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In Memoriam: Albert Hofmann (1906–2008)

Nathaniel S. Finney* and Jay S. Siegel*

Abstract: Commentary on the life achievements of Albert Hofmann (1906–2008), one of UZH's most honored alumni.

Keywords: Hofmann, Albert

Introduction

The legendary Dr. Albert Hofmann passed away on 29 April, 2008, at the age of 102. Though remembered by most as the 'Father of LSD',[1] his other numerous scientific accomplishments, and personal dimension as a kind and generous scholar paint a vivid picture of the man cited in 2007 as the top living genius.[2]

Fig. 1. Albert and Anita on Rittematte

*Correspondence: Dr. N. S. Finney, Prof Dr. J. S. Siegel
Institute of Organic Chemistry
University of Zurich
Winterthurerstrasse 190
CH-8006 Zurich
Tel: +41 44 635 4281
Fax: +41 44 635 6888
E-mail: finney@oci.uzh.ch

Brief Biography

Albert Hofmann was born in Baden (Aargau) in 1906, the eldest of the four children of a toolmaker. When his father fell ill, Hofmann had to support his family and set aside his formal studies to undertake a commercial apprenticeship. At the same time he continued his pursuit of Latin and other languages, and later completed his Matura at a private school in Zurich, with the support of an anonymous benefactor. He completed his Matura studies at age 20 – just as most students who did not go through a commercial apprenticeship. In 1926 he started to study chemistry with Prof. Paul Karrer at the University of Zurich, where he earned his PhD with distinction after only four years (Fig. 2). In 1929 he took a job with Sandoz Laboratories in Basel, where he stayed for more the four decades, retiring in 1971 as then head of the department for natural medicines.

Over the course of his career, Hofmann authored more than 100 scientific articles and a number of books. After his retirement he was increasingly recognized for his pioneering work, and received several honorary doctorates (ETH Zurich, Stockholm University, Berlin Free University).

Graduate Research at the University of Zurich

Hofmann began his PhD studies in chemistry directly after completing his Matura, without an intermediate University degree, following an educational path no longer possible today but not uncommon at the time. His graduate research with Professor Paul Karrer was remarkable in several respects.

First, Hofmann's thesis, 'On the Enzymatic Degradation of Chitin and Chitosan', describes one of the first preparations of chitinase, an enzyme that very efficiently degrades chitin (β-1,4-poly-*N*-acetylglucosamine): the crude extracts of a common snail (*Helix pomatia*), collected during Hofmann's walks on the Weinberg, near the University campus, contain a high level of chitinase activity[3] (Fig. 3). Using the enzyme as a tool, Hofmann conclusively demonstrated that chitin is, indeed, a polymer of *N*-acetylglucosamine. The use of snail digestive enzymes for chitin degradation remains a common biochemical tool to this day (although the units of activity are no longer measured by the number of snails used).[5]

Second, through a combination of acidic and enzymatic degradation, Hofmann was also able to show that chitosan (partially deacylated chitin) is a polymer containing both glucosamine and *N*-acetylglucosamine (Fig. 4). While we take these structures for granted, and both chitin and chitosan have widespread medicinal use, these structures were a matter of great interest and debate at the time of Hofmann's work – resolved, in part, through his early contributions.

Finally, this work was completed with only a few months of experimentation – a level of productivity remarkable by any standard.

All Was not LSD – Hofmann's 'Other' Research at Sandoz

Hofmann's professional career continued with his acceptance of a position at Sandoz, in Basel, to which he was particularly attracted because it provided him an opportunity to continue his studies of biologically active molecules of natural origin. His earliest work at Sandoz focused on determining the structure of cardiotonic glycosides from Mediterranean Squill, a flowering plant native to Southern Europe and the Middle East. While the structure of the carbohydrate portion of the active component had been established, Hofmann was

Fig. 2. Professor Paul Karrer's group in 1928 with Albert Hofmann fourth from the left.

