FROM NATURAL PRODUCTS TO CURATIVES:
Refrections on Arnold Brossi's career and contributions

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Arnold Brossi, Scientist Emeritus of the National Institutes of Health and Visiting Research Professor at Georgetown University of Washington, D.C., recently completed 70 years of his life and half century of creative research, an occasion which his friends celebrated in a special "MONA SYMPOSIUM" at the University of the West Indies, Jamaica, January 3 - 7, 1994.

Life's journey is not long in the companionship of a good friend: this was pointed out by his many firends present at this testimonial and again in this issue of "HETERO-CYCLES", the "Fest-Schrift" published in his honor.

"Life is a festival, but only to the wise", this insight comes to mind when we view Arnold's past years as a felicitous blend of hard work and unforgettable conviviality. The select group of friends and colleagues at the biannual Summer Symposium in Laax, Grison (Switzerland) remeber these moments of work and leisure as "IKKOKU SEN KIN " ("each instant worth a thousand gold pieces"). Reservoirs of international goodwill and cooperation were created by these symposia resultng in collaboratgive ventures that became a hallmark of Arnold's *modus operandi.*

His love for chemistry, according to testimony of his wife Hanni and his mother, started early during high-school years in a make-shift lab, installed in the backyard's chicken house. Steins and stenches caused adverse publicity with family and neighbors, a predicament that was relieved when Arnold left for the ETH, the Federal Technical Highschool in Zurich in 1946. His mentor Oskar Jeger guided his thesis work and, in conjunction with Professor Placidus Plattner kindled his enthusiasm for natural products, initially di- and tri-terpenes[1-5]. In 1952 Arnold left academy for *industry, viz. Hoffmann-La Roche, first in Basel then at Nutley, New Jersey, where in a* productive career spanning 23 years (1952 - 1975) numerous patents (Table I) testify to his skills in developing drugs from traditional medicinal plants.

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His gift for ready invention was further amplified during his fruitful career at the National Institutes of Health (1975 - 1992) when the US-patents listed in Table I were issued to him as inventor or co-inventor.

Brossi's great achievement is his reliance on the great Zürich tradition for natural products in carrying it forward to the frontier of modern medicine, so that progress is based on tradition not only preserved but revitalized. His research reminds us all that the plant kingdom must still hold in reserve many potential drugs that are awaiting discovery. Long before chirality emerged as a key issue in pharmaceutical research [cf. Stu Borman, *Chemical & Engineering News,* July 9, p. 10 (1990)] and led to a wave of new enantiomeric chiral drugs [cf. *Chemical & Engineering News,* September 27, p. 38 - 65 (1993)]. Arnold Brossi preached his gospel for chiral purity and became a pioneer for chirotechnology by the conversion of academic asymmetric syntheses and resolutions of racemates into procedures that are commercially feasible. He joined an animated discussion with Ernest Eliel [cf. *Chemical & Engineering News*, July 22 (1991) whether a chiral compound is racemic or "aracemic","eutomeric" or "distomeric" by preferring the terms "enantio-enriched" and "enantio-pure".

Brossi's contributions to medicinal agents, ranging from amebicides and antimalarials to antidepressants and potential curatives for cognitive disorders, such as Alzheimer disease, are summarized in Table II, his major research activities in Table III.

His lifelong attachment to alkaloids deserves special mention and consideration, because he not only preserved and continued a great tradition as Editor of "THE ALKALOIDS", Volume 21-40, but breathed new life into old structures: Table IV.

When 6-hydroxydopamine was suspected as a possibly endogenous biogenic amine damaging adrenergic nerve terminals, Brossi synthesized the parent amino acid (Table V) which many years later surfaced as a new natural amino acid at the active site of bovine serum amine oxidase [*Science*, **248**, 981 - 987 (1990)].

Antimalarials, Table VI, deserve special mention, because his arteether, a modification of artemisinin from Artemisia annua or sweet wormwood, is effective against chloroquine-resistant Plasmodium falciparum. As a Member of the Steering Committee of Malaria Chemotherapy of the World Health Organization from 1978 - 1989 he helped in the clinical development of arteether and mefloquine.

Several major research accomplishments were summarized by him in review articles: Colchicinoids [*The Alkaloids* , 23, 1-70, **1984** and *ibid.*, 41, 125-172, **1992**]; Physostigmine [351, 369]; Mammalian Alkaloids [362, *The Alkaloids,* 43, 119 -183, **1993**].

