her passion for it. She maintained the utmost admiration for them and after graduating continued to study for her Master's degree which she obtained in 1931 under Turner's supervision. A bibliographic search reveals two of her first papers (under the name of Pitt-Rivers) with E.E. Turner published in the *Journal of Chemical Society* in 1931 and 1932 on the reactions of substituted ammonium aryloxides and cinchona alkaloids, respectively. These were the result of her Master's Degree project.

In 1931, Ros married George Lane-Fox Pitt-Rivers, to be followed a year later by the birth of their son, Anthony. She consequently gave up her plans to pursue research towards obtaining a doctorate and spent the next few years at the Pitt-Rivers estate at Hinton St Mary in Dorset. Although she never mentioned this to her friends and colleagues, later in life her son could not help wondering to what extent her career in research was held back by her feeling of responsibility towards him.

## MARRIED LIFE

Sylvia Henley's feelings were mixed when her daughter Ros became engaged to her cousin, Captain George Pitt-Rivers. He was already divorced and, from the point of the Stanleys, resembled too much his eccentric grandfather, founder of the Pitt-Rivers Museum of Anthropology in Oxford. Perhaps one favourable circumstance was the wealth of the Pitt-Rivers relative to Ros's family, especially after 1925 when Sylvia Henley had become a widow with three daughters. Sylvia Henley quickly came to dislike her son-in-law after their marriage in 1931, a sentiment he reciprocated enthusiastically. The marriage rapidly deteriorated after the birth of their son, Anthony, in the following year. By hindsight it is easy to understand the failure of the marriage of two intelligent people, one of whom was unable to tolerate any sort of argument or discussion and expected complete obedience from his wife and family. George Pitt-Rivers' increasingly eccentric, and dangerous, scientific and political opinions must also have contributed to the inevitable breakdown. Ros did her best to tolerate his extreme right wing political activities and, during the 1936 general election, accompanied him to what were distasteful and rowdy election meetings in the midst of Mosley's fascist supporters. Perhaps a saving grace was that during much of her married life Ros was in charge of running the relatively small home farm at Hinton, which she loved and explains her romantic affection for farming for the rest of her life. As it turned out, she left Hinton and the Pitt-Rivers estate in 1937, her departure soon to be followed by acrimonious divorce proceedings. Fortunately, this move brought her back to science when in the autumn of 1937 she joined Sir Charles Harington, then in the Department of

Pathological Chemistry at University College Hospital Medical School, London, as a research student. She worked for her Ph.D. degree under Professor Albert Neuberger, F.R.S., on methyl glucosaminides and their hydrolysis by snail enzymes.

## EARLY WORK WITH HARINGTON AND THE OUTBREAK OF WAR

After obtaining her Ph.D. degree in 1939, Ros moved to Harington's own laboratory to carry out research on the biosynthesis of the thyroid hormone, L-thyroxine, and iodinated peptides. Harington had previously acquired worldwide fame by his brilliant chemical determination of the structure and synthesis of L-thyroxine (Harington & Barger 1927), to be followed by a series of successes in the biochemistry of thyroidal as well as extra-thyroidal iodinated proteins and peptides (Harington, 1933). Many, in the UK and abroad, were of the opinion that this work merited the award of a Nobel Prize. Not surprisingly, Ros soon became an admirer of Harington's not only as a brilliant chemist, but also as her mentor, an admiration she retained for all her life. There is no doubt that, more than anyone else, it was Harington who shaped her thinking and work as a research scientist. In 1941, Ros was firmly established in Harington's group while still at University College Hospital Medical School. A year later, when he joined the National Institute for Medical Research (NIMR), the largest unit of the Medical Research Council (MRC) then located in Hampstead (London), Harrington took Ros with him as a member of the MRC's scientific staff. She was to remain at the NIMR until her retirement in 1972, firmly committed to research on her favourite topic of thyroid hormones for much of this period of 30 years. At the time of his move to NIMR Harington was interested in the biological and immunological properties of various proteins and peptides and in the biosynthesis of thyroid hormone (at that time L-thyroxine was the only thyroid hormone known). Two highly significant papers, one on the preparation of thyroxine from iodinated casein and the other on a novel synthesis of thyronine (desiodothyroxine, the iodine-free skeleton of thyroxine, an important requirement for proving the structure of L-thyroxine), resulted from her early studies with him on this topic (6, 7)*. At about the same time, reports had begun to appear from American laboratories that simply adding iodine to various proteins would result in the accumulation of small amounts of L-thyroxine. For a while, Harington did not believe the reports from the US that iodination of proteins in the test tube, other than thyroglobulin, would give rise to thyroxine. However, Ros was soon to change his mind with the analysis of iodoamino acids released from iodinated casein, a finding which proved to be conceptually important for later work on the biosynthesis of thyroid hormones. Her procedure for iodination and analysis of resulting iodoproteins was simpler and replaced that of Harington's developed 16 years earlier. Unfortunately, research with Harington was interrupted by the outbreak of war.

World War II disrupted Ros Pitt-Rivers' progression of an independent research career at a crucial moment, especially considering that she had got back into full-time research rather late in life. For seven months in 1940–41 she worked at the South-East Blood

* Numbers in this form refer to entries in the bibliography on the accompanying microfiche.

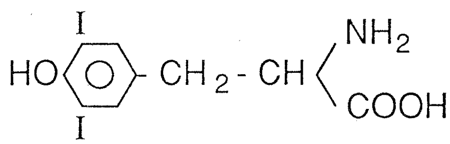
Transfusion Unit in Maidstone (Kent) under Dr Montagu M. Maizels, F.R.S. For a brief period (two months) in 1941 she worked with Dr Derek Richter under Professor Aubrey Lewis at the Maudsley Hospital which at that time had been evacuated to Mill Hill School. She rejoined Harington at University College Hospital Medical School to work on artificial iodoproteins, part of a wartime project to increase milk yield in cows. Towards the end of the War in 1945 she was seconded to the 21 Army Group to go to Belgium. There she joined Dr Charles Dent, and Dame Janet Vaughan, F.R.S., to carry out a nutritional study on force-marched prisoners of war. It ended by her spending three weeks at Belsen concentration camp upon its liberation by the Allies. The horror of what she saw there remained strongly etched in Ros's memory, and on numerous occasions for the rest of her life she recounted her shock at seeing the inmates and witnessing the painful recovery of the fortunate few. She told her friends that this terrible episode turned her into a heavy smoker, for which she was to pay a high price with her health 25 years later.