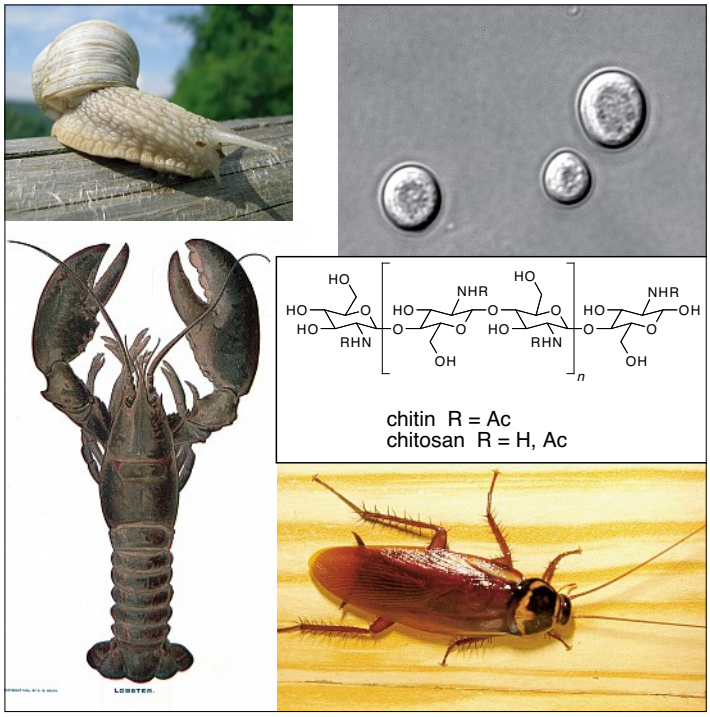

Fig. 3. Natural sources of chitin: 'Weinberg snail' (*Helix pomatia*), baker's yeast (*Saccharomyces cerevisiae*), cockroach (*Periplaneta americana*), and American lobster (*Homar americanus*). These organisms are united by the presence of chitin as an integral structural component; the snail contains chitin in its mandible,[4] as well as a generous supply of the chitin-degrading enzyme chitinase in its gut.

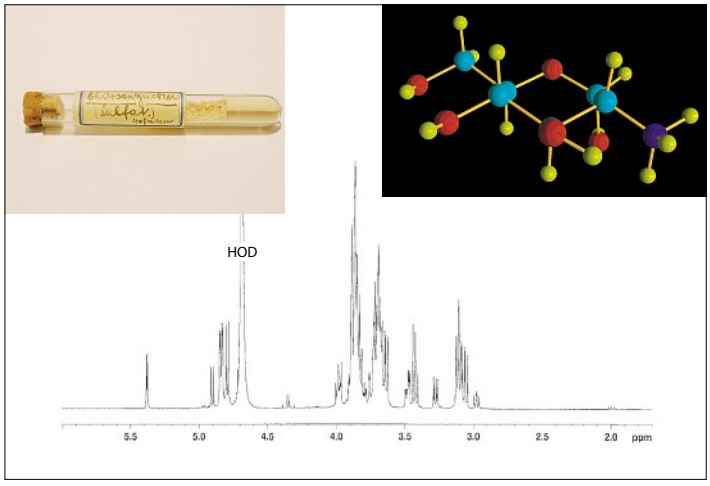

Fig. 4. ^{1}H NMR spectrum (D_2O) of a sample preserved in the archives of the Organic Chemistry Institute from Hofmann's 1929 graduate work. The material, labeled as 'Chitosanzucker, sulfat' is tentatively assigned as a mixture of mono-, di-, and trisaccharides of glucosamine (hydrogen sulfate salts).

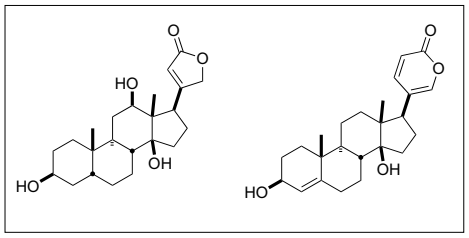

Fig. 5. The aglycones of *Digitalis* and *Scilla* cardiac glycosides

able to demonstrate that the core aglycone was closely related to the toxins isolated from the skin of toads (Fig. 5), and thus similar to but distinct from the aglycone of the *Digitalis* cardiac glycosides (on which he also worked).[6]

Hofmann's important work on the ergot alkaloids, and the semisynthesis of new pharmacophores such as LSD, has been described and discussed in detail (Fig. 6).[7] Overshadowed by the stature of LSD itself, however, is the fact that the ergot alkaloids inspired Hofmann (and many others) to explore the medicinal chemistry of other ergot-related structures (Fig. 7). Perhaps even more important, the study of the ergot alkaloids motivated chemists to evaluate much simpler indole-containing compounds. Based in part on the structural homology between LSD, psilocybin (also first characterized by Hofmann *et al.*) and serotonin, numerous new medicaments were developed, both at Sandoz and elsewhere (Fig. 8).

Gentleman & Scholar in Private Life

Many of Hofmann's achievements in ethnopharmacology were conducted as private endeavors. For example, his trip to Mexico to investigate the active agent in Ololiuhqui occurred on his own personal time and not as part of his Sandoz-based research. Others had tried to isolate active fractions but had always failed. Hofmann recognized that normal animal models would not be capable of leading researchers to active substances because the effect was based in the human psyche, which was not shared with other organisms. Only through his unparalleled expertise in organic chemistry and his intense passion for understanding the chemical basis for cognition could such fundamental problems of the molecular basis of psychoactivity be unlocked.[8]

Sorrowfully, much focus is placed on the activities surrounding the abuse of LSD. Hofmann's work constitutes a serious advance in our ability to probe and understand the meanings and operations of cognitive processes. Hofmann always emphasized that the importance of LSD is not as a recreational drug but as a poten-

Fig. 6. *Secale cornutum* on ear of rye and ergotamine (1), the first chemically pure ergot peptide alkaloid. (From ref. [7], R. K. A. Giger, G. Engel, *Chimia* **2006**, *60*, 83, used with permission.)