Brossi was editor-in-chief of *Org. Synthesis* Vol. 53 and is now on its Advisory Board.

As is already mentioned, he was from 1983 - 1991 editor-in-chief of The Alkaloids and has Volumes 21 -40 to his crtedit, sharing with G. A. Cordell co-editorship for Volumes 41 and 44 (in press). Under Brossi the term alkaloid was used more lucidly, allowing him to include nitrogen-containing substances from marine organisms and from mammals. He insisted that biological data when available be reported. Brossi, for keeping this book series alive, was in 1991 awarded Honorary Membership in the American Society of Pharmacognosy. He was from 1978 - 1989 a member of the Steering Committee of Malaria Chemotherapy at WHO, Geneva, and the development of mefloquine and arteether was greatly facilitated by his presence.

Besides having benefited during his NIH tenure from the good work of 42 postdocs coming from 17 different countries, Brossi maintained an active collaboration with the following scientists:

Colin F. Chignell, Laboratory of Molecular Biophysics, Natioanl Institute of Environmental Health Sciences, Research Triangle Park, NC (cochicine);

Charles D. Hufford, School of Pharmacy, University of Mississippi, Oxford, MS (*morphinans and colchicine*); Creed W. Abell, *School of Pharmacy*, University of Texas at Austin, TX (MPTP and isoquinoline alkaloids); Ernest Hamel, National Cancer Institute, NIH, Bethesda, MD (perhydrohistrionicotoxin and physostigmine);

Philippe Gros, Department of Biochemistry, McGill University, Montreal, Quebec, Canada (colchicine); H. Thomas, Univeristy of Ulm, Department of Physiology, Ulm, Germany (mammalian alkaloids); J. L. Flippen-Anderson, Laboratory of the Structure of Matter, Naval Research Institute, Washington DC. (X-raying alkaloidal substances);

Jiaxiang Shen, Beijing Unipharm Laboratories Beijing, China (physostigmine); and Qiansheng Yu, Shanghai Institute of Organic Chemistry, Shanghai, China (physostigmine).

For many years Brossi kept in close touch with Bernhard Witkop (Institute Scholar, NIH), and Nelson J. Leonard (*Visiting Professor, Department of Chemistry and Chemical* Engineering, Caltech) and - in his own words - his work has greatly benefited from their advice and counsel.

While the artist's communication is linked forever with its original form, that of the scientist is modified, amplified and fused with the ideas and results of others and melts into the stream of knowledge and ideas which contribute to man's benefit and progress. The first forty years in a man's life form the text; the next thirty years are commentary. At age seventy our friend Arnold is a well-commented text with room for expansion in many promising directions.

TABLE I PATENTS

Brossi is named as an inventor and co-inventor on many patents which were issued during his association with Hoffmann-La Roche (1952 - 1975) [8, 9, 12, 16, 18, 19, 21, 22, 26, 30, 32, 48, 50, 53, 66, 76, 90, 97, 108, 109, 116, 117, 118].
The following US-patents bearing his name as an inventor or co-inventor have been issued during his tenure at NIH:

4,388,463	June 14, 1983	6-ketomorphinan analgesics
4,390,699	June 28, 1983	6-ketomorphinans belonging to the 14-hydroxy-series
4,533,675	August 6, 1985	carbamates of colchicine for the treatment of gout
4,552,962	November 12, 1985	antitussive 6-ketomorphinans of the (+)-series
4,692,463	September 8, 1987	antiinflammatory 2,3-di-demethyl-cochicine derivatives
4,900,748	February 13, 1990	carbamates related to (-)-physostigmine as cholinergic agents
5,039,801	August 13, 1991	thermal fragmentation of methyl-benzylurea diastereomers of secondary amines and preparation of optically active secondary amines
5,175,342	December 29, 1992	esters of 3-demethylthiocolchicine and N-acyl analogs
5,171,750	December 15, 1992	substituted phenserine as specific inhibitors of acetylcholinesterase

