

Obituary

Alfred Pletscher

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Alfred Pletscher, one of the pioneers in advancing science-based medicine, died on December 12, 2006 in his 90th year. As long-time director of research at Hoffmann-La Roche, he was instrumental in introducing the first monoamine oxidase (MAO) inhibitor, the benzodiazepines, and levodopa into medicine. The rise of biological therapies for psychiatric disorders and the introduction of an effective treatment for Parkinson's disease in the second half of the last century will always be linked to his name.

Alfred Pletscher studied medicine and chemistry in Geneva, Zurich, and Rome. His lifelong aim was to turn the advances in basic science into clinical reality, an aim that he pursued first at the Science Department of the University Hospital in Basle, Switzerland, and later, beginning in 1955, at Hoffmann-La Roche in Basle, where he held leading positions including that of Director of Corporate Research and member of the Board of Directors (1967–1978). Before taking up his functions at Roche, Pletscher was fortunate in spending a year at the National Institutes of Health (NIH), in the laboratory of Bernard Brodie. He later wrote, 'The time in Brodie's laboratory was one of the highlights of my scientific career'. The creativity of this laboratory was an extraordinarily stimulating experience, surrounded, as he was, by colleagues such as Parkhurst Shore, Sidney Udenfriend, Julius Axelrod, John Burns, Sidney Spector, Herb Weissbach, with Nathan Kline or Arvid Carlsson being among the visitors. Pletscher maintained and cherished friendships with some of them all his life.

Together with Park Shore and Steve Brodie, Pletscher demonstrated that reserpine, an alkaloid used clinically as a tranquillizing and antihypertensive agent, caused a long-lasting depletion of serotonin in the brain, which was thought to reflect its tranquillizing effect. Conversely, he found that the Roche MAO inhibitor iproniazid reversed the effects of reserpine, pointing to a psychostimulant effect of MAO inhibition. These results gave rise to the serotonin hypothesis of antidepressant drug action, which, in modified form, continues to be valid to this day. Iproniazid became the first modern antidepressant in clinical practice.

Back in Basle and inspired by his experience at the NIH Pletscher established Neuropsychopharmacology as a focus of research at Roche, a decision that proved to be visionary. In 1957, as interim director at Roche in Nutley, New Jersey, he selected—together with the head of clinical research, Barney Mattia—several drug candidates for clinical development, among them the compound that later became known as 'Librium', soon to be followed by 'Valium'. The pursuit of 'beautiful chemistry' by Leo Sternbach and astute pharmacology by Lowell Randall had resulted in the discovery of benzodiazepines as a new class of minor tranquillizers, and ushered in the era of the benzodiazepines in medicine. Apart from being clinically effective drugs, benzodiazepines became sophisticated tools in neuroscience. The discovery of the benzodiazepine receptor in 1977 and its association with diverse GABA-A receptors continues to inspire drug development even today.

Another major milestone was Pletscher's role in advancing a revolution in the treatment of Parkinson's disease. In 1960, in Vienna, Ehringer and Hornykiewicz showed that the dopamine content in the striatum was dramatically lower in patients who had died of Parkinson's disease, compared to controls. Birkmeyer and Hornykiewicz, as well as Barbeau and colleagues, went on to treat such patients with intravenous levodopa. At a visit to Roche in 1961, both groups reported almost miraculous results. Although, initially, the effects were difficult to reproduce under oral administration, levodopa, in combination with benserazide, continues to be a pillar of the treatment of Parkinson's disease to this day.

In order to remain at the forefront of research, Pletscher strongly supported the new field of molecular biology and identified immunology as an upcoming growth area. Consequently, he founded the Institute of Molecular Biology in Nutley and the Basle Institute of Immunology, with the latter including three Nobel Prize winners (Niels Jerne, Georges Köhler, and Susumu Tonegawa). At the same time, Pletscher continued his own research on monoamine storage, metabolism, and pharmacology, driven by a formidable energy, which he also exercised as a skier and regular participant in the Engadin ski marathon.

In 1978, Pletscher returned to academia as Professor of Pathophysiology and continued to act as a powerful advocate of basic science in Switzerland, first as founder and head of the Department of Research at the University

Hospital of Basle (1978–1988), then as head of the Swiss National Science Foundation, the main funding organization for Swiss science (1981–1987), and as president of the Swiss Academy of Medical Science (1988–1992). Pletscher's advice was held in high esteem and his commitment to science was honored by the highest award of Swiss science, the Marcel Benoist Prize, and by honorary degrees from multiple European universities. He remained a voice in the politics of science almost to the end of his life.

Alfred Pletscher will be remembered as an engaging and scientifically visionary personality, who never insisted on

ceremony but impressed everybody by his intellectual presence and his lifelong devotion to the cause of science-based medicine. With the death of Alfred Pletscher, Switzerland and the world has lost an eminent scientist.

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