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Review Article

Samson Wright, the Man and his Research -

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ABSTRACT

Samson Wright (1899-1956) was better known for his international reputation as a teacher of physiology rather than for his experimental work. This article explores Wright's experimental work on the role of acetylcholine transmission in the Central Nervous System (CNS). A biographical appendix is included of Samson Wright and his co-experimentalists.

Keywords: Samson Wright; Acetylcholine; Physiology; Neurology

INTRODUCTION

Samson Wright (1899-1956) was appointed at the early age of 31 to the John Astor Professorship of Physiology at the Middlesex Hospital Medical School. He built a reputation as a brilliant undergraduate and postgraduate teacher and students came from all over the world to study under him.

Teaching overshadowed his research endeavours, which took place both before and after the Second World War; nevertheless, his book became known as the 'bible of experimental physiology'. His research on acetylcholine's role in the central nervous system showed him to be both a practical experimenter and a team leader. His team included Alfred Schweitzer, Italo Calma, H E S Pearson and Michael Kremer in his Department at the Middlesex, and a collaboration with Professor Edgar Steadman in Edinburgh. The influence of his work extended beyond the Middlesex, notably on Michael Kremer, who had initially worked with him at the Middlesex Hospital Medical School but continued his line of experimentation at the Postgraduate Medical School. His work influenced the clinical management of spinal injury cases under Ludwig Guttmann during his directorship of the Spinal Unit at Stoke Mandeville Hospital.

Apart from obituaries in scientific journals such as in Nature, the British Medical Journal, and Munk's Roll, there are two posthumous publications devoted to Samson Wright's oeuvre: an article celebrating the centenary of Wright's birth by Alex Sakula, a student of Wright's, later, a chest physician, who describes him as a physiologist extraordinary and briefly outlines his achievements; and an In Memoriam, which was a homage to Samson Wright produced by The Friends of the Hebrew University of Jerusalem. These articles failed to do justice to the wider impact of his research work, hence our review.

Samson Wright (1899-1956) – short biography (Figure 1) [1]

Samson Wright was born on 5 May 1899 to a Jewish penniless refugee couple from Pinsk on the Marsh in Byelorussia, who immigrated to London when Samson was two. He was brought up in London in what is today Tower Hamlets and his father worked in a furniture business. His mother and the author's grandmother were sisters. The two families shared a house. As a result, a close bond was formed between Samson Wright and his cousin, the author's father, Aaron Gideon Silver, which lasted throughout their lives. At 17, Samson obtained an entrance scholarship to the Middlesex Hospital Medical School where he qualified in 1920 (Figure 2). He gained the Gold Medal in the M.B examination in 1922 and was appointed senior demonstrator in the Physiological Department under Professor Swale Vincent. He took the Membership of the Royal College of Physicians and proceeded to the degree of Medical Doctorate in 1925. Apart from a short interlude of a year working at King's College Hospital Medical School as a lecturer in physiology in

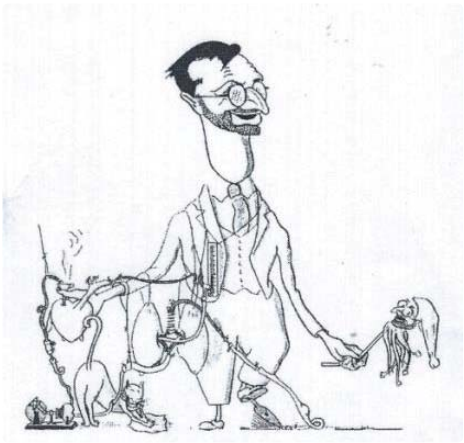

Figure 1: Cartoon of Samson Wright (from Middlesex Hospital Journal 1936; 36(3)). Reproduced with permission from UCLH arts and heritage, UCLH NHS Foundation Trust.

Figure 2: The Middlesex Hospital, London. Reproduced with permission from UCLH arts and heritage, UCLH NHS Foundation Trust.