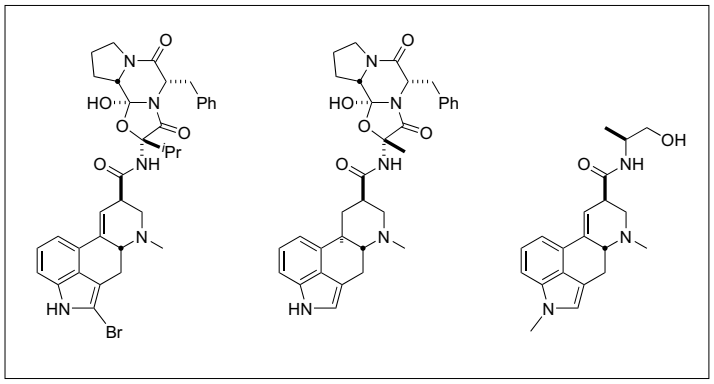

Fig. 7. Other biologically active ergot derivatives, with representative therapeutic indications: left to right, bromocriptine (Parkinson's), dihydroergotamine (vascular headaches), methylsergicide (migraine).

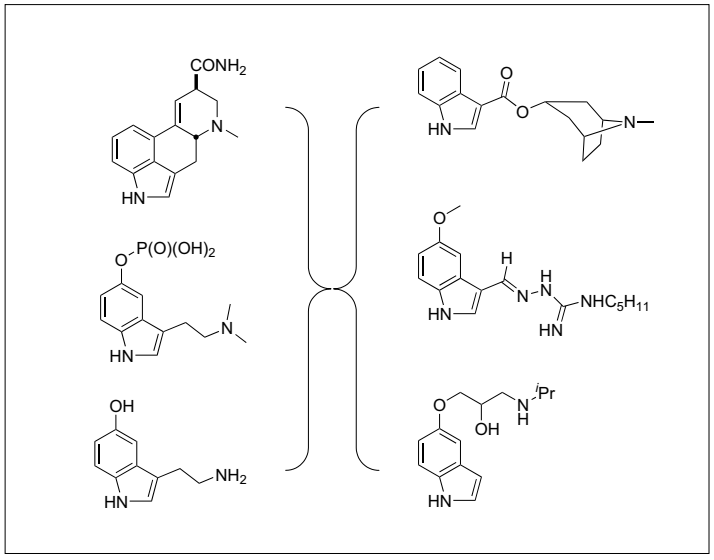

Fig. 8. Therapeutic substances inspired by ergotamine, psilocybin and serotonin: tropisetron, tegaserod and pindolol.

Fig. 9. After baking Zwetschgenwähe at Rittematte (Left to right: Baldridge, Hofmann, and Siegel)

Fig. 10. After the Centennial Lectures at UZH (Left to right: Hofmann, Siegel, Baldridge, and Finney)

tial tool for understanding the human mind and its functions. He often wished that the cult component had not dominated LSD's image as it was that cult character which induced a ban on the sorely needed research studies. Such studies could still have a great impact on our understanding of the highest level of neurochemical activity.

Hofmann's discoveries revolutionized our perspective on how chemicals affect cognitive function, which in turn opened new vistas for cognitive and psychological sciences in general. In 2006, Hofmann received national thanks for his achievements from Bundespräsident Leuenberger, who cited him as the greatest researcher of the human psyche.[9]

It was always a pleasure to visit Hofmann at home in Rittematte (Fig. 9). He and his wife Anita welcomed visitors regularly. He was an uncomplicated and open host with whom one could share a glass of his homemade schnapps, or even collect fruit from his orchard and bake fresh 'Zwetschgenwähe' (Swiss plum tart). He enjoyed playing with each moment of life, in that he truly valued the special many-faceted character of human sentience.

Hofmann remains an honored alumnus of UZH, and spoke fondly of his time at UZH with Karrer. In 2006 he became 100 years old and many events took place worldwide to mark the occasion.[10–12] The OCI of UZH organized a symposium of three Centennial Lectures in honor of his 100th birthday (Fig. 10).[11,12] Hofmann played an active role in the selection of topics and speakers. At that symposium he posed difficult questions and offered critical commentary worthy of any scholar in their prime. When we founded the Hofmann Centennial Medal one year later, Hofmann endorsed strongly Princess Chulabhorn Mahidol as the first recipient. The Centennial Medal lectures will live on as an annual memoriam of Hofmann and his lifelong contribution to chemistry.[13]

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[12] For details about the symposium see: *http://www.oci.unizh.ch/diversa/hofmannSymposium/A_Hofmann.html*
[13] Friends wishing to sponsor scholarly activities in Albert's memory should contact the Institute of Organic Chemistry at *hofmann.fund@oci.uzh.ch*