## Immediate post-war period

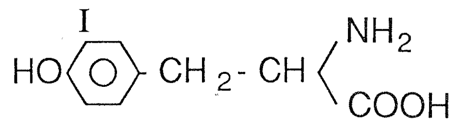
The War ended, Ros returned to Harington's laboratory at NIMR (Hampstead) and applied herself with full vigour to his ongoing research on enzymic digestion (particularly with pepsin) of iodinated and non-iodinated peptides and the synthesis of thyroxine from 3,5-diiodotyrosine. A series of papers were published between 1945 and 1950 on these studies with Harington, S.S. Randall, J.M.L. Steven and R. Michel, a visiting worker from Paris (8, 10, 11, 15, 17, 20, 21). During this period Harington was becoming increasingly preoccupied with his administrative duties with the impending move to Mill Hill. At the end of the War the MRC had undertaken to furbish the present-day NIMR in this leafy suburb of London, although the building had been completed before the outbreak of the War. Harington was appointed director and moved to the new laboratories in 1950 and took Ros with him to join the Biochemistry Division which he headed until 1955, to be replaced by Dr T.S. Work. With Harington being tied down by his heavy commitments as director, Ros rapidly acquired a fully independent status in her laboratory. At the same time she continued to help Harington with his research until some years later it proved impossible for him to run a sustained research project and the Institute simultaneously. Her dedication to Harington's research projects impressed many around her. For example, T.S. Work writes:

> Sir Charles was of course extremely busy with administration of the new Institute and I admired the way in which Ros was able to act as his deputy in that she carried out a research programme which enabled CRH [Harington] to rush into the lab for a couple of hours, do an experiment, and leave Ros to tidy up the loose ends. That was typical of her always unassuming and generous approach.

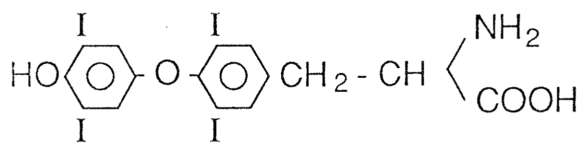
In the post-war period of 1945–50, before the move to Mill Hill laboratories, Ros was able to prepare separately the optical isomers of thyroxine by methods that precluded the risk of racemization. This was important since in earlier work it could not be shown that the unnatural optical isomer D-thyroxine was devoid of biological activity (18). Another piece of work, which was more relevant to later work was the identification of monoiodotyrosine (3-iodo-L-tyrosine, MIT) in thyroid gland (9). It was the availability of radioactive isotopes and the advent of paper chromatography in the 1940s that enabled these workers to identify MIT in thyroglobulin. Earlier Harington & Randall (1931) had shown 3,5-diiodotyrosine



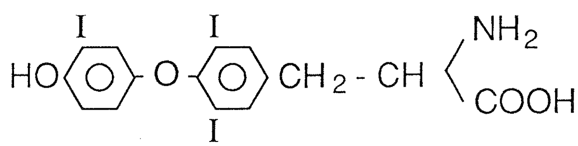
3, 5-Diiodo-L-tyrosine
(DIT)



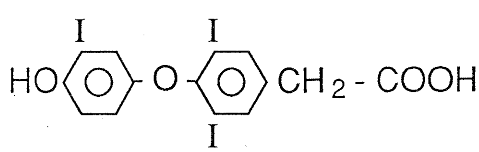
3-Monoiodo-L-tyrosine
(MIT)



L-thyroxine ($T_4$)



3, 3', 5-Triiodo-L-thyronine ($T_3$)



3, 3', 5-Triiodothyroacetic acid (Triac)

FIGURE 1. Chemical formulae of the two thyroid hormones, $T_4$ and $T_3$, and some related

(DIT) to be a constituent of thyroglobulin, accounting for 14% of thyroidal iodine, but had failed to detect MIT.

In other work from Harington's laboratory in the 1930s, each molecule of L-thyroxine was shown to be formed from the condensation of two molecules of 3,5-diiodotyrosine. In Jean Roche's laboratory at the Collège de France in Paris this process was confirmed to take place *in vivo* within the thyroglobulin molecule. It was then argued, both in Paris and Mill Hill, that if MIT was also present in thyroglobulin, then one ought to find other products of iodotyrosine coupling, namely 3,3′,5- and 3,3′,3′-triiodothyronines from one molecule each of MIT and DIT, and 3,3′-diiodothyronine from two molecules of MIT (see figure 1). This was basically the background to a race that was to ensue between the French and British laboratories to identify these naturally occurring analogues of thyroxine. It also turned out to be the beginning of the most fruitful period of Ros Pitt-River's research career.

## Discovery of triiodothyronine

In the autumn of 1950 a young Canadian anatomist and endocrinologist, Dr Jack Gross, came to the NIMR as a postdoctoral fellow to work with Ros. Before coming to Mill Hill, Gross had worked in Montreal at McGill University under Professor Charles Leblond, F.R.S., who pioneered with Frédéric Joliot-Curie at the Collège de France the use of radioactive iodine ($^{131}I$) in investigating thyroid physiology, particularly the formation and secretion of thyroid hormone. In Leblond's laboratory at McGill, Gross had worked on the application of chromatography to the analysis of radioiodinated proteins in human blood following radioiodine therapy for thyroid disorders. (In the early 1950s, it was common practice to administer very massive doses of $^{131}I$ for thyroid gland ablation.) He could not have come to a better place since at that time the NIMR was a leading centre in the world for paper chromatography. A.J.P. Martin, F.R.S., who had just received the Nobel Prize for his work on the development of this analytical technique, was working at the Mill Hill laboratories. Furthermore, rapid progress was being made there in the application of paper and agar electrophoretic analysis. Thus Gross came with the best credentials to perhaps the best laboratory in the world working on thyroid hormone chemistry when he joined forces with Pitt-Rivers.

In 1951, Gross and Leblond had described in the plasma of rats given $^{131}I$ the presence of an unknown radioactive compound called 'unknown 1' that migrated close to thyroxine in two-dimensional chromatography. Gross had insisted that he and Ros continue this line of work in humans with utmost speed and vigour. Thus it was not long after his arrival that in their first paper together Gross and Pitt-Rivers (24) confirmed the presence in human plasma of 'unknown 1', as well as describing a second unidentified $^{131}I$-labelled compound obtained from one hyperthyroid and four euthyroid patients having received therapeutic doses of radioactive iodine. They also made the important observation that the kinetics of labelling of 'unknown 1' was similar to that of plasma thyroxine. At about the same time Roche's group in Paris (Roche, Michel, Lissitzky & Michel 1951) had described a deiodinating activity in sheep thyroid gland, thus raising the possibility that the unknown compound could be a less iodinated analogue of $T_4$, possibly triiodothyronine ($T_3$).