1929, Wright spent all of his working life at the Middlesex. At the early age of 31, he was appointed as professor of physiology upon Swale Vincent's retirement, a position he held until he died in 1956. When he applied for the professorship, the local appointment committee favoured, possibly through prejudice, another candidate but it was only at the insistence of Sir Charles Sherrington, the external assessor who had arrived late at the meeting, that the decision was overturned and Samson was preferred [2]. In 1931 he delivered the Oliver-Sharpey lectures at the College of Physicians, on certain aspects of the reflex control of the circulation. In 1933 he was elected a Fellow of the Royal College of Physicians, a rare accolade in those days for a non-practising doctor. He served as an external examiner for the Royal College of Surgeons and at many universities. Anxious to integrate physiology into the medical curriculum, he introduced a program of clinical demonstrations to illustrate different diseases. He

also ensured that a physiologist was appointed at his medical school to translate experiments from the laboratory into clinical medicine. To this end, EJM Campbell was appointed. He made an outstanding contribution to the physiology of respiration and eventually became a Professor of Medicine at McMaster University in Canada.

A gifted teacher, Wright could explain complex concepts with great simplicity and clarity of thought. His lectures were renowned throughout Britain and a prerequisite for virtually all students studying for the Primary Surgical Fellowship. He regarded physiology as a cornerstone of medicine and, in 1926 this led him to write a seminal textbook Applied Physiology (now in its 13th Edition) [3]. He believed in the application of physiological principles to clinical medicine. This soon became the physiology bible for medical students around the world. The book has been translated into French, Italian, and Spanish. In addition, between 1938 and 1949 he edited the abstracts of the Journal of the Physiological Society.

Before and during the Second World War, Samson Wright worked tirelessly to ameliorate the misfortunes of Jewish refugees. He was a member of the Aliens committee of the British Medical Association from 1943 to 1951. He worked tirelessly to sponsor Jewish refugees from Nazi Germany, finding them positions in his own department or at other universities.

Samson was devoted to Jewish causes, always supportive of Jewish students. He was a staunch supporter of the State of Israel and served as president of the Hebrew University. The laboratory of the Hebrew University's Physiology Department in Israel is named after him. Wright's pre-eminence as a teacher should not detract from his outstanding research contribution and when Samson Wrights' textbook is described as 'perhaps the greatest of all his scientific achievements', this does not give credit to his significant contribution to research [4]. His obituaries mention his research only briefly yet Samson Wright carried out detailed experimental research both on man and animals, published widely on the role of vitamins in nutrition, on the reflex control of the circulation, the physiology of the circulation and respiratory function, alkaline phosphatases and most specifically on the role of chemical transmitters including acetylcholine in the central nervous system. He helped lay the foundation for subsequent research in this field.

Historical background to knowledge of the function of acetylcholine [5]

The knowledge that acetylcholine was the transmitter at the endplate of the synapse, that its action is terminated by the naturally occurring cholinesterases and the development of our knowledge of blocking agents to this by neostigmine, was hailed at the time, as remarkable. This became the basis for the development of such modern drugs as the monoamine oxidase inhibitors and the use of dopamine analogs in the treatment of Parkinson syndromes.

Before the 1920s, it had been presumed that a nerve impulse proceeded from cell to cell or cell to muscle by an electrical event. This had been previously questioned by Claude Bernard after he carried out experiments on a frog by applying it with curare. He dissected the animal, which appeared dead although its heart was beating. Stimulating the muscles directly produced violent contractions but he could not obtain a reaction by stimulating the nerve endings through electrical stimulation. He concluded that he motor nerves were the only tissues affected by curare. The mechanism of nerve transmission was eventually solved in 1921 by Otto Loewi, an Austrian professor of pharmacology. He used two frogs' hearts, one of which had the vagus nerve severed and the other, the control heart; the vagus nerve had been left intact. In the intact heart, stimulation of the vagus caused the heart to stop beating. The hearts were then both perfused with Ringers' solution. When Loewi stimulated the vagus nerve of the heart in which the vagus was intact, he transferred the fluids from that heart into the denervated heart. This *"vagusstoff"* caused the second heart similarly, to cease beating. Loewi postulated that the vagus nerve secreted a substance into the ventricle of the heart which caused the heart to cease beating. He suggested that the *"vagusstoff"* might be acetylcholine.

Henry Dale (1875-1968), an English pharmaco-physiologist with H W Dudley, had isolated acetylcholine by extracting naturally occurring acetylcholine from equine spleens. He then demonstrated that acetylcholine was involved in the action of peripheral nerves.

