Diabetologia (1982) 23: 72–75

Diabetologia

Historical Notes

Alloxan Diabetes: The Sorcerer and his Apprentice

N. G. B. McLetchie, Department of Pathology, Lakes Region General Hospital, Laconia, New Hampshire, USA

Summary. The remarkable discovery of alloxan diabetes came about between a Professor of Pathology and an apprentice who was foisted on him. The Professor (J. Shaw Dunn) had a lifetime behind him largely dedicated to studies on the kidney and particularly reno-tubular necrosis. The apprentice (McLetchie), despite overburdening duties and discouragement against endocrine research in wartime, developed a passion for endocrine investigation. A Colonel Sheehan (later to be enshrined in Sheehan's syndrome) in a brief wartime collaboration with the apprentice left him with a vivid description of hypoglycaemia associated with post-partum pituitary necrosis. The apprentice saw this behaviour paralleled in rabbits which had been given alloxan in a vague belief that it would further wartime research on the Crush Kidney syndrome. And so, alloxan diabetes was born. Shaw Dunn achieved some posthumous recognition and World War 2 closed over the other actors in the scene.

Since 40 years have passed, it is time to write the early history of alloxan diabetes. Animals can be rendered diabetic by a single intravenous dose of a simple chemical compound: alloxan. Rendered diabetic in this way, animals are studied wherever insulin is assayed and wherever diabetes is intensively investigated. The discovery was made in Glasgow in 1941–1942 at the Institute of Pathology of the University and Western Infirmary ('The Western'). Pathology in Britain was dominated for almost half a century by Sir Robert Muir. I was the medallist in the last class of pathology conducted by Sir Robert in 1936 when he was 72. By the time I graduated in medicine in 1938, I had already spent most of my final year in pathology. In what in America would be called a rotating internship, since war clouds loomed, time seemed short for me to get into my chosen field: pathology. So my clinical instructors allowed me to come in early, finish abbreviated clinical work, to spend the rest of the day attending autopsies, and studying in the Museum of Pathology.

By the time I graduated, Sir Robert had been succeeded by Professor John Shaw Dunn, who after service in France in World War I, succeeded to the Chairs of Pathology at Birmingham, then Manchester, then Glasgow Royal Infirmary. The 'Royal' was the alternate and junior Chair to the Chair held by Sir Robert at 'The Western'. Both Infirmaries had Institutes of Pathology and shared the undergraduate teaching. Some time before graduation, I called on Sir Robert to obtain a reference in support of a very junior post in pathology at the London Postgraduate School of Medicine. Sir Robert took me by the ear and marched me down to Shaw Dunn with instructions to start my apprenticeship after graduation. Money was not mentioned in those days. I had to supply my own microscope, microtome knives, glassware, ovens, dyes, etc. However, under the aegis of Sir Robert, I was made a Research Scholar with a stipend of £100 ($ 450) per annum. I worked as a hired assistant in general practice two evenings a week in the slums of Glasgow and on weekends as an assistant in general practice to a Dr. Stewart of Hamilton, arriving after lunch on Saturdays and leaving with the first bus on Monday morning, having early and quietly taken a guinea (a pound and a shilling) left under a brass candlestick in the study. In this way, I was able to support myself and pursue pathology.

Shaw Dunn deeply resented Sir Robert's continuing presence. There being no pension system, Sir Robert, mainly for financial reasons, had held onto the Chair too long. Shaw Dunn inherited, despite the fame abroad, what he considered to be a very run down department. As a legacy from Sir Robert, there were three senior assistants in morbid anatomy; none showed signs of moving onto a Chair so that the tradition of half a century seemed to be at a standstill. Moreover, Shaw Dunn was very much an experimental pathologist and

0012-186X/82/0023/0072/$01.00

none of the assistants worked with animals. (Personally, I owe a great deal to all of them for guidance during my early years). So-called 'Clinical Pathology' was housed separately from the Institute in a building attached to the hospital with its own staff. It was very much run down. Although Shaw Dunn's early interest had been in haematology, this subject had been largely relegated to 'side-room' laboratories in each hospital ward. Although Sir Robert was a father figure of immunity, this discipline was largely relegated to a rigid, funereal process of doing Wasserman Reactions in bulk for the city of Glasgow. The distinguished Professor of Bacteriology, Carl Browning, a pupil of Ehrlich, continued as a pioneer of chemotherapy, but very much in a private world of his own. Although the standard texts on bacteriology were by Muir and Browning, clinical bacteriology was very much neglected. A separate chemical pathologist had been appointed but chose to make infrequent visits and had no contact with the other members of the staff.

