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Review Article

Hartmann Stahelin (1925–2011) and the contested history of cyclosporin A

Cheng M. Hartmann Stahelin (1925–2011) and the contested history of cyclosporin A.

Abstract: The aims of this study are twofold: (i) to pay tribute to Hartmann Stahelin for his scientific research on cyclosporin A; and (ii) to consider possible lessons for future pharmacological innovation by revisiting Stahelin's personal struggles to obtain fair recognition for his contribution to transplantation medicine.

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A defining characteristic of cyclosporin A is its potent ability to constrain the activity of the immune system.[1] Cyclosporin is a metabolite derived from the fungus, *Tolypocladium inflatum Gams*. It is the active agent in the immunosuppressant drugs, Sandimmune® and Neoral®, both manufactured by Sandoz Pharmaceutical Corporation (1–3).[2] Due to promising data from initial animal experiments, cyclosporin was embraced by the transplantation community with enthusiasm and eager anticipation. As Fox and Swazey noted, "hundreds of medical journal articles described it as the most "important," "unique," "interesting," "remarkable," "exciting," "powerful," "effective," "superior," agent yet discovered in the effort to combat rejection" (4). Indeed, cyclosporin was even referred to as "the penicillin of transplantation" (5). Compared to earlier immunosuppressive drugs, cyclosporin demonstrated a greater capacity to overcome acute graft rejection and improve patient survival in the short to medium term.

While regulatory approval for clinical use was issued by the Food and Drug Administration in 1983, a sophisticated scientific understanding of cyclosporin required further research and long-term clinical study. As physicians have come to appreciate, cyclosporin is not a drug without side effects. Its primary drawbacks include renal impairment and chronic rejection. Thus, cyclosporin is generally prescribed as part of a multidrug regime to achieve a synergistic therapy with lower toxicity. Notwithstanding its limitations, the clinical application of cyclosporin was a "watershed" in the field of transplantation medicine (6). The significance of this metabolite is explained by Cooper and Lanza as follows:

> From the perspective of the patient and the transplantation surgeon, however, cyclosporine is worth every penny of its cost. Its introduction was a quantum leap in the care of organ transplant patients, and for many, it has made the difference between life and death. (7).

A key figure in the cyclosporin story is Hartmann Stahelin. He was born on October 20, 1925 in Walenstadtberg, Switzerland. Following in the footsteps of both his parents, Stahelin studied medicine in Basel, Zurich, and Florence. Upon graduation, he conducted research on *anthrax bacilli* at the Institute of Microbiology, Basel University. In 1954, he was awarded a postdoctoral fellowship by the Swiss National Foundation

to investigate *phagocytosis* in the Department of Bacteriology and Immunology at Harvard Medical School. While working as a postdoc, Stahelin was recruited by Sandoz to join their pharmacology laboratory in Basel. He was appointed to lead a research working group on cancer and immunology.

By the late 1950s, Sandoz had commenced its work on identifying fungal metabolites as possible new pharmaceutical drugs. One of their corporate priorities was to search for immunosuppressive agents without major cytotoxicity. The company initiated a "General Screening Program" in the early 1970s (8). Stahelin contributed to this program by devising a novel screening procedure, which facilitated dual testing for anti-cancer activity and immunosuppression. In collaboration with his colleague, Sandor Lazary, Stahelin confirmed that only one laboratory mouse was necessary to effectively perform the two tests (8). The screening program assessed approximately 20 samples each week.

In December 1971, Sandoz employees applied the usual screening procedure to a sample numbered 24-556. This preparation was derived from soil samples collected by an employee while on holiday in Norway. The test results for 24-556 were first documented by a laboratory assistant on January 31, 1972 and forward to Stahelin for review (8). Through the analysis of the screening program, 24-556 demonstrated an unusually high level of immune-suppression. In the following year, the sample was purified and its chemical structure ascertained. The chief compound in 24-556 was subsequently "baptised cyclosporin A" as it was a cyclical peptide derived from spores (8). Following further clinical studies, Stahelin and his colleagues reported their scientific findings on cyclosporin in academic journals in 1976 (9, 10). Since these publications, cyclosporin has been the focus of many laboratory studies and clinical investigations. The accumulated body of knowledge on this metabolite has substantially enhanced our scientific understanding of the immune system and facilitated the development of new immunosuppressants including tacrolimus or FK-506.