In 1936, Dale and his co-workers presented evidence to show that acetylcholine was secreted in response to electrical stimulation of motor nerve fibres. Dale and Loewi were jointly awarded the Nobel Prize in 1936 for their respective work on the function of acetylcholine. Dale pursued his research by demonstrating that acetylcholine was secreted by the nerve innervating the muscle. Scientists recognized in the twitch of muscles under stimulation that a nerve impulse was brief and transitory. However, if the impulse was chemically transmitted, the transitory nature was hard to explain, since a chemical applied by one cell to another would remain at the point of contact and continue to produce nervous activity. Loewi and E Navratil showed that acetylcholine was broken down and destroyed by cholinesterase enzymes. In turn, they showed that the cholinesterase could be inhibited by an anti-cholinesterase such as the alkaloid physostigmine (eserine). This newly discovered property of physostigmine led M.B Walker to suggest its use for the treatment of myasthenia gravis and its accompanying abnormal muscular fatigability having found that hypodermic injections of physostigmine salicylate had a striking if temporary reversing effect [6]. She suggested that it might allay a fatal myasthenic respiratory crisis by promoting improved swallowing. In a later presentation to the Royal Society of Medicine, she remarked that clinically it was better to prescribe the anti-cholinesterase, prostigmine, a synthetic drug analogous to physostigmine, as it had a lesser depressing effect on the heart and inhibited the action of the esterase which destroyed acetylcholine [7]. Dale and Loewi revealed fundamental information on the chemical transmission of the peripheral nervous system. Meanwhile, there remained little evidence of the action of transmitter substances in the central nervous system. The problem was that in the brain and spinal cord, the smallest nerve cells of all were packed together, making it virtually impossible to obtain enough chemicals released by specific cells for analysis. Edith Bulbring and JH Burn (1941), despite Feldberg's contrary view, showed that acetylcholine was the central nervous system transmitter [8].

Samson Wright and the significance of acetylcholine

Samson Wright's research was directed to studying the role of acetylcholine, eserine and prostigmine within the central nervous system. Fortunately, Samson Wright's views on acetylcholine can be gained from studying successive editions of his book Applied Physiology from the first edition in 1926 to the last edition for which he was solely responsible, in 1952. In the first edition of his book, while he devotes 120 pages to the nervous system, and discusses the different roles of the synapse, there is no awareness of the

function of acetylcholine and anti-cholinesterases at the ganglia or at the endplate. The first two editions make no mention at all of the acetylcholine being a transmitter of the nerve impulse. The first account is in the third edition in 1929 when he describes the role of the "Vagus Substance" (a substance he had not yet identified as acetylcholine) which he attributed to the pioneering work of Loewi in stopping the heart.

Vagus Substance, a considerable amount of evidence has now accumulated to show that the vagus nerve causes to be liberated in the heart of a chemical body probably an acetyl derivative of choline which is the agent responsible for the inhibitory effects produced by the nerve. This work has been extended and it is now suggested that the effects of the vagus and of the other parasympathetic nerves are similarly due to the liberation of an 'acetyl-choline-like' substance [9].

By the 5th edition, in 1934, Samson Wright was firmer in his views that the chemical transmitter was probably acetylcholine and that it was broken down by an enzyme to an inactive substance, choline "The injection of acetyl-choline reproduces the effects of parasympathetic stimulation. Acetyl-choline is probably destroyed almost as soon as it is formed in the body by the action of an enzyme (esterase)" [10].

By 1936, in the 6th edition, he was discussing the action of acetylcholine at different sites and how this action could be inhibited by eserine "In blood and in the tissues generally there is a specific enzyme choline esterase, which greatly accelerates the rate of destruction. It is very important to note that the action of this esterase is inhibited by means of weak solutions of eserine" [11].

His direct involvement in elucidating the problem of the transmission process in the CNS by direct action on the nerve elements is described in the 7th edition, 1940; "The anti-cholinesterase's influence transmission processes in the central nervous system presumably by a direct action on nervous elements. The tertiary ammonium anti-cholinesterases probably facilitate central transmission processes by increasing the concentration of acetylcholine within the nerve cells of the spinal cord" [12].

He realized that the action of acetylcholine must be blocked by an enzyme since the nerve impulse was only transient, whilst if it was chemically mediated and if not broken down, it would carry on for much longer.

While the action of acetylcholine on the peripheral nerve system was well documented, he was puzzled by its actions in the Central Nervous System and to elucidate the problem, he initiated research involving animal experiments in his own Department.

