THOMAS BOTHWELL

TOP THREE AWARDS

- Gold Medal of the South African Medical Research Council
- John FW Herschel Medal of the Royal Society of South Africa, 1993
- Science-for-Society Gold Medal of the Academy of Science of South Africa, 2005

DEFINING MOMENT

The publication of my first scientific article in an international journal (*Journal of Laboratory and Clinical Medicine*) in 1951.

ACROSS MEDICAL FRONTIERS

The son of Scottish immigrants to South Africa, Thomas Hamilton Bothwell was born on 27 February 1926 in Johannesburg. Having received a scholarship to attend St John's College, he matriculated first class in 1941. From here, he went on to attend the University of the Witwatersrand (Wits), obtaining a Bachelor of Medicine and Bachelor of Surgery in 1948. He received the Bronze Medal of the Southern Transvaal Branch of the Medical Association of South Africa for the most distinguished medical graduate of the year, as well as being awarded the Medical Graduates Association Prize for the best final-year student in Medicine.

Bothwell later explained, in his reflections on his career, that this period was one of crossing numerous frontiers in medical training in the country, for the first time establishing a formalised clinical medical faculty with dedicated researchers – prior to this, medical students were largely trained by practising medical doctors contracted to the university. During this time he was taught by, among others, Professor William Craib, a pioneer of electrocardiography, and Professor Raymond Dart, best known for uncovering the Taung skull. In his class was another legend in the making, Sydney Brenner, who was destined for enormous success in the field of DNA research.

Bothwell's own research would further develop findings made by Archie Strachan, his Professor of pathology, whose MD thesis documented the high prevalence of iron overload in the black population of South Africa. Bothwell's interest in haematological research began in 1948 when, as a young intern, he encountered a patient admitted with cardiac symptoms, hepatomegaly and hypogonadism. This was indicative of idiopathic haemochromotosis, a genetic disorder in which iron accumulates in the body leading to overload of the mineral. With little known about iron balance at the time, Bothwell undertook research to establish links between idiopathic haemochromotosis and abnormally high levels of iron absorption in the gut, using radioactive iron to measure the absorption of his patient against a control subject, comparing intake of iron to the levels excreted in stool samples. (He recounts the humorous aspect of this study, when other workers in the building complained of the smell in the corridors. Happily they never succeeded in hunting down the source thereof.) He found that his patient showed significantly higher levels of absorption when contrasted to the control subject. The study of the various facets of this problem, and related conditions, formed the basis of Bothwell's lengthy and illustrious research career.

From 1954 to 1957, Bothwell spent some time furthering his research career abroad – first attending Oxford on a Nuffield Fellowship, and then continuing his research on iron metabolism at the University of Washington, Seattle. This time would prove a turning point in his career, developing lifelong research partnerships. Working in the Nuffield laboratory at Oxford was a worthwhile experience for the young Bothwell, as he expanded his knowledge of laboratory techniques while conducting numerous ferrokinetic measurements in patients with a variety of blood diseases. In addition, he developed a new method for measuring iron in blood serum, which was published in the *Biochemical Journal* and became the standard for a number of years. Indeed, there were times where Bothwell was not only researcher, but research subject. One experiment involved his taking blood samples from himself in his room at Balliol College throughout the night. However, this proved more difficult than anticipated and the next morning the room attendant was met with blood-splattered sheets and a very embarrassed young research worker.

Whilst attending a congress at the Sorbonne, Bothwell made the acquaintance of Dr Clem Finch, who would later become a collaborator in numerous research projects and publications, as well as a long-standing personal friend. The work on internal and external iron transport that Bothwell had been undertaking coincided with the research of Finch, who consequently invited him to join his laboratory in Seattle, at the University of Washington's Department of Haematology. The work undertaken in this laboratory at this time would lead to pioneering developments in haematology over the following decades. During this time, Bothwell's research focused on factors regulating the transport of iron in the system, including iron absorption and iron transport to the erythroid marrow and foetus.

Returning to South Africa in 1957 to continue his research at the University of the Witwatersrand, Bothwell was disappointed in the limited research facilities and funding at his disposal, placed as they were in the cardio-pulmonary unit rather than in other disciplines, including haematology. In order to establish a laboratory which would satisfy the immediate needs, a veranda needed to be enclosed and converted. While still comparatively modest, these facilities were adequate to fulfill the original intentions of this unit in studying autopsy subjects and documenting the prevalence and severity of iron overload in the black population in Johannesburg. Findings soon demonstrated the impact of iron overload on tissue, and within a short period, numerous spin-off studies were being undertaken with unanticipated results, including the highlighting of the relationship between high concentrations of iron and ascorbic acid deficiency extending to scurvy. The connection of these factors to osteoporosis was also under investigation.