Three more papers were published on this subject by Gross and Pitt-Rivers in *The Lancet* in the four to six months that followed, each within two months of the other (25–27). The first of these, entitled 'The Identification of 3:3′:5-L-Triiodothyronine in Human Plasma' is now history and must surely rank as the most important publication in Ros' whole career. In it they described the results of analysis with two-dimensional paper chromatography and Kieselguhr column chromatography of n-butanol extracts of plasma of patients with thyroid cancer or hyperthyroidism who were treated with $^{131}$I at doses ranging from 100 Ci to 100 Ci of $^{131}$I. The radioactive spot earlier named 'unknown 1' behaved exactly as authentic 3,3′,5-triiodo-L-thyronine. They argued that it could not be an artefact but was a normal constituent of blood. The two *Lancet* papers that followed showed convincingly that synthetic $T_3$ possessed substantial biological activity, as determined by the goitre-prevention assay in rats (26) and, in collaboration with Dr W.R. Trotter at University College Hospital, London, by its activity in reversing the effects of myxoedema in human subjects (27). Looking back, the evidence presented in these *Lancet* papers was rather meagre, and it is hard to see how they would be accepted for publication these days in most biochemical or clinical journals of high repute. But Gross and Pitt-Rivers drew the right conclusions and finally that is what counts. However, it was not long before more rigorous evidence did follow.

It is interesting at this point to digress a little and describe Harington's reaction to the identification of triiodothyronine as a normal constituent of human blood. Thirty years after the identification of $T_3$ in the autumn of 1951, in a long series of correspondence with Dr Clark T. Sawin (VA Medical Center, Boston), Ros described as follows how Harington first responded to her findings with Gross:

> When Jack Gross and I rushed into his [Harington's] room (Fall 1951) and announced that unknown 1 was $T_3$, he remarked 'Oh, how disappointing'! (I'm not sure why. Maybe he thought it was a breakdown product of $T_4$ of no significance). When, two weeks later, Jack and I again rushed into his office with the news that $T_3$ was 3–4 x [times] more active than $T_4$ in the goiter prevention assay, he was overcome with surprise. The news evidently contradicted his long established beliefs.

The disappointment was only a transient reaction since the bioassays were done so quickly after the identification of $T_3$ in blood. (It is now difficult to imagine how this could have been done within a few weeks, when a goitre prevention test with a new compound would require a new project licence from the Home Office, satisfying the institutional veterinarian, the local animal ethics committee, and so on.) Harington's scepticism about $T_3$ must have had to do with his failure to detect it in the thyroid gland when, 20 years earlier, he was purifying thyroxine from this tissue. According to Ros, his failure to detect $T_3$ must be due to a trivial reason relating to the procedure that Harington used to precipitate thyroxine from thyroid extracts as its barium salt, whereas the Ba salt of $T_3$ is more soluble and must have been thrown away with the supernatant. In fact, she actually confirmed this possibility by chromatographic analysis that there was abundant $T_3$ in the supernatant made according to Harington's procedure.

That $T_3$ was present in blood and that it was physiologically at least as potent, if not more, as $T_4$ could possibly mean that it was an extrathyroidal derivative of $T_4$. To qualify it as a true hormone, on an equal footing with $T_4$, meant that it had to be shown to be synthesized in the thyroid and then secreted from it along with $T_4$. Within five months of the publication of the *Lancet* papers, two detailed papers were submitted to the *Biochemical Journal*, both appearing in 1953, in which not only was this issue settled but more extensive data were also presented on the chemical nature and physiological activity of $T_3$ (31, 32). The first of these (31) described in detail the synthesis of 3,3′,5-triiodo-L-thyronine by iodination of 3,5-diiodo-L-thyronine ($T_2$). At the same time the D-$T_3$ and racemic DL-$T_3$ were also synthesized and their chromatographic separation from $T_4$ described. In the same paper, the identification of radioactive $T_3$ in thyroid hydrolysates of rats given $^{131}$I-iodide was reported, along with the large-scale isolation of non-radioactive $T_3$ from ox thyroid glands. The yields obtained were 30.4 and 1.2 mg of $T_4$ and $T_3$, respectively, i.e. $T_3$ represented only 4% of the gland's $T_4$ content. At the end of the paper was an appendix by Dr Olga Kennard, F.R.S., in which she compared X-ray diffraction patterns of crystals of L-$T_3$ with L-$T_4$ and L-$T_2$ and which confirmed convincingly that unknown 1 in blood was identical to synthetic L-$T_3$.

The second *Biochemical Journal* paper (32) dealt with the physiological activity of L-$T_3$ by a variety of assays based on the known actions of L-$T_4$. Thus, L-$T_3$ was shown to be five times more potent than L-$T_4$ in the goitre prevention test in rats, whereas D-$T_3$ and DL-$T_3$ possessed 7% and 59% of the potency of L-$T_3$. Next, 1 μg L-$T_3$ injected daily into thyroidectomized rats restored their total body growth rate but, as would be expected, a dose of 20 μg was found to reduce the growth rate. Although they had no direct, or even indirect, evidence to support it, Gross and Pitt-Rivers drew the conclusion that 'triiodothyronine is the peripheral thyroid hormone and that thyroxine is its precursor'. Once again, whether or not one calls this simply 'intuition', later work from many other laboratories proved them to be right. On the other hand, it is still a controversial issue as to whether or not, at the cellular level, $T_4$ has no activity on its own and that it has obligatorily to be converted to $T_3$ for its physiological activity as a thyroid hormone, thus qualifying it as a 'pro-hormone'.

By the time the above two Gross and Pitt-Rivers papers had appeared, Roche's group in Paris had published two short papers in *Comptes rendus de l'Académie des Sciences* (1952*a*, *b*) in which they also reported the synthesis of L-$T_3$ from L-$T_2$ and the identification of radioactive $T_3$ in hydrolysates of thyroids of rats which had been given $^{131}$I-iodide. Thus, each of the two groups had simultaneously confirmed the other's work. At this point, it is interesting to consider as to what extent the two groups felt that they were in competition with each other in identifying $T_3$. Although nearly 35 years later, in Ros's lengthy correspondence with Sawin, she played down any competition, a statement in that letter which immediately followed the denial revealed that the two groups were indeed competing:

> Jack [Gross] and I were in a state of feverish excitement and hardly left the lab. It was probably November 1951. We went to Paris in December (some sort of chemical meeting) and I was somewhat dismayed by Jack telling Roche's group that we had identified unknown 1 as $T_3$.

Then, in another letter to Sawin, she mentions how the editor of *The Lancet* had offered, in view of the competition between the French and British laboratories, to publish her paper (when each group was aware of the other's ongoing work) within two weeks of receiving the manuscript. The writer of this memoir, who was at that time a student in Roche's laboratory, and also visited Gross and Pitt-Rivers at NIMR while the studies on $T_3$ were being actively pursued, can definitely confirm that the atmosphere in both labs was filled with the excitement of competition. What is debatable is whether it was Lissitzky, Michel and Roche (the three authors of the *Comptes rendus* papers) in Paris or Gross and Pitt-Rivers in Mill Hill who took the competition more seriously. Be as it may, this 'healthy rivalry' turned out to be indeed beneficial, not only because it hastened the identification of $T_3$ as a thyroid hormone, but also because the work of the two groups produced mutually complementary data. The Roche group studied in greater detail the biosynthesis and secretion of the two thyroid hormones, whereas Gross and Pitt-Rivers focused on $T_3$ in blood and its physiological activity.