By 1945, in the 8th edition of his textbook, there was no generally accepted account of the mechanism of transmission of the nervous impulse from neuron to neuron in the CNS. Samson Wright quotes his own research "The effect on the spinal cord varies with the exact experimental conditions, and may be excitatory or inhibitory" [13]. He concludes: "That acetylcholine could act both as a central excitatory and central inhibitory agent within the spinal cord and that the level of activity of anterior horn cells may depend on the relative concentrations of acetylcholine within and without these cells" [14]. This was all based on animal experiments. Finally, in the 9th Edition, his last, of 1952 he reaffirms these views [15].

Samson Wright's research

Apart from the work with his team in his own laboratory he influenced, inspired and collaborated with disciples who left his laboratory and worked independently [16-18]. From the outset of his professional career, Wright was interested in the role of acetylcholine as a transmitter substance in the CNS. Working single-handedly at King's College, he investigated the control of the vaso-motor center in cats. He looked at the synapse and how the surface membrane could be modified by the release of a substance (acetylcholine) and how this could be blocked by ergotamine and other drugs. The experiments were carried out on vagotomised cats to exclude reflex inhibition of the heart. The ends of the peroneal and popliteal nerves were stimulated. One or both common carotid arteries were obstructed to stimulate pressor reflexes. Depressor and mixed depressor-pressor reactions were produced by stimulation of the central end of the vagus. He demonstrated that ergotamine in small doses prolonged the latent period for the depressor reflex, decreased the rate and extent of the fall of blood pressure and finally abolished the reflex completely. When central vagus stimulation gave a mixed effect (initial rise followed by a fall or after-fall) ergotamine could convert the response into a pure rise. This led him to suggest that the results obtained were opposed to the view of the direct transmission of the excitation process through the vaso-motor 'centre'. He accepted the view that transmission in the CNS was mediated across the synapse by an intermediate substance. He calculated that if there was the direct transmission of the nervous impulse through the center, it would take 100 years for the transmission to take place! He speculated therefore that the transmission must be taking place across the synapse or that ergotamine prevented access to the central excitatory and inhibitory states to the cells of the 'centre, possibly by modifying the condition of the surface membranes [19]. He was opposed to the view of the direct transmission of the excitation process through the vaso-motor 'centre' and thought that there had to be some other mechanism involved.

He continued his research when he returned to the Middlesex Hospital in a series of experiments in collaboration with Schweitzer. He showed that acetylcholine, prostigmine and other anti-cholinesterase's also exerted a direct inhibitory action on the spinal cord. They studied cats under chloralose anaesthesia, the hind limbs were fixed and the patellar reflex was elicited. In some animals, the hind limbs were rendered ischemic and the effects of various preparations of eserine were determined. As a result of these complex experiments, he believed that the anticholinesterases of the prostigmine group acted on the spinal cord by inhibiting the cholinesterase which is present in the CNS, stating that:

It is not our intention to discuss the mechanism of normal transmission of impulses in the central nervous system of the intact organism. The processes are more complex than in autonomic ganglia, as both central inhibition and excitation can occur. Suffice it to point out that our results suggest that acetylcholine could act both as a central excitatory and central inhibitory agent within the spinal cord and that the level of activity of anterior horn cells may depend on the relative concentrations of acetylcholine within and without these cells. Arguments are advanced to support the view that the central action of both the excitatory and depressant anticholinesterases is due wholly or in part to their inhibitory action on cholinesterase in the spinal cord. It follows that variations in the concentration of acetylcholine in various regions of the grey matter of the central nervous system may influence transmission process, producing either excitation or inhibition [20].

In a preliminary report that extended their experiments from animal to man, Kremer, Pearson, and Wright (1936) studied the effect

of intrathecal injections of 1-1.5 mg of prostigmine in eight patients; one with cerebral diplegia, one with spastic paraplegia and six with hemiplegia. They showed that the intrathecal injection of 1mg of prostigmine into the cerebro-spinal fluid of patients with hemiplegia decreased or abolished tendon reflexes and muscle tone in the legs and sometimes in the arms too, without a change in sensation [18].