A hardy Scottish custom entitled a new Professor to see his predecessor's assistants out of the door as gently but as quickly as possible in order to install his own staff. Shaw Dunn, shy and reticent, did not sweep the deck, albeit unwillingly. Worse, he looked on the three senior assistants, owing allegiance to Sir Robert, as something to be suffered. While I made a very bad start as yet another of Sir Robert's protegees, the scene quickly changed. Shaw Dunn started to cultivate me as his very own, his blue-eyed boy. Basking in the light of the all powerful Professor, a popular tutor, carrying out Shaw Dunn's research – many must have asked, 'What next?'

When World War 2 broke out our world fell apart. Staff in the military reserve was called up. Trainees in pathology were told to find work more appropriate to war. War time duties extended to fill the vacuum created by no more training of pathologists, at least in the initial years of the war. Some decisions seemed to me hasty and unwarranted, but I had no cause for personal complaint. I woke up with war declared, promoted to Lecturer in Pathology and assistant pathologist to the Western Infirmary. In these days, this was a relatively high title, above instructor and assistant. There was, however, one catch. Along with the accolade, Shaw Dunn explained, 'You are coming on too fast, so you will only get half pay.' This was achieved by making the office of assistant pathologist unpaid so that I had to live on the lesser University salary.

Shaw Dunn was a Presbyterian which means that pleasure is all right provided one does not enjoy it. Within thinking man, there is the eternal conflict between expediency and morality, as sharply focused in Burma in World War 2: *should I leave my sick or wounded comrade to die and move on hoping to save myself?* Shaw Dunn's philosophy always courted an extreme morality; a sense of duty which often seemed beyond reason and harshly applied to juniors. Since a terrible war was on, he ordered that experimental and other non-routine work had to be done in evenings only. Among other duties, I was seconded to the Glasgow Royal (now Beatson) Cancer Hospital and (for its time) large cancer research department. My duty was to cover the pathology including the examination of the laboratory animals. I was directed to run this work strictly as a lunch-time and early evening project. Hence, my duties ran from morning, by electric tramcar to the Cancer Hospital at lunchtime, back to the Cancer Hospital after supper, the rest of the evening at 'The Western', walking home to my lodgings long after the last 'tram' had gone.

Graduation in medicine was by MB, ChB (Bachelor of Medicine and Surgery). A Sword of Damocles then hung over an aspiring academic pathologist: to obtain an MD by thesis. This was granted in four categories: ordinary, with commendation, with high commendation, and with honours. It was better in academic circles to be without than to be an MD qualified as 'ordinary'. As an MD with honours, one joined an exclusive club since only about 1% of MB, ChB's ever reached this pinnacle. Also with 'honours' all written and clinical examinations were excused; the research thesis stood on its own merits. One had to think of a subject on one's own and pursue it alone. Indeed, one might easily never get beyond the thinking stage far less the years ahead in part-time research. Once this thesis was completed, printed, and bound, it was lodged along with a fat fee. The latter largely went to three external examiners chosen for eminence in the field of the thesis. They sent a recommendation to Faculty. Nor was there any substitute: no Colleges of Pathology where one could be a Member or a Fellow; no specialty Boards in those days.

I chose the investigation of seeds for hormonal effects: hardly a patriotic choice with war all around. A subject like wound healing would have been more acceptable and so my interest was never mentioned in the polite talk of the wartime Institute. My reasoning was that many of our avian migrants coming from sunny Africa break out into full nuptial song in our much less sunny spring. For the hardbills, I connected nuptial exuberance with eating seeds among the heather and thickets. Hence, I determined to feed young rats on seeds. The seeds handiest to come by in quantity were rape and turnip seeds which I got from a farmer. These brassica seeds were ground up and served mixed with an equal amount of ground-up proprietary rat 'nuts'.

The young rats did not grow up, their thyroid glands enlarged and microscopically were depleted of colloid and filled with dividing cells. After the initial burst of proliferation, the cells sorted out in their original architecture except that there was permanent enlargement of the gland (colloid goiter). In those days, interference with hormone synthesis and feedback mechanisms of control were not part of systematic thought. Despite the initial hypercellularity, I insisted that the rats were thyroid-deficient. I tried to explain this to Shaw Dunn who

was startled with my ideas that ground-up turnip seed be fed to victims of hyperthyroidism.