Given the importance of effective immunosuppression for organ allograft, it is not surprising that scientific research on cyclosporin was marred by public controversy. Due recognition for the discovery of the immunosuppressive effects of cyclosporin became a critical point of contestation between Stahelin and his supervisee, Jean Borel. Shortly after commencing work at Sandoz, Borel assumed the position of head of the Immunology Laboratory. According to Heusler and Pletscher, "Borel carried the main responsibility for the characterisation of the immunological properties of cyclosporin. He could, however, base his work on methods previously used by Lazary and Stahelin" (11). Subsequently, Borel received numerous scientific awards, prize monies as well as honorary degrees from two Swiss universities for his work on cyclosporin.

In response to public statements and acceptance speeches made by Borel (12), Stahelin presented "another point of view" regarding the scientific research conducted on cyclosporin at Sandoz. His claim for public recognition took the form of a review article, which was published in the journal, *Experentia,* in 1996 (8). This article included statements acknowledging the contribution of other scientists. "Many persons have, of course, contributed to CsA, some of them directly, others more indirectly", wrote Stahelin (8). In the following year, tensions between Borel and Stahelin were further complicated when Flowers and Melmon published an article in *Nature Medicine* arguing for the recognition of Roy Calne and David White as "clinical champions" in the development of cyclosporin (13, 14). The dispute between the two Sandoz employees was not resolved until an independent inquiry was commissioned. The inquiry took place after Sandoz merged with Ciba-Geigy to form Norvatis International.

In 2000, upon the suggestion of the Swiss Academy of Medical Science (SAMS), Novartis appointed two senior scientists to conduct the inquiry: Karl Heusler and Alfred Pletscher.[3] Apart from scientific papers and other public documents, Heusler and Pletscher examined company files and interviewed former Sandoz employees who may or may not have been involved with the scientific research on cyclosporin. They published their report in June 2001 in the *Swiss Medical Weekly* (11). The report clearly articulated and acknowledged the scientific work of both Stahelin and Borel. Moreover, it also duly recognised the contribution of other scientists working in Sandoz.

> The discovery of cyclosporin occurred in the course of a general screening programme, which included a large team of scientists, including microbiologists, chemists, biologists and pharmacologists.… in our opinion, based on the available documented evidence, both Borel and Stahelin played instrumental roles in the discovery of the biological effects of cyclosporin, the contribution of Stahelin at least equally relevant as that of Borel. However, as the discovery was made in the course of an established screening

programme with clearly defined aims, earlier inputs from other scientists were also important (11).

Public controversy concerning cyclosporin, within and outside of Switzerland, demonstrate the critical importance of according due recognition for scientific merit and contribution throughout the complex process of drug discovery and development. Yet, the prevailing structure for scientific recognition and rewards fail to adequately take account of the contributions of scientists working in collaborative teams. This is clearly evidenced by the numerous awards issued for research on cyclosporin. Thus far, Borel has received at least eleven awards including the prestigious Prix de la Sante issued by the Artois-Baillet Latour Foundation in 1993.[4] By contrast, only one award was given to Stahelin, namely, the Pascoe Research Prize for Natural Medicine (2003).[5] Notably, all twelve awards named only one individual. Such awards suggest that independence is the necessary and determining criterion for public recognition in biomedical science. As Goldstein and Brown observed, "… somehow, we believe that a scientist can achieve greatness only if he or she produces a body of work in an independent fashion" (15). To the contrary, the story of cyclosporin clearly illustrates that successful biomedical research requires a complex network of actors endowed with a diverse set of skills and expertise, including the ability to work within and across different disciplines, institutions, and jurisdictions.