Competition or no competition, recognition, honours, invitations to lecture and write reviews, requests to come and work in her laboratory, all came thick and fast for Ros Pitt-Rivers following the discovery of $T_3$. Worth noting are the award to her of the William Julius Mickle Prize in 1952 and three excellent, succinct reviews between 1952 and 1954 on biochemistry of the thyroid gland and $T_3$ in *British Medical Bulletin* (29), *Vitamins and Hormones* (36) and *Recent Progress in Hormone Research* (39). The Medical Research Council also made a good deal of money from the royalties ensuing from the patenting of $T_3$, which is now widely used therapeutically and for diagnosis of thyroid disorders. But the ultimate accolade for discovering a new hormone was undoubtedly her election as Fellow of the Royal Society in 1954. This was no mean achievement as she was elected only two years after the first report on the identification of triiodothyronine, and even more remarkable when one considers the very few women elected as Fellows of the Royal Society then and the overall fewer Fellows elected annually in the 1950s than now.

### Period immediately after the discovery of $T_3$

Having discovered in $T_3$ a more potent hormonal analogue of thyroxine, it was logical to then assess the biological activities of compounds chemically related to the two thyroid hormones. Jack Gross had left Mill Hill to take up an appointment in New York not long after the *Lancet* and *Biochemical Journal* papers on $T_3$ had caused quite a stir. Ros therefore embarked on a search for more potent or more rapidly acting analogues. But there was an interruption to follow. She had decided to spend a sabbatical year, her first, in 1953–54 in the United States with Dr John Stanbury. The space allocated to her was in the laboratory of Dr Fritz Lipmann, then at the Massachusetts General Hospital in Boston. This was to turn out to be an auspicious year for both of them. Pitt-Rivers was elected to the Royal Society and Lipmann awarded the Nobel Prize.

Among the first compounds to be tested for their physiological activity in any great detail were the acetic acid analogues of $T_4$ and $T_3$, tetra- and tri-iodothyroacetic acids (Tetrac and Triac), respectively, synthesized at Mill Hill. Both compounds exhibited varying degrees of biological activity in the goitre prevention assay, but Triac was particularly active in enhancing the metabolic rate of rats (34) and in restoring plumage in thyroidectomized chickens (37). Ros also synthesized and tested a large number of analogues of thyroid hormones in which bromine and fluorine replaced iodine, some of these assays being performed during her sabbatical year in Boston (38, 40). Most of these halogen-substituted compounds turned out to have low or no biological activity, so that it was Tetrac and Triac that occupied her attention, especially Triac, over the next few years.

A characteristic feature of the physiological activity of thyroid hormones is the relatively long latent period of action. In the mid-1950s there was considerable interest in explaining this latency, for which two major experimental approaches were then popular. One was to find an early biochemical process which would set off a chain of cellular events leading to the physiological action. Thus in the mid-1950s to early 1960s the prevailing opinion was that the stimulation of metabolic rate or oxygen consumption by thyroid hormone was brought about by an immediate hormonal interaction with mitochondria so as to uncouple or modify oxidative phosphorylation. The second approach was based on the assumption that $T_4$ and $T_3$ were themselves not the active thyroid hormones but that they had to be converted to their derivatives which would have an immediate effect. Ros (and others) therefore decided to investigate Tetrac and Triac as possible candidates for such intracellular derivatives.

An investigator in Paris, Dr Odette Thibault, working at the Laboratoire de Physiologie at the Sorbonne, joined in a collaboration with Ros to look at the acetic acid analogues of $T_4$ and $T_3$ (Ros' role was largely one of supplying the compounds). In 1955 three brief notes appeared in *Lancet* and *Comptes rendus* and *Comptes rendus de Société de Biologie* signed by Thibault and Pitt-Rivers in which it was stated that whereas $T_4$ and $T_3$ had no immediate effect on the respiration of kidney and liver slices obtained from thyroidectomized rats, Tetrac and Triac (at $10^{-6}$M) had an immediate effect on $O_2$ consumption of these tissue slices (41, 42, 45). It was therefore concluded that these were the active forms of the hormones. These papers provoked enormous interest and many laboratories soon attempted to repeat these investigations *in vitro* with tissue slices and subcellular preparations from a variety of sources. Interest in such studies was further heightened by the findings from Roche's laboratory at around the same time that Tetrac and Triac were formed in various tissues from $T_4$ and $T_3$. Unfortunately, virtually no one was able to reproduce the Thibault and Pitt-Rivers results nor could these compounds be shown to provoke an immediate response in other biochemical systems. By the mid-1960s it began to emerge that the latency of thyroid hormones could best be explained on the basis of their action via the regulation of transcription and selective protein synthesis (Tata, 1964). The failure of Tetrac–Triac work, so soon after the brilliant work on $T_3$, was naturally a great disappointment to Ros. One can only wonder as to what extent the discovery of $T_3$ exerted undue pressure to come up with another major discovery. In later years Ros preferred not to talk about this particular collaborative effort. In spite of this disappointment, she did not completely give up the idea for a while that there may be other hormonal derivatives active at the cellular level, as can be judged from the following statement in one of her letters to Sawin:

> The moral of this story has convinced me that it is rash to assume that one is ever at the end of the elucidation of a biological chain of events. Nevertheless, the relative inactivity of the many metabolites of $T_4$ discovered since $T_3$ makes one wonder whether this story is ended.

Another offshoot of the studies on $T_3$, and one with a happier ending, was the question of its origin in blood and extra-thyroidal tissues. Roche's group favoured the idea of it being mostly derived from the coupling of one molecule each of mono- and di-iodotyrosine residues of thyroglobulin in the thyroid gland. Whereas this coupling could be easily reproduced with free amino acids in the test-tube, the reaction is difficult to demonstrate within the thyroglobulin molecule *in vivo*. For this reason, and the observation in 1951 by Gross and Leblond that radioiodinated 'unknown 1' appeared in the kidney and faeces following the administration of $^{131}I\text{-}T_4$ to thyroidectomized mice, Ros decided to pursue this problem further. In 1955, from studies carried out in Stanbury's laboratory during her sabbatical year in Boston, she described the detection of small amounts of $T_3$ in the blood of six athyreotic humans after the administration of $^{131}I\text{-}T_4$ (43). Although the controversy about the origin of $T_3$ from thyroidal coupling of iodotyrosines versus peripheral deiodination of $T_4$ lingered on for a while, it has now ceased to generate much interest among thyroidologists. Most investigators would now agree that both pathways may operate and that they are not mutually exclusive.