Kremer left the Physiology Department at the Middlesex and went to the Postgraduate Medical School where he extended these studies to 37 patients (including normal controls), injecting prostigmine of varying dosage into the lumbar theca 73 times (1942). Some of the patients had to be revived with Coramine and others had to be catheterised. He found that the action was central on the spinal cord. In all cases, it produced a depression of muscle tone and reflexes by a direct action on the spinal cord. The distal part of the cord was involved first and the depression gradually ascended to involve the centres controlling the arms. Nausea, vomiting, and drowsiness commonly occurred and bladder emptying was temporarily abolished. Despite being commissioned into the army as a consultant in neurology in 1939, Kremer carried on writing up his work and published it in 1942 [21]. After the war, Kremer was demobilized. Until such time as ex-army neurologists could find civilian appointments, the Army found them positions at Stoke Mandeville Hospital. Kremer came to visit the neurological ward. These neurologists shared the treatment of the patients, visiting them at different times of the day and changing the treatment often to the patient's detriment.

At Stoke Mandeville Hospital, Ludwig Guttmann was looking after spinal injury patients in adjacent wards. One of the problems he encountered was intractable spasticity. To address this, Foerster, Guttmann's teacher in Germany, had developed the operation of posterior rhizotomy. Guttmann thought that was too drastic a measure and wanted a temporary means of relieving the spasm to see if it was effective before proceeding to either an anterior rhizotomy or an alcohol block. He was aware of Kremer's work on depressing the reflexes by giving intrathecal prostigmine and he used this procedure to ameliorate the spasticity. He also discovered fortuitously that while the reflexes were depressed, erections and ejaculation were induced.

In the course of study on the depressant action of intrathecal injection of prostigmine on the skeletal spastic muscles (Kremer and Wright 1941), he (Guttmann) found in 1946 that a dosage of only 0.3 mg was sufficient to elicit erections and emissions in traumatic paraplegics with complete transverse lesions of the spinal cord, who hitherto, had been thought to be completely impotent and unfertile. My own studies on fertility in paraplegics and tetraplegics started in 1946, when I discovered an amazing and selectively stimulating effect of prostigmine on the function of the reproductive organs following intrathecal injection [22].

EPILOGUE

The importance of Samson Wright and his group in elucidating the transmission within the CNS was recognised by Wilhelm Feldberg in 1945 in a review article on acetylcholine and the CNS, he quotes Calma and Wright four times, Kremer and Wright twice, Kremer alone nine times and Samson Wright nine times so that his work was significant and acknowledged at the time. The work influenced other doctors and as a result of Kremer showing that the central action of prostigmine was to depress the reflexes, Guttmann used this technique which was not a permanent procedure prior to carrying out an alcohol block and fortuitously discovered that the prostigmine caused ejaculations and so was a stimulus for further work to address fertility problems, paraplegic patients. This was the beginning of the extremely valuable research which enabled paraplegic patients to father children and lead fulfilled lives to their great satisfaction.

The work ceased when Samson Wright was at the height of his powers and the most productive part of his career. He suffered a series of setbacks. He suffered from severe angina leading to a coronary thrombosis aged 50 which for a year brought his research to a halt. At the same time, his wife died prematurely in 1950. After this, he returned to work but with diminished activity.

During the war, the medical schools were preoccupied with teaching and could not be expanded but after the war, there was an emphasis on opening up new universities and medical schools. The research team assembled by Samson Wright dispersed and was disbanded; Schweitzer went to University College London to become a reader, Calma went to Liverpool and Kremer followed a career as a clinical neurologist at the Middlesex Hospital, the Maida Vale and at the National Hospital for Nervous Diseases, Queen Square.

BIOGRAPHICAL APPENDIX

Alfred J. Schweitzer (1910-1952)

Schweitzer, a distant relative of Albert Schweitzer, graduated in Medicine in Cologne in 1932. After qualifying, he gained a scholarship to study the autonomic nervous system and the physiology of the heart and circulatory system under Professor E. Koch in Bad Nauheim. He left Germany after the Nazi regime forbade him from practicing medicine. He arrived in England in 1935 securing a research position at the Middlesex in Samson Wright's Department of Physiology. Wright secured his funding and with CARA (Council for Assisting Refugee Academics) encouraged him to obtain British medical qualifications. Unable to produce the necessary Licence to practice from his time in Germany, Schweitzer was refused a dispensation so could not sit the examination. The rules changed in 1936, but Schweitzer opted instead to study for a Ph.D. degree in pharmacology. He worked in the Physiology Department until 1939 when his work permit was revoked and he was interned as an Alien on 8th August 1940. CARA and Samson Wright wrote to the Home Office Aliens Department: "it is surely the highest form of irony that the Home Office should be interning Schweitzer as a dangerous person at the same time as his work is about to appear and will greatly help the treatment of our wounded and injured" (ref 17th July 1940 letter CARA archives).