TABLE II CONTRIBUTIONS TO MEDICALLY USED DRUGS

TETRABENAZINE(Antidepressant):*Merck Index 11th ed.* 9118 (1989) [11,20,25, 37,55, 57,65,70]
IPRONIDAZOLE(Histomonastat):*Merck Index 11th ed.* 4966 (1989) [126]
ASTIBAN AND 2,3-DIMERCAPTOSUCCINIC ACID (Schistosomiasis):*Merck Index 11ed.*, 8788 (1989) [33]

VERSIDYNE = METHOPHOLINE*(Analgesic):*Merck Index 8th ed.*, 676 (1968) 31,36,40, 45,56,64,336]
MEFLOQUINE(Antimalaria):*Merck Index 11th ed.* 5683 (1989) [195,369]
DEHYDROEMETINE(Amebicide): *Merck Index 11th ed.*, 2860 (1989) [29,34,42, 44,49,95]
TRIMETHOPRIM(Antibacterial):*Merck Index 11th ed.*, 9624 (1989) [113,125,221]
ARTEETHER(Antimalarial)**:[243,244,303,307,325,354]
PHENESERINE(Cognitive Disorders)***[305,313,329,374]

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* The introduction of Versidyne, a combination of methopholine with aspirin, was stopped because of unexpected toxicity seen in dogs, but later found not to be drug related.

** Arteether, an analog of artemether which is used in China as an antimalarial drug, is presently undergoing clinical trials.

*** Phenserine, the most effective agent to treat cognitive disorders, is scheduled for chronic toxicity.

TABLE III MAJOR RESEARCH ACTIVITIES

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1. GRISEOFULVIN [24,35,38,41,43,51]
This work includes the first total synthesis of natural (+)- and unnatural (-)-griseofulvin [41], showing that the unnatural enantiomer was practically devoid of antifungal properties.

2. EMETINE/DEHYDROEMETINE [27,28,29,34,39,42,44,49,69,71,387]
This work culminated in another total synthesis of natural emetine and its unnatural enantiomer [27]. Enantio-selectivity of the amebicidal action was reported [387]. Dehydroemetine was introduced as an amebicide [34]. This also included the synthesis and chemical exploitation of 2-oxo-hexahydrobenzo[a]quinolizidines. [1,20,25,55,57,65,37,70]

3. MAMMALIAN ALKALOIDS [131,146,139,147,151,183,207,232,279,294,316, 344, 362,381,388,389].
This work includes the first synthesis of optically active 1-methyl- and 1-benzyl-6,7-dihydroxytetrahydro-isoquinoline-1-carboxylic acids [294], and signaled that norreticuline could be a precursor of mammalian morphine [381].

4. MORPHINANS AND MORPHINE-ALKALOIDS [6,7,3,14,15,104,153,156,159, 160,165,166,167,176,181,186,193,198,200,201,203,206,209,210,213,215,216,217, 219,220,222,282,231,249].

This work includes an improved synthesis of unnatural (+)-morphine [159], a synthesis of 3-deoxymorphine and dihydro-congeners [167], a total synthesis of (±)-4-hydroxy-N-methylmorphinan-6-one [217], (-)-2-hydroxy-N-methyl-morphinan-6-one [216], (-)-1-hydroxy-N-methyl-morphinan-6-one [222], and a total synthesis of (±)-3-deoxydihydro-morphine [231].

5. COLCHICINOIDS AND THIO-CONGENERS [162,171,180,182,190,191,192, 196,199,226,229,230,245,256,261,262,269,276,283,285,289,298,304,334,339,324, 322,341,345,350,351,356,358,367,368,369,371,372,326,339,377,378,382,386,255].

This work includes a revision of the structures of epoxycolchicine [182], and that of cornigerine [199]. It also includes a simple conversion of colchicine into demecolcine [172], a synthesis of colchifoline [192] and improved procedures to prepare 2- and 3-demethylcolchicine [196], and of unnatural (+)-cochicine [196,276] and of colchicide [285]. The crucial importance of the an S-absolute configuration for binding of cochicinoids to tublin was recognized [304,345,271]. Chloroacetates of 2- and 3-demethylthiocolchicine bind covalently to the beta-subunit of tublin [378, 382].

An intact phenyltropolone backbone and an amino or amide group at C-7 were recognized as important for interaction with *p*-glycoprotein implicated in muti-drug resistance [386].

6. PERHYDROHISTRIONICOTOXINS [205,211,233,242,248,315].

This work includes a total synthesis of (-)-perhydrohistrionicotoxin and its unnatural (+)-enantiomer [205], and dealkylated analogs of the (±)-series [248,315].