At the same time as Gross and Pitt-Rivers were busily investigating unknown 1 and $T_3$, Dr Hugh Gordon in the Biophysics Division at NIMR was experimenting with the separation of plasma proteins by paper electrophoresis. In a collaborative effort, the two groups studied the distribution of radioactivity (largely representing $^{131}I$-labelled $T_4$) associated with human serum proteins separated by paper electrophoresis from an euthyroid subject 5 days after the administration of 100 mCi of $^{131}I$-iodide for the treatment of thyroid carcinoma (28). The autoradiogram of the electropherogram clearly showed that much of the circulating hormone migrated with a protein intermediate in mobility to that of $\alpha_1$- and $\alpha_2$-globulins. The protein was later termed thyroxine-binding globulin, commonly known as TBG, which is the major carrier of circulating thyroid hormones. Three years later in studies from Stanbury's laboratory, she was able to confirm this association for both $T_4$ and $T_3$ in the blood of human subjects of different clinical thyroid status (44). These findings also provoked enormous interest and was followed by work from many laboratories, particularly that of Drs Jack Robbins and Ed Rall, with whom she was to be associated during a later sabbatical period in the United States.

## LATER RESEARCH

Ros's research work from the late 1950s until her retirement from the Medical Research Council in 1972 can best be considered in three areas: (a) an extension of her work on metabolism and biological activity of triiodothyronine and its derivatives; (b) research on the structure of thyroglobulin and its formation in the thyroid gland; and (c) preparation and use of immunochemical reagents.

Several years of investigations on biological activities of various deaminated and halogen-substituted analogues of thyroxine and triiodothyronine did not lead to the discovery of any derivatives of significant physiological importance, except the acetic acid analogues. These were further studied for a few years, with collaborators other than Thibault. Nothing of major importance emerged from these investigations except that, from work carried out with Dr Claire J. Shellabarger (a visiting scientist from the Brookhaven National Laboratories in the United States), Triac and Tetrac were shown to be physiologically more active in the amphibian metamorphosis test than $T_3$ and $T_4$, respectively (64). It is now well known that these acetic acid analogues bind to thyroid hormone receptors with higher affinity than do the parent hormones, which explains their higher physiological potency. With Shellabarger, Ros had also demonstrated the presence of $T_3$ in the blood of chickens, a species in which, unlike in mammals, $T_3$ is no more potent than $T_4$ (60). Interestingly, it was shown soon afterwards by Tata and Shellabarger (1959) that the most likely reason for this difference between avian and mammalian species is that birds lack TBG in their blood so that both hormones enter into tissues at equal rates, even though the chicken thyroid hormone receptor has a higher affinity for $T_3$ than $T_4$ as in mammals. By 1960, Ros had started to wind down her investigations on the distribution and activity of thyroid hormone derivatives and turned her attention to studying the biosynthesis of thyroid hormones and the properties of thyroglobulin.

Work on thyroglobulin occupied the major part of her last 12 years at the NIMR. Five short papers published in 1961–1963 dealt with such issues as iodine pools and metabolism (with Dr Nicholas Halmi) and free iodotyrosines (with Dr Ralph Cavalieri) in the rat thyroid gland (77–79, 81, 83). The main outcome of these studies was that they clarified such issues as whether $T_3$ was the precursor of $T_4$, or the other way round, within the thyroglobulin molecule *in vivo*. The exceptionally large protein molecule of thyroglobulin is exclusively synthesized in the thyroid gland and it is within this molecule that thyroid hormones are synthesized, which renders the analysis particularly difficult. In preliminary studies Pitt-Rivers and Cavalieri (83) had noticed different rates of release of $^{131}$I-MIT, according to the time of labelling with $^{131}$I, from thyroglobulin in rat thyroids digested with crude calf thyroid protease. This suggested a structural heterogeneity of thyroglobulin and led them to undertake a more detailed study on the release of labelled iodotyrosines from rat thyroglobulin, this time by measuring the rates of release following autolysis of the protein with endogenous proteases (88). It became clear that further progress on this problem would require unravelling the subunit structure of thyroglobulin.

In the years 1959–60 and 1963–64 Ros spent sabbatical periods of several months each in the laboratories of Dr Ed Rall and the late Dr Harold Edelhoch at the National Institutes of Health (NIH), Bethesda. With Rall she carried out some studies on radioiodine equilibrium in rats before the days when sensitive radioimmunoassay procedures were available. She was able to confirm some of her earlier work on the amount of $T_3$ in the thyroid gland, blood and tissues, while also eliminating the possibility of circulating iodotyrosines, which had then been claimed by some. Edelhoch was a world authority on questions concerning the physical chemistry of thyroglobulin, kinetics of iodination of tyrosyl residues of the protein and synthesis of thyroid hormones. Working with him reinforced her interest in the structure of thyroglobulin and was a major factor governing her decision to continue to pursue work on this subject. A study published in 1966 of work carried out during the second sabbatical period at the NIH with Drs Benoit DeCrombrugghe and Edelhoch reported how cleavage of only a few disulphide bonds of thyroglobulin produces a smaller molecule of the same size as when all S–S bonds were reduced (90). The large subunit of this protein of molecular weight of 500 000 was thus cleaved into two equal or similar sized molecules. Several papers, including one from University College London, where she worked after her retirement from NIMR in 1973, dealt specifically with this question of subunit structure of thyroglobulin (97, 100, 103, 104). The essence of these studies was to progressively chop down in size the different subunits of this protein. In her last paper on this topic published in 1976, she was able to produce subunits of human and rat thyroglobulin of molecular mass of 165 kDa (104), although several years earlier from NIMR she had also described stable subunits of pig thyroglobulin as small as 35 and 20 kDa (97).

When in 1962 Sir Peter Medawar, F.R.S., took over the directorship of NIMR from Harington, he appointed Dr N.A. (Avrion) Mitchison, F.R.S., as the Head of Division of Experimental Biology to succeed Sir Alan Parkes, F.R.S. Mitchison's major interests were largely to do with cellular immunology. His laboratory was adjacent to Rosalind's and soon the two developed a strong friendship, which continued after her retirement from NIMR, and the two often spent long periods discussing their problems. In the early 1960s Mitchison was looking for suitable haptens that would enable one to easily track antibodies in various mouse tissues and sought Ros' help in preparing $^{131}$I-labelled antibody molecules that could be easily identified. This collaboration led to some highly original and important work on the iodine-containing synthetic immunological determinant 4-hydroxy-3-iodo-5-nitrophenylacetic acid (NIP).