In August 1940, Samson Wright threatened to write to the Chancellor of London University remarking that Schweitzer must be unique in being awarded a Ph.D. degree whilst in prison and may publish his next paper from H. M. Internment camp! He was released nearly three months later.

He is listed on the Medical Register, foreign list in 1943 and 1947. He served as Medical Officer in the 8th West Riding Home Guard Battalion. In 1947, he was naturalized British and appointed reader of physiology at University College. Schweitzer sadly died in 1952 after a mountaineering accident in the French Alps.

Italo Calma (1915-?)

Born in Italy, Calma described how by 1938 anti-Semitism in Germany had spread to Italy. After completing his medical degree in Milan he came to England and worked in Wright's research team, initially unpaid and subsequently as a lecturer. In 1940, he was interned on the Isle of Man but later released to act as an interpreter

in the BBC Italian Service. After the war, he moved to Liverpool and worked as a medical physiologist at Liverpool University. In 1946 he is listed as an assistant lecturer in physiology and by 1962, as a senior lecturer in experimental physiology. He was still an active member of the Association of Jewish Refugees in 2012.

Edgar Steadman (1890-1975)

Stedman graduated in 1915 and fought with the Royal Engineers from 1916 to1918. After the war, he graduated in Chemistry at Birkbeck College, University of London and was appointed a lecturer in Professor Barger's biochemistry department at Edinburgh University. His Ph.D. was on the physiological activities of the alkaloid physostigmine (eserine) a subject on which he published over 60 articles. In 1939, he collaborated with Schweitzer and Wright to describe the central action of anticholinesterases. He was greatly influenced by the work of Loewi and Navratil (1926) on the effects of physostigmine on the heart and he sought to study the effects of some of the synthetic urethanes on various esterases. It was his elucidation of the constitution of physostigmine which enabled him to synthesize synthetic urethanes for widespread clinical use by pharmaceutical companies.

Michael Kremer (1907 - 1988)

Kremer was a gifted neurologist, endowed with insight, empathy, and knowledge. He studied at the Middlesex Hospital and obtained an honors degree in Physiology. He qualified in medicine and in 1932 he became a member of the Royal College of Physicians and gained his doctorate of medicine. He worked as a demonstrator in the Physiology Department with Samson Wright. He entered clinical medicine at the National Hospital for Nervous Diseases at Queen Square. At the outbreak of war, he joined the RAMC and served as a neurologist in the Middle East and returned to the United Kingdom to work in the neurological and neurosurgical unit established for the Army and the RAF at St Hugh's in Oxford. Soon after his return to civilian life, he was appointed to the consultant staff of the Middlesex Hospital as a neurologist, and to Maida Vale Hospital for Nervous Diseases as a physician. He resigned the latter appointment when he joined the National Hospital, Queen Square and remained on the staff of the Middlesex and the National Hospital until his retirement in 1973. Kremer had a prolific career in research before becoming a neurologist until his wife was tragically rendered tetraplegic in a road traffic accident on their honeymoon. To pay for her care, he decided to opt for private practice rather than pursue research. Kremer never mentioned his significant work on the spinal cord or the action of prostigmine. It was when working with Guttmann that I discovered the role he had played. It is a fitting tribute that Ludwig Guttmann suggested he should be appointed the first professor of neurology at Queen Square.

Ludwig Guttmann (1899-1980)

Ludwig Guttmann was the founder of the National Spinal Injury Centre at Stoke Mandeville Hospital and the paraplegic sports movement. Born in Germany, he was trained by Otfrid Foerster in neurology, neurosurgery, rehabilitation and research. When the Nazis came to power, Guttmann was expelled from his post, his professorship Venia Legend was withdrawn and he could only work in the Jewish Hospital at Breslau, treating Jewish patients. In 1939 he escaped to England with his family. Unable to practice as a doctor, he obtained a post in Oxford where he worked with G Weddell, P Medawar, E Gutmann, D Whitteridge and JZ Young. In 1944 Guttmann was appointed Resident Medical Officer at Stoke Mandeville Hospital. He made an outstanding contribution in setting up the National Spinal Injury Centre. When Samson Wright brought the physiological society to Oxford and he saw tetraplegic patients standing he was heard to say: thanks to Guttmann that is applied physiology.

CONFLICT OF INTEREST

The author declares that there are no conflicts of interest.

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