Approximately 20 per cent of black adult males who came to necropsy showed levels of iron concentrated in the liver similar to those of patients with idiopathic haemochromotosis, as had been the case with the patient who had initially sparked Bothwell's interest in research as a young intern. However, findings in other subjects over the years suggested that iron overload was not due to an abnormality in absorption but was due to excess iron in the diet. Research by Dr ARP Walker was the first to find that the diets of many Africans at the time were exceptionally high in iron. This was due in part to the consumption of home-brewed beer routinely brewed in large iron drums – a result of legislation at the time curtailing the purchase of liquor by blacks. Not only was the level of consumption of iron in this beverage excessive; the iron also appeared to be particularly well-absorbed through this medium.

When the liquor laws were eventually altered in 1963, there was a corresponding decrease in prevalence of iron overload in this population. Eventually, this led to a subsequent shift in the direction of the laboratory's research; a shift with impetus added by the World Health Organisation's interest in analysing the prevalence and causes of nutritional anaemias, as well as developing strategies through which these deficiencies could be counteracted. Studying numerous liver samples, Bothwell was struck by how disparate iron concentrations were found to be in populations of different countries, particularly the low levels of iron in subjects originating in India. In addition to this, Bothwell undertook research collaborating with researchers across three continents in order to delineate the limits of iron excretion in humans. The data gathered in this study underlined the limited capacity of the body to excrete iron through sweat, or other means.

RESEARCHER TO TEACHER

In 1967, Bothwell was appointed as Academic Head of the Department of Medicine at Wits and Chief Physician at the Johannesburg Hospital, a position he held until 1991 – an intense administrative load added to a flourishing research career. The Department of Medicine was the largest in the country and Bothwell developed a teaching ethos for generations of medical students that put him in the forefront of medical educators in South Africa. Parallel to his teaching and administration, Bothwell spearheaded the Iron and Red Cell Metabolism Unit. This was a research programme funded by the CSIR.

Taking on this role in 1963, Bothwell was able to conduct his research focusing on iron deficiency anaemia through this platform. This unit was taken over by the South African Medical Research Council upon its establishment in 1969. Continuation in this programme was ensured under the auspices of the International Atomic Energy Agency despite the withdrawal of South Africa from the World Health Organisation. The programme was later absorbed into the activities of the International Nutritional Anaemia Consultative Group, part of the US Agency for International Development. Through intensive research carried out over the span of over three decades, Bothwell was able to make numerous contributions to the field. In his own writings, Bothwell describes the two most noteworthy contributions as being the demonstration of the widespread pathologic sequelae of dietary iron overload as well as the delineation of the factors affecting the manner in which dietary iron is absorbed.

These latter findings represented a major shift in the understanding of nutritional iron intake – rather than focusing merely on the amount of iron

provided through diet, it was found that the exact composition of the diet plays an important role as well. Thus, meat and ascorbic acid were found to act as enhancers of iron absorption, stimulating the uptake of dietary iron into the bloodstream. On the other hand, largely cereal-based diets rich in phytates and polyphenols (such as the tannins found in tea) were found to suppress the absorption of iron. Utilising the findings which had been made, Bothwell was involved in numerous studies around the issue of iron fortification of foods. These iron-enriched foods could contribute to programmes aimed at preventing future cases of iron deficiency over the long term. Supplementary to these studies, the potential of organic acids, particularly ascorbic acid as well as the chelate NaFeEDTA, was explored as an enhancer of dietary iron absorption. The value of NaFeEDTA was confirmed in a large-scale pilot fortification trial carried out in Durban with curry powder being used as the vehicle and NaFeEDTA as a fortificant. Similar studies have been conducted subsequently, in Vietnam with fish sauce as the primary vehicle, and in China with soya sauce.

In 1992, Bothwell was appointed as Dean of the Faculty of Medicine at Wits. He held this position until his retirement, whereupon he was made an Honorary Research Fellow. As a specialist in his field, he has acted as an expert advisor to a number of ministerial task teams.

Over the course of a distinguished career spanning more than five decades, Bothwell has published over 300 full-length academic articles, served on numerous committees and panels, been a frequent presenter at conferences and has supervised eighteen doctoral students. He has also served as editor and reviewer on numerous renowned journals**.** He was a member of the Scientific Advisory Council of the Prime Minister from 1983 to 1986, and was President of the South African Society of Haematology.

Bothwell received abundant honours as a researcher, as well as in the role of a teacher. In 1973, he was made a Fellow of the Royal Society of South Africa, and in 1975 he was awarded the honorary position of Fellow of the American College of Physicians. He is also a Fellow of the Royal College of Physicians of Edinburgh and of London, and in 2001 was elected as a Member of the Academy of Science of South Africa. He has been awarded honorary doctorates from the universities of Cape Town and Natal as well as his *alma mater*, Wits.

His keen perception and sense of humour are evident in his written account of his career, *Iron in the Soul*. While some of the anecdotes are extremely comical, this portrait also highlights some of the nutritional challenges facing South Africa. Throughout these decades and those to come, Thomas Bothwell's groundbreaking contributions remain fundamental to efforts being made to reduce nutritional anaemia and inform future researchers in the field of iron balance.

Professor Thomas Bothwell passed away in 2016.

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Legends of South African Science

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