The report prepared by Heusler and Pletscher was accompanied by an editorial prepared by Ewald R Weibel, Emeritus Professor of Anatomy at Berne University (16). Weibel posed the question of "What lessons can be drawn from all this?" After articulating the need to strictly observe "the principle of fair sharing of responsibility and recognition," he concluded that "there is no harm and no loss of prestige in acknowledging partnership in a research project: otherwise honesty is at risk" (16). He also conceded that the cyclosporin controversy was "highly damaging to both the scientists and the entire research enterprise" (16).

Perhaps another question which the scientific community might consider is how can future collaborations be encouraged and administered such that scientists are not compelled to contest claims for public recognition to defend their professional reputation? In other words, how can the scientific community take responsibility to address the existing norms that contributed to the cyclosporin controversy? Clearly, ethical collaborative practices could be fostered through research training and incorporated into the promotion system in the academy and private industry. The process of issuing awards can also be modified to recognise and reward teamwork and not just individual achievements. Notably, Stahelin and his colleague, Albert von Wartburg, were joint winners of the Bruce F Cain Memorial Award in 1990. This accolade is made by the American Association for Cancer Research to honor "outstanding preclinical research in the fields of medicinal chemistry, biochemistry or tumour biology, related to drug discovery" (17).

More recently, the Norwegian Nobel Committee has adopted an expansive interpretation of its remit by recognising the importance of scientific work for the promotion of global welfare and security. While the Nobel Prize in Physiology or Medicine is limited to a maximum of three recipients, the Nobel Peace Prize may be awarded to individuals and/or organisations. For example, in 2007, the Peace Prize was jointly awarded to Al Gore and the UN Intergovernmental Panel on Climate Change for "their efforts to build up and disseminate knowledge about man-made climate change, and to lay the foundations for the measures that are needed to counteract such change" (18). Similarly to the public announcement of this award in previous and subsequent years, the 2007 Peace Prize generated considerable public discussion and debate in the media around the world. Regardless of what views one may hold on the selection processes and the merits of the recipients, it is clear that simultaneously acknowledging individual and group contributions is a sensible approach in the context of promoting a common good for the benefit of the global community.

Last year marked the 40th anniversary of the date upon which Stahelin first observed the immunosuppressive effects of cyclosporin. It was also the year he passed away. Stahelin was 85 yr old. He is survived by his wife, two daughters, two sons, and 11 grandchildren. The recent anniversary year affords an opportunity to pay tribute to Stahelin and to many other individuals who participated in the discovery and development of cyclosporin and, in the process, contributed to the establishment of transplantation medicine.

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Notes

[1]Cyclosporin A is also referred to as cyclosporin, cyclosporine, cyclosporine, and cyclosporin. Hereafter, the latter term will be used.

[2]In 1996, Sandoz merged with Ciba-Geigy to form Novartis International AG. Apart from organ transplantation, cyclosporin is also used to treat other conditions including psoriasis and rheumatoid arthritis. Sandimmune and Neoral consist of different formulations of cyclosporin. The scientific properties of cyclosporin were initially documented and characterised by three teams of Sandoz employees.

[3]Karl Heusler is a former Director of Pharmaceutical Research and Development at Ciba-Geigy, and Alfred Pletscher is a former Head of Research at Hoffmann-La Roche and former President of the Research Council of the Swiss National Science Foundation.

[4]The prizes awarded to Borel include the Max Cloetta Prize (Zurich, 1984), Friedrich Sasse Prize (Berlin, 1984), J. Allyn Taylor International Prize of Medicine (London, Ontario, 1985), Gairdner Foundation International Award (Toronto, 1986), Paul Ehrlich and Ludwig Darmstädter Prize (Frankfurt am Main, 1987), Ciba-Geigy Drew Award in Biomedical Research (Madison, New Jersey, 1987), Pharmacia-ASPET Award for Experimental Therapeutics (Las Vegas, 1988), Discoverer's Award of the Pharmaceutical Manufacturers Association (Washington, 1988), Gift of Life Award of the National Kidney Foundation of Illinois (Chicago, 1988), American Liver Foundation Distinguished Humanitarian Award (New York, 1988), and the "Prix de la Santé" of the Artois-Baillet Latour Foundation (Brussels, 1993).