In two comprehensive papers published in *Immunology* in 1966 with Mr. Alan Brownstone (her assistant then for nearly 15 years) and Mitchison (91, 92), they gave details of chemical and serological properties of NIP and related compounds, followed by biological studies with these determinants. The first described the immunization of mice with chicken ovalbumin and serum globulin conjugated to NIP which showed that they bound various N$^{131}$IP-compounds. This approach allowed the measurement of antibody at concentrations down to 0.1$\mu$g ml$^{-1}$, while inhibition data showed that it is the iodine atom in NIP, and not the carrier protein, which contributes to the binding site. A second paper in the same issue of the journal focused on biological studies with NIP and related compounds in which the antisera to NIP-protein conjugates were assayed by binding to N$^{131}$IP-ε-amino-*n*-caproic acid. It described optimum conditions for efficient immunization and how secondary responses could be obtained by stimulation *in vivo* and *in vitro* of spleen cells transferred from primed donors. Several publications from Mitchison's and other laboratories then followed describing the further exploitation of the NIP approach in various ways. Five years after the first studies, a joint paper with two colleagues from the Max-Planck Institut für Immunobiologie in Freiburg, Germany, Pitt-Rivers and Mitchison described the synthesis of a monovalent DNP-hapten, α, N-(-4-hydroxyphenylacetyl)-E, N-DNP-L-lysine in which the 4-hydroxy-phenacetyl residue was radioiodinated to high specific activity. It led to the development of a method based on salt precipitation to measure the capacity of anti-DNP sera, which was more generally applicable to other haptenic groups which can be bound to the E-amino group of lysine. Clearly, the pooling of Ros's expertise in organic chemistry and that of Mitchison's laboratory in immunology turned out to be a valuable combination leading to a mutually profitable collaboration. It was most fitting that this joint effort bore fruit during her last active years at the bench at NIMR. It is thus most appropriate to cite what Mitchison had recently written about the significance of this collaborative work with Pitt-Rivers:

> One upshot of all this, and it is one by which the lasting importance of this piece of Ros' science can be judged, is that a whole generation of immunologists happily chat about NIP and NP, without having

the least idea of who she was. And one can peruse the catalogue of Biosearch Inc. of California, who market a range of her compounds, without seeing her name mentioned. That is real fame.

In the late 1960s, the MRC decided to disband the Division of Chemistry at NIMR, for many years one of its most active laboratories, with such illustrious members as Sir John Cornforth, F.R.S. Pitt-Rivers was asked to act as Head of Division in 1969, a position she held until her retirement from NIMR in October 1972. During this period she had the unenviable task of disbanding a once highly successful division, which she accomplished with much tact and with no unpleasantness over relocation of staff and facilities.

Not long before her retirement, Mitchison had taken up the professorship of Zoology at University College London (UCL), a chair once held by his mentor, Sir Peter Medawar. He offered Ros laboratory space in his department on an MRC grant, so that her departure from NIMR did not mean the end of her activities at the laboratory bench. In 1975 she transferred to the Department of Pharmacology at University College, then headed by Sir James Black, F.R.S., where she continued to enjoy enormously her contacts with many of her old and new friends at UCL who visited her regularly. During her few years at UCL she particularly enjoyed her lunches with her old friends like Dr W. Robert Trotter, Professor Desmond Lawrence, Dr Eric Ross, Dr Mary Whittear, Dr Richard Freeman, and many others from the Departments of Zoology and Pharmacology, and occasionally from Chemistry or Anatomy. Although with time she did little experimental work, she was busy writing, talking to students and seeing a steady stream of visitors. Her failing health in no way diminished the liveliness of her conversation. Of course, she missed there the facilities and resources of her laboratory at NIMR, not least the technical help from her assistant, Alan Brownstone. Nevertheless, she persevered as best she could on her own with her investigations on the subunit structure of thyroglobulin and its proteolytic cleavage. This work resulted in her last two publications (as the sole author) of experimental work in 1975 and 1976. With progressively failing health (arthritis, asthma, and the loss of sight in one eye during the ensuing ten years), she retired finally from UCL in November 1985 at the age of 78 and moved close to her son and daughter-in-law at the Pitt-Rivers estate at Hinton St Mary in Dorset.

## Books and Reviews

In 1957 Ros Pitt-Rivers was approached by the late Captain Robert Maxwell to write a monograph on thyroid hormones as part of a new venture by Pergamon Press under the title 'International Series of Monographs on Pure and Applied Biology'. Until then the only useful book on the subject was that written by Harington and published in 1933: *The Thyroid Gland, its Chemistry and Physiology*. It concentrated mainly on the chemical nature and synthesis of thyroxine, whereas many developments had taken place in the 1940s and 1950s on the biochemistry of $T_4$ and $T_3$, besides the rapidly growing interest in their mechanism of action. After some hesitation, she agreed to do so if a co-author could be found, and eventually she asked me to be that co-author – only 27 at the time, I had joined her laboratory the previous year. The book, entitled *The Thyroid Hormones*, was written in nine months and published in 1959 as the first volume of the International Series. It is worth recalling here an amusing anecdote concerning this book. The completed manuscript was handed over to Captain Maxwell personally at lunch in the NIMR canteen. When Ros asked him how many copies of the book were expected to be sold, Maxwell's reply was '2000 more than if the two of you were called Smith and Jones'. Whether or not he was right, the book was highly successful, sold out rapidly and has been frequently cited as one of the most authoritative and comprehensive works on this subject.

A second Pitt-Rivers and Tata book on *The Chemistry of Thyroid Diseases*, published in the following year by Charles C. Thomas in the United States, was less successful. She did not venture to write any more books but edited the Proceedings of The Fourth International Thyroid Conference for Pergamon Press in 1960. Four years later Ros co-edited, with Dr W. Robert Trotter, a highly successful two-volume treatise on *The Thyroid Gland.*

As already mentioned, the discovery of triiodothyronine resulted in many invitations to write reviews and chapters in various journals, serial publications and books. Among those that she wrote and that were received enthusiastically by thyroid hormone researchers, were those that appeared in *Vitamins and Hormones* in 1953 and *Recent Progress in Hormone Research* in 1954, both written with her co-discoverer of $T_3$, Dr Jack Gross. Among others worth a special mention are those entitled 'What are thyroid hormones?' (51), 'Iodine metabolism in the thyroid gland' (79), and 'Sir Charles Harington and the structure of thyroxine' (89), written between 1954 and 1964. In 1972 she co-authored with the late Sir Harold Himsworth, a Royal Society Biographical Memoir on Sir Charles Harington (102). Her last review, written with Dr Ralph Cavalieri, on 'The effects of drugs on the distribution and metabolism of thyroid hormones' appeared in 1981 in *Pharmacological Reviews* (106).