7. 1-METHYL-4-PHENYL-1,2,3,6-TETRAHYDROPYRIDINE (MPTP) [240,246, 247,253,254,258,259,268,270,272,273,274,287,292,317,266].

This work includes the synthesis of $MPDP^+$, a reactive intermediate in the oxidation of MPTP [266], and the disproportionation of $MTDP^+$ into MPP^+ and MPTP at physiological pH [253], and X-ray analysis of MTPT [266].

8. PHYSOSTIGMINE, CARBAMATE ANALOGUES AND RING C-HETERO-CONGENERS [275,277,280,293,305,311,313,314,319,323,328,329,343,351,374, 375,379,380,383,385].

This work includes a novel route to optically active amines by fragmentation of urea precursors in high boiling alcohols [277]. The morphine-like activity of (-)-eseroline was substantiated [280]. An easy conversion of physostigmine into (-)-eseroline was reported [293] and the structure of genserine was clarified [328]. A simple synthesis of natural physovenine was reported [343,361]. Phenylcarbamate analogs of physostigmine were recognized as valuable agents to treat cognitive disorders [374, 375].

TABLE IV ALKALOIDS*

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1. *SIMPLE ISOQUINOLINE ALKALOIDS*

Isoquinoline Cactus alkaloids [52,54,58,60,102,124]; petaline[72,80,119]; (±)-korpaverine [79]; cherylline [94,99,107];corypalline [100]; demethylpapaverines[106]; precursors of multi- floramines[89]; bicuculline [132]; 8-methylcorypalline[130]; laudanosoline [137, 183, J. Med. Chem., 15, 845, 1972 not listed]; salsoline and isosalsoline[139]; reticulines [91,178,214,238,384]; cryptostylines[121]; rhoeadine[122]; weberines[208]; deglucopterocereine [251]; (±)-1-phenyl-tetrdydroisoquinoline [284]; salaolidines[338]; tetrahydroisoquinoline-1-methanols[330]; norcoclaurine [347]; 1-benzyl-isoquinolines[197].

2. APORPHINE ALKALOIDS [152,158,168,170,171,236,145,161,357].

This work includes a novel synthesis of aporphines from 3-phenyl-phenethylamines [171, a synthesis of aporphinans from octahydro-isoquinolines[236], a first synthesis of an aporphine-dimer [145], and a novel dibenzopyrrocoline obtained as a by-product [357].

3. BERBINES [92,93,98,147,149,151].

This work includes the first synthesis of homoberbines [92,98], and a novel synthesis of berbines from benzo[a]quinolizidines [93].

4. ALKALOIDS OF DIVERSE STRUCTURES

Sanguinarine [62]; oxazole alakloids halfordinol and annuloline [63]; protostephanine [67,77,87]; pavinan and isopavinan alkaloids [179]; Schöpf"s base VI [136]; nornarceine [*Monatshefte Chem.*, 103, 1210 (**1972**)]; allocriptopine [143]; templetine [142]; ellipticine analogs [148]; dibenzoindolizidines [175]; pyrrolizidines [204,318,331]; 4-demethyl-mescaline [96]; 4-demethyltrichocereine [103]; pyrrolidines [299,300]; flazin [301]; tetrahydroharmine [340]; nortropane alkaloids [366]; benzazocines [138,115,111]; benzazepine alkaloids[123,127,133,134,286,290].

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* For reference to emetine, benzoquinolizidines and morphinan alkaloids see TABLES II and III.

TABLE V COMPOUNDS NOT RELATED TO ALKALOIDS

Retinylidene-1,3-diketones [173,184,187,189]; irazepine [177]; hormothamnione[302]; methylenemescaline trimer [333]; di(2,2,2-trichloroethyl)-carbonate [353]; 6-hydroxy-dopa [112].

TABLE VI ANTIMALARIALS

[85,95,129,135,188,195,243,244,281,307,325,354,369,291,303]
The antimalarial arteether derived from artmisinin is now undergoing a clinical evaluation [303]. Both enantiomers of dihjydroquinine were equally effective antimalarials when tested in Plasmodium berghei infection in mice [129]. The absolute configuration of (+)-primaquine was determined to be (S) [291].