Obviously, the next step was to isolate the active principle in the seeds. That it might be in the watery extract was too simple for me. I began with ether and benzol extracts to end up with an oil. Indeed, it turned out that the oil could be bought in shops. Since, in wartime, glycerine was needed for explosives, the pharmacological substitute was an oil expressed from rape seeds (rape oil). When I injected the oil into rats, I produced not thyroid disease but acute tubular disease of the kidneys. This was a line of research attractive to Shaw Dunn since he was above all a kidney pathologist and an experimental one to boot. So he encouraged me to forget my startling propositions retreating of hyperthyroidism and to concentrate on rape-oil nephrosis since it resembled a wartime problem, the so-called 'Crush Kidney'. Some years later, I learned that the same rape-seed experiments had been going on in New Zealand with the final isolation of thiourea, the active principle which inhibited the synthesis of thyroid hormones. With fall in blood levels of this hormone, the pituitary gland responded by an abortive stimulation of the thyroid. Thiourea was the first highly active anti-thyroid principle and its demonstration in rape seed came to be known as the brassica response, a milestone in endocrine research: an honour which had passed me by.

Despite Shaw Dunn's wishes, my interest in endocrine glands was not diminished [1–4]. Harold Sheehan was the first assistant appointed by Shaw Dunn when he took up the Chair at Manchester long ago. During the course of my work, I obtained an autopsy example of necrosis of the pituitary gland following a complicated childbirth, a condition which later became known as Sheehan's syndrome. I contacted Dr. Sheehan, who had been pathologist to Glasgow Royal Maternity Hospital and from the outbreak of World War 2 a Senior Medical Officer in the Army. Together we published the case [5]. One of the features of the syndrome is hypoglycaemia. Sheehan was a very gifted conversationalist. In our meetings, he left me with a rich image of acute hypoglycaemia.

At this time, air raids on London were prevalent. Samples of the 'Crush Kidney' were sent to Shaw Dunn for expert appraisal. Damage to the tubules of the kidney came about secondary to the thighs being crushed by a beam in victims of air raids. The 'Crush Kidney' [6] rekindled Shaw Dunn's interest in the pathology of tubules of the kidneys (he had published extensively in the field). Shaw Dunn instructed me to read his old publications and to start thinking as to what might be released from crushed muscle which could be toxic to the kidney. After discussion with him concerning phosphates and sulphates and ionic imbalance with which we were well-acquainted [7], Shaw Dunn lifted a chemical almanac from a library shelf and started fingering through products of protein break-down. Without explanation, he suddenly fingered an entry: alloxan. 'Try that', he said. So it followed that among other substances, rabbits were given intravenous injections of a solution of alloxan. Twenty-four hours later, the alloxan rabbits had a peculiar reaction: staring eyes, jerky movements, a lack of awareness of their surroundings. To me, this recalled Sheehan's rich description of acute hypoglycaemia. I therefore told Shaw Dunn that the rabbits had hypoglycaemia secondary to pituitary necrosis! While Shaw Dunn was startled at this unlikely and very tangential explanation, he told me to go ahead: examine the kidneys, measure the blood glucose and examine the pituitary. To be sure the rabbits were hypoglycaemic, I made a complete examination of the endocrine glands and returned to tell Shaw Dunn, 'Not pituitary necrosis; necrosis of the islets of Langerhans, Sir.' Within a short time, we produced diabetes in rabbits and rats. The initial hypoglycaemia is due to release of insulin from the damaged islets. Once this acute phase is over, the permanently damaged islets lead to hyperglycaemia and diabetes mellitus [8–11].

A communication was sent to the Lancet. After a long delay, it was returned. This shattered Shaw Dunn. It took years to get a complete answer to the imbroglio. It turned out that the Editor of the Lancet had sent the article to Professor Harold Himsworth for review. He apparently repeated the simple experiments and getting no pancreatic damage, pushed the dose of alloxan to eventually get liver damage. All of this was because Himsworth had boiled the alloxan solution which nullifies the action.

The first article published in the Lancet was by Shaw Dunn, Sheehan, and McLetchie [8]. Sheehan was incorporated for another mechanism of pancreatic damage which he had worked on long ago under Shaw Dunn in Manchester. In the meantime, Shaw Dunn was showing signs of a grave and disturbing illness.

In 1943, I was called up into the Army Medical Corp. The first mail I received in Normandy in 1944, after the great invasion across the channel, had two pieces of salutory news: Shaw Dunn was dead at the age of 61; Glasgow University had awarded me an MD with honours for my thesis on the relationship of the basophils of the pituitary gland to the adrenal cortex [12]: a subject which was to become very topical after the war with the isolation of cortisone.