## ROSALIND PITT-RIVERS AS A SCIENTIST

There is no simple formula for success in scientific research. For Ros Pitt-Rivers, it could be said that luck or chance, her background and upbringing, teachers at Bedford College, apprenticeship with Harington and, not least, her flair as a chemist and enthusiasm for new ideas, all contributed to her successful research career. In one of her many letters to Sawin, she mentioned how she started her scientific life as an organic chemist who turned to biochemistry and became an endocrinologist at the end of her career. It is unlikely that her governess, teaching at home, or four years of formal schooling, played any part in building up her enthusiasm for science. Her undergraduate and postgraduate teachers, E.E. Turner and Margaret Murray, were certainly responsible both for nurturing her appreciation of chemistry and, although interrupted for several years by her marriage and child rearing, for her decision to resume her training as a research student. But, undoubtedly, it was her association with Harington, first as a Ph.D. student and then as a postdoctoral scientist, that had the most profound influence on her research career. Not only did he train her as a competent organic chemist at the bench but also imparted a lifelong enthusiasm for thyroid hormones. Harington was a very shy person and not too outgoing in his discussions with those who were not chemists. Ros, by comparison, was an extrovert, equally at ease in talking to biochemists, physiologists and clinicians. There was also her aristocratic background which, besides giving her self-confidence, also helped to liberate her from middle-class inhibitions and concern about status. This trait was reinforced by her Stanley ancestors' genes, resulting in a freshness of approach, to everyday as well as scientific problems, and an unusual readiness to contemplate new ideas. Her self-confidence is best illustrated by the following brief statement in one of her letters to Sawin, upon being asked to comment on why she thought someone (a Dr Lassiter in Stanbury's laboratory in Boston) was unable to reproduce one of her findings: 'I suppose Lassiter was not so good a biochemist as I was!'

This combination of her easily communicating with specialists in other disciplines, her self-assurance and Harington's shyness and rigorous discipline as a chemist contributed substantially to her success. It paid off handsomely with the discovery of $T_3$, since Jack Gross had a clinical and anatomical background when he came to work at NIMR. But it is true to say that luck and timing also played an important part in this her most successful venture. As Sir Peter Medawar has said in his marvellous essay 'Lucky Jim' on the discovery of the DNA double helix by Watson and Crick that, had they not elucidated the structure of DNA, others would have done so within a maximum of three years. The coming together at a given time of two people with different backgrounds and personalities was a major factor in rapidly drawing the right conclusions about the double helix. The success of many other scientific discoveries can be similarly explained. It seems to be also so for $T_3$, except that it would have taken much less time for others to discover the second thyroid hormone. Certainly, Roche's group in Paris would have identified $T_3$ in blood within a few months after finding it in the thyroid, while several laboratories in the United States were also working on an iodinated amino acid in the plasma that resembled Gross and Leblond's 'unknown 1'. It is the chance and timing of Gross and Pitt-Rivers coming together, the tapping of analytical techniques developed in other laboratories at the NIMR and the self-assurance of being right with the minimum of data that gave them the edge over others.

As a scientist, Ros' greatest love was the laboratory bench. She was truly a single-minded experimentalist who took her science seriously but had fun doing it. She preferred to tackle problems in small bits, one at a time, and then move on to the next once the results of the first operation were known. She worked with no more than three or four people at any one time and practised what Bruce Alberts calls 'small science'. Quite rightly she avoided 'big science' and it is almost certain that she would not have succeeded in managing a large-scale research operation. This is not to say that broader concepts relevant to her immediate experimental work did not interest her, but she did not let them detract her from her day-to-day problems to be solved at the laboratory bench. New ideas, particularly technical advances, fascinated her and she never hesitated in exploiting them for her own work, which is best illustrated by her rapid adaptation of chromatography and electrophoretic techniques in work leading to the discovery of $T_3$ and TBG.

Although in her later years she would be classified as an experimental biochemical endocrinologist, she took great interest in the clinical aspects of thyroid gland function and the physiology of thyroid hormones. She regularly attended meetings where thyroid clinical topics were discussed and had built up strong links with thyroid clinicians. One of her American clinical colleagues who had worked with her at NIMR, Dr Ralph Cavalieri (VA Medical Center, San Francisco) has the following to say on this matter:

> Ros had a remarkable understanding of clinical thyroidology. Her keen powers of observation and deductive reasoning were not confined to the research laboratory. I remember in particular one of her

many visits to my laboratory in the 1970s. After having a brief chat with one of my colleagues, she drew me aside to suggest that his thyroid function ought to be tested, as she noticed that his voice was more hoarse than she remembered it on a prior visit and he was wearing two 'woolies' in September. The tests confirmed her clinical suspicion of hypothyroidism.

## FRIENDS, COLLEAGUES AND FAMILY

Many of us who knew Ros well like to remember her as a close friend and colleague as well as a respected scientist. Her friendliness and informality, devoid of any snobbishness, struck you within minutes of first meeting her, when she would often insist on being addressed as 'Ros'. The only person with whom she maintained a degree of formality throughout their association over 25 years was Harington, each addressing the other as 'Sir Charles' and 'Dr Pitt-Rivers'. She was, however, a stickler for etiquette, the correct form of addressing people and convention. For example, in replying to one of Sawin's letters when he did not address her correctly she wrote: 'P.S. I don't suppose F.R.S. means anything to an American – I am one too!'

Ros was genuinely interested in the problems, however mundane, of all around her, from janitors to heads of departments. One was always certain of a sympathetic hearing from Ros and a willingness to help you out of your difficulties. She had a genuine simplicity and desire to make friends. When she visited an institution that was new to her, it was never very long before she was on equally friendly terms with director and tea-lady, and knew all about the family problems of both.

Ros had a wonderful wit and humour which she retained until the very end. This was a great attraction for many who worked around her. Lunches at NIMR were particularly memorable occasions; her table would get crowded soon after she sat down. There were 'regulars', comprising such illustrious scientists as James Lovelock, F.R.S., Professor Tony James, F.R.S., Sir John Cornforth, F.R.S., the late Professor Rodney Porter, F.R.S., the late Professor John Humphrey, F.R.S., Dr Don Elliott, and even occasionally Harington, to be followed by much lively discussion of not just bouncing off one another the latest ideas in science but anything from the day's crossword puzzle in *The Times* to what the critics had to say about a new novel (Ros was a voracious reader), to dissecting public figures. Outside the NIMR she had built up lifelong friendships with many, particularly with clinicians who shared an interest in the thyroid. Those who often saw her socially included such people of distinction as the late Lord Max Rosenheim, one-time President of the Royal College of Physicians, Dr Raymond Greene, brother of Graham, thyroid clinician and Himalayan climber, Mr Selwyn Taylor, distinguished thyroid surgeon and ex-Dean of Royal Postgraduate Medical School, and Dr W. Robert Trotter, another well-known thyroid clinician. She regularly attended meetings of the London Thyroid Club where she enjoyed initiating lively discussions with them and many UK thyroid clinicians.