[5]In April 2003, Stahelin received the Pascoe Research Prize for Natural Medicine at the German Meeting of Internal Medicine in Wiesbaden. The prize is awarded for "outstanding scientists in the field of evidenced-based application of natural agents."

References

1. Dreyfuss M, Harri E, Hofmann H, Kobel H, Pache W, Tscherter H. Cyclosporin A and C: new metabolites from *Trichoderma polysporum* (Link ex Pers) Rifai. Eur J Appl Microbiol 1976: 3: 125.
2. Ruegger A, Kuhn M, Lichti H et al. Cyclosporin A, ein immunsuppressiv wirksamer Peptidmetabolit aus *Trichoderma polysporum* (Link ex Pers.) Rifai. Helv Chim Acta 1976: 59: 1075.
3. Petcher TJ, Weber HP, Ruegger A. Crystal and molecular structure of an iodo-derivative of the cyclic undecapeptide cyclosporin A. Helv Chim Acta 1976: 59: 1480.
4. Fox RC, Swazey JP. Spare Parts: Organ Replacement in American Society. Oxford: Oxford University Press, 1992: 3.
5. Editoral. Lung transplant surgeon seeks donors. The Nevada Herald Sun, 1982: 6.
6. Calne R. Cyclosporine as a milestone in immunosuppression. Transplant Proc 2004: 36(Suppl 2S): 15S.
7. Cooper DKC, Lanza RP. Xeno: The Promise of Transplanting Animal Organs into Humans. Oxford, UK: Oxford University Press, 2000: 238.
8. Stahelin HF. The history of cyclosporin A (Sandimmun®) revisited: another point of view. Experientia 1996: 52: 5.
9. Borel JF, Tuegger A, Stahelin H. Cyclosporin A: a new antilymphocytic agent (abstract). Experientia 1976: 32: 777.
10. Borel JF, Feurer C, Gubler HU, Stahelin HF. Biological effects of cyclosporin A: a new antilymphatic agent. Agents Actions 1976: 6: 458.
11. Heusler K, Pletscher A. The controversial early history of cyclosporin. Swiss Med Wkly 2001: 131: 299.
12. Borel JF. The history of cyclosporin A and its significance. In: White DJG, ed. Cyclosporin A: Proceedings of an International Conference on Cyclosporin A. Amsterdam: Elsevier, 1982: 5.
13. Flowers CR, Melmon KL. Clinical investigators as critical determinants in pharmaceutical innovation. Nat Med 1997: 3: 136.
14. Stahelin HF, Flowers CR, Melmon KL. Cyclosporin and the clinical investigator (Letters to the editor). Nat Med 1997: 3: 590.
15. Goldstein JL, Brown MS. The clinical investigator: bewitched, bothered, and bewildered – but still beloved. J Clin Invest 1997: 99: 2803.
16. Weibel ER. Who did what? The human side of the science enterprise. Swiss Med Wkly 2001: 131: 289.
17. AACR-Bruce F. Cain Memorial Award [Internet]. Philadelphia, PA: American Association for Cancer Research [Updated 2012 August 7; cited 2012 August 13]. Available from: http://www.aacr.org/home/scientists/scientific-achievement-awards/aacr-cain-award.aspx
18. The Nobel Peace Prize 2007 [Internet]. Oslo, Norway: The Official Web Site of the Nobel Prize [Updated 2012 June 28; cited 2012 August 14]. Available from: http://www.nobelprize.org/nobel_prizes/peace/laureates/2007/