Shaw Dunn, in our more personal conversations, always told me that he wished he had stayed in Manchester, that shifting around was no good, that he had succeeded to the prestigious Muir chair far too late, and that Cappell of Dundee, who was much younger, should have taken over from Muir. History was to repeat itself. Shaw Dunn was succeeded by Cappell, a protegee of Muir, who had come to the Chair at Dundee at the early age of 29. But the war years took their toll. Cappell had carried on the duties of Dean of the Medical School, Professor of Pathology, and pathologist to the main hospitals and had organized from scratch a wartime blood bank system for his region of

Scotland. Indeed, without technical help, he had become an outstanding authority on Rh and related problems. Cappell, however, did not repeat what Shaw Dunn had taken to be a fundamental mistake: he formed his entire staff from people he had trained in Dundee. This was not without hardship for those coming back from World War 2 since medical-institutional life was in a state of paralysis awaiting the nationalized medical service which was still years away. Hence, there were few positions available in pathology, and even fewer paying the modest equal of a pathologist in the Armed Forces. So, returning from the Far East, I did not linger long in Britain but emigrated to Saskatchewan to the life of a hospital pathologist.

It is said that discovery comes to a prepared mind but for fulfillment, there has to be a happy confluence of time and place. War clouds, the malady which overtook Shaw Dunn, war service, the bitterness which went with post-war reconstruction, financial strain, a galaxy of scientific papers on many aspects of endocrine disease, all make a memorable pot-pourri where alloxan is not the spice it should be but a bitter pill. For the gloomy Shaw Dunn, no matter how he tried, there only seemed one way for the Muir School of Pathology to go: down. When recognition suddenly appeared in the shape of alloxan, it soon distilled into enigmas worse than anything Hamlet saw in the mists of Elsinore. Graduation exercises in Glasgow were gloomy affairs under Principal Sir Hector Hetherington. With war raging and only a medical class to graduate (the University was otherwise closed), the occasion was even more somber in 1944. As a citation was read which recalled Shaw Dunn and McLetchie, the student body rose in a demonstration so long and so loud as to make local history. So ended with a bang the brief but illuminating wartime partnership of professor and apprentice. Like a wartime order of the day to come later in Burma: *someday you will look back with pride and say – I was there.* Without Shaw Dunn no almanac would have been opened at the entry: *alloxan.* Without McLetchie ably tutored by Sheehan, no one would have made the fertile suggestion: *hypoglycaemia due to pituitary necrosis.*

References

1. McLetchie NGB (1944) On staining the basophil cells of the human hypophysis. J Endocrinol 3: 323–331
2. McLetchie NGB (1944) The pituitary basophilism syndrome of Harvey Cushing. J Endocrinol 3: 332–346
3. McLetchie NGB, Scott LDW (1944) Carcinoma of an adreno-cortical rest associated with hypophyseal abnormality. J Endocrinol 3: 347–355
4. McLetchie NGB (1944) Adrenal virilism, Br J Surg 32: 90–98
5. Sheehan HL, McLetchie NGB (1945) Simmond's disease due to post-partum necrosis of the anterior pituitary. J Ob Gyn of B.E. 50: 27–30
6. Dunn JS, Gillespie M, Niven JSF (1941) Renal lesions in the Crush Syndrome. Lancet 2: 549–552
7. McLetchie NGB (1943) Renal lesions in a case of excessive vomiting. J Path Bact 45: 17–22
8. Dunn J Shaw, Sheehan HL, McLetchie NGB (1943) Necrosis of the islets of Langerhans produced experimentally. Lancet 1: 484–487
9. Dunn J Shaw, McLetchie NGB (1943) Experimental alloxan diabetes in the rat. Lancet 2: 384–386
10. Dunn J Shaw, Kirkpatrick J, McLetchie NGB, Telfer SV (1943) Necrosis of the islets of Langerhans produced experimentally. J Path Bact 45: 245–257
11. Dunn J Shaw, Duffy E, Gilmour MK, Kirkpatrick J, McLetchie NGB (1944) Further observations on the effects of alloxan on the pancreatic islets. J Physiol 103: 233–243
12. McLetchie NGB (1942) Studies on the relationship of the basophil cells of the hypophysis to the adrenal cortex. MD Thesis: University of Glasgow

NGB McLetchie, MD
Lakes Region General Hospital
Laconia, NH 03246, USA