Young people not having yet made their mark came to Ros also. She had much respect, and even a great deal of fascination, for the junior scientists and their ideas. She was known to be extremely generous with young people having difficulties. This generosity extended equally to financial assistance as to helping them with problems of work, jobs and family. In contrast to this benevolence, she spent little on herself. For some things, she could indeed

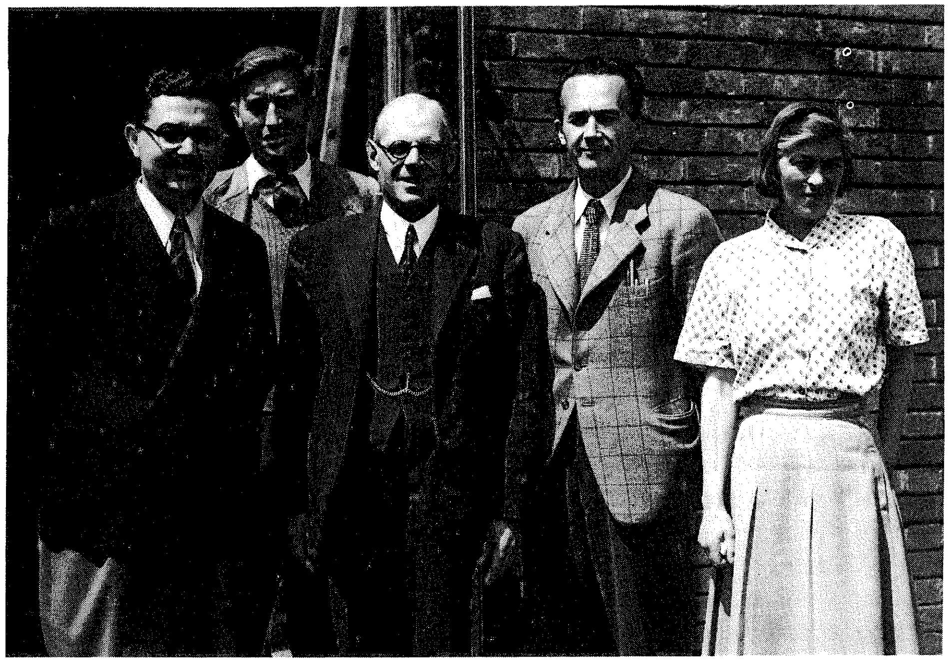


FIGURE 2. Rosalind Pitt-Rivers with some colleagues outside the National Institute for Medical Research, soon after the discovery of triiodothyronine (T3). From left to right: Dr Jack Gross, Dr Tony James, F.R.S., Sir Charles Harington, F.R.S., and Professor George Popjack, F.R.S.

be parsimonious, as posting letters in re-used envelopes or recovering postage for material mailed to institutions.

She maintained strong bonds with many who had worked with her at the start of their research careers, such as her student, Dr Valerie Galton, and several young American post-docs, particularly Dr Ralph Cavalieri, Professor Benoit de Crombrugghe, Dr Jan Wolff and Dr Harold Schwartz. At NIMR, junior staff frequently sought her help and advice on all matters, scientific or otherwise, and she would vigorously take up their cause, especially if she felt that injustice was involved. One reason they came to her was because of her reputation of not exploiting the younger scientists to further her own ambitions. She did not suffer fools gladly. She had little patience with 'pompous old fools' or over-zealous administrators and would not hesitate, with her exquisite manners, to set them right on matters of fact and even convey her low opinion of them. Ros displayed intense loyalty to those who had worked with her or those with whom she had had a fruitful association.

If it is true that to some extent luck was on her side for her most important achievement, then no better person deserved to be lucky. Above all, Ros personified much that is good about scientific research. To her friendship and sharing with others what she knew was as important as her own science and career. A good illustration of this point is her reply to Sawin when asked why she gave her French competitor a sample of $T_3$ that she had synthesized: '$T_3$ *never* came between our friendship.'

Ros was very attached to her family. Many of her friends admired her concern for her mother and sisters Kitty and Juliet. When failing health finally forced her to leave London in 1985, she was very happy to be near her son and daughter-in-law, Anthony and Val, at the Pitt-Rivers estate in Hinton St Mary in Dorset. There, during her last years, she continued to read a great deal. She subscribed to *Nature*, *Lancet* and *British Medical Journal* and frequently sent out to her friends cuttings of articles in these journals which she thought might interest them, as they almost invariably did. But most of all, she enjoyed visits from her family and friends and the conversation was as witty and sparkling as ever.

Those of us who were privileged to know Ros closely will always remember her openness, warmth and genuine interest in others, combined with her wit, knowledge and charm. No wonder that so many continued to see her or to correspond with her during her last years in her beautiful village in Dorset.

## Honours and Awards

| | |
|---|---|
| 1952 | William Julius Mickle Prize |
| 1954 | Fellow of The Royal Society |
| 1956 | Member of Bedford College Council |
| 1959 | Honorary Member of the Society of Endocrinology of Mexico |
| 1959 | Member of Council, Society of Endocrinology |
| 1960 | Member of Council of University College Hospital Medical School |
| 1965 | President, London Thyroid Club |
| 1965 | Distinguished Service Award, American Thyroid Association |
| 1966 | Porter Lectureship in Medicine, University of Kansas School of Medicine |
| 1971 | President, European Thyroid Association |
| 1971 | Dunhill Memorial Lecture, European Thyroid Association |
| 1973 | Fellow of Bedford College, London |
| 1977 | Honorary Member, Society for Endocrinology |
| 1980 | Honorary President, International Congress of Endocrinology, Melbourne |
| 1983 | Honorary Fellow of Royal Society of Medicine |
| 1986 | Honorary Fellow of Royal College of Physicians |

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Edward Rall, Dr Ralph Cavalieri, Dr Anthony T. James, F.R.S., Sir John Cornforth, F.R.S., Dr Donald F. Elliott and Mr Alan Brownstone. I also thank Mrs Ena Heather for preparation of the manuscript.

## References to other authors

Harington, C.R. 1933 *The Thyroid Gland, its Chemistry and Physiology.* London: Oxford University Press.
Harington, C.R. & Barger, G. 1927 *Biochem. J.* **21**, 169.
Harington, C.R. & Randall, S.S. 1931 *Biochem. J.* **25**, 1032.
Gross, J. & Leblond, C.P. 1951 *Endocrinology* **48**, 714.
Roche, J., Michel, R., Lissitzky, S. & Michel, O. 1951. *C.R. Acad. Sci., Paris* **232**, 2148.
Roche, J., Lissitzky, S. & Michel, R. 1952*a* *C.r. hebd. Séanc. Acad. Sci., Paris* **234**, 997.
Roche, J., Lissitzky, S. & Michel, R. 1952*b* *C.r. hebd. Séanc. Acad. Sci., Paris* **234**, 1228.
Tata, J.R. 1964. In *Actions of Hormones on Molecular Processes* (ed. by G. Litwack & D. Kritchevsky), p.58. New York: John Wiley.
Tata, J.R. & C.J. Shellabarger. 1959. *Biochem. J.* **72**, 608.