



Mentored and inspired by Mimo: A tribute to Erminio Costa

A B S T R A C T

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Throughout his long productive scientific career, Erminio Costa demonstrated several scholarly traits that illustrate a pattern for paths of successful achievement that should guide young scientists. Not only did he seek excellent training, he got and gave good mentoring. That guidance allowed him to ask important questions and to develop the methods necessary to obtain definitive answers by pursuing those questions in depth. Without question, he blazed trails in neuropharmacology that have been an inspiration to many others and me.

This article is part of a Special Issue entitled 'Trends in Neuropharmacology: In Memory of Erminio Costa'.

1. Introduction

It is a personal pleasure and an honor to be among several of Mimo's colleagues, collaborators and admirers to contribute to this well deserved publication of tributes. I have adapted this personal essay from the keynote talk that I gave at his scientific fest following the Society for Neuroscience meeting in Chicago in the fall of 2009.

As I noted then, sometimes having an event called a tribute carries the connotation that the honoree is never to be heard from again. I frankly doubted then that this would be the case for Mimo, but unfortunately death claimed him soon after the Fest. In fact, I viewed my mentorship by Mimo in much the same way that I did with Francis O. Schmitt, the innovator of the Neurosciences Research Program, where Mimo was until recently on the Board of Trustees. I went to 3 retirement tributes for F.O. Schmitt. To Schmitt, the meaning of *re-tire-ment* was to get a new set of tires and head off in a new direction. Therefore, in my view this tribute to Mimo is clearly celebratory.

1.1. Earning a tribute

Not every scientist with a lengthy career will be recognized by students and colleagues with a tribute. Many worthy academic colleagues simply stop working and disappear from the scientific scene. Those deemed worthy of tributes from their colleagues require super-ordinate contributions to their fields, and Mimo exemplified such contributions. My own association with Mimo began when he was already in the third phase of his post-graduate career, having completed medical school with an honors thesis on the pathology of neonatal bronchopneumonia, his early training in pharmacology at the University of Cagliari, and his collaboration with Harold Himwich at the Thudichum Laboratory in the early days of neuropsychopharmacology. Mentoring me in the ways and whys of neuropharmacology began in 1963.

1.2. My early collaborations with Costa

In the early 1960s, Mimo joined the laboratory of B.B. Brodie who was his great mentor. After a few years, Brodie agreed to Mimo's request to come 2 days a week to the William A. White Building at St. Elizabeth's Hospital in Washington, to investigate single cell neuropharmacology using the 5-barrel micropipettes and the delivery method of microiontophoresis developed by Nino Salmoiraghi. I had the good fortune to be a Research Associate in Salmoiraghi's lab at the time. With Mimo's guidance, I was able to get my first paper in the *Journal of Pharmacology and Experimental Therapeutics* (Bloom et al., 1965), and a review in the *Annual Reviews of Pharmacology and Toxicology* (Salmoiraghi et al., 1965). Subsequently, we worked together in many capacities in the almost 50 years since then.

2. A checklist for those aspiring to tributes

Since not everyone has such good luck, and since one of the goals of mentoring is to inspire the next generation of scientists to take our places, I thought I would mention a few of the steps one needs to attain in order to earn your own tribute. For those who follow David Letterman, I offer you (with a salute to Barney Carroll, see Carroll, 2006) and in the interests of time, Floyd's top 5 reasons to deserve a scientific tribute.

2.1. Reason number 5. He got good training

Too many of the young scientists I have worked succumb to an internal, self-perceived pressure to cut short on their research training to accept—in my view—premature academic appointments. Although it need not curtail subsequent research productivity, I can identify from my trainees several who were initially promising, but who nevertheless failed to develop scientifically after taking on faculty or administrative responsibilities, and then left the field of their research bitter and cynical. Clearly, this was not the case for Mimo Costa.

Mimo began his research training during medical school and spent 6 years in the Department of Pharmacology in Cagliari to acquire a record of accomplishment in research. As a practicing scientist, I knew he and I shared a perspective, (he probably trained me to think this way) that we are always learning and training.

2.2. Reason number 4: he found good mentors

Although one cannot choose their parents, you can choose your mentors. In fact with good mentors early in your career, one has their guidance far longer than the influence most parents have on their children. As pointed out by Barney Carroll (Carroll, 2006), “a mentor must not only be wise but also an advisor and monitor. A mentor does much more than teach. Good mentors strive for the independent development of their trainees, assesses the potential of the inexperienced young scientists and subtly provides them with suitable doses of reality testing”.

As mentors, we guide trainees to job, speaking and training opportunities and spend a goodly number of years recommending them for promotions and awards. We introduce our trainees to colleagues at other institutions, and help them find their way through the often-opaque process of writing and reviewing journal manuscripts and grant applications.

When we worked together at St. Elizabeth's Hospital the second time, from 1968 to 1975, Mimo showed me how to coach our fellows before their presentations at the Federation meetings in Atlantic City, and later at the meetings of the Society for Neuroscience. We took the view that every time our Fellows spoke in public, it was a reflection of the training and research data we shared with them. I later carried this training intention with me when I started my group at The Salk Institute, in what we called the Special Thursday AM Training and Education Conferences (STARTREC) where they were video taped both as presenters and as members of the audience questioning speakers, a training that many of my younger colleagues always recall as significant in their own training of fellows.

Another feature I learned from Mimo was not to compete with our trainees when they go on to their own careers, although it was always a pleasure to have them subsequently become collaborators. If we had selected a research target wisely, the work they began with me could provide career long opportunities, and that left me free to pick a new area with a new Fellow. The scientific program that Sandro Guidotti arranged for Mimo's Fest and much of this Special Issue confirmed the degree to which Mimo's trainees became his loyal and diligent collaborators and then the independent scientists he had always sought to develop.

Good mentors are hard to find, and rarely do their academic institutions recognize their generous contributions. Mimo had the great fortune to learn and work with outstanding mentors at Galesburg with Harold Himwich in the early days of neuropsychopharmacology and with Bernard Brodie at the Heart Institute of NIH. They were his inspiration, his models, guides and eventually his colleagues. They imparted all their knowledge about studying mood disorders, and they gave him the freedom to carve out his own niche in the study of monoamines underlying the drugs used to treat mental illnesses.

2.3. Reason number 3: he asked good questions

From Dr. Brodie, Mimo learned how to ask crucial experiments to establish a scientific rationale and develop hypotheses. But he also learned from them to remain emotionally detached from the experimental results. Importantly, he learned to be alert to the subtle signals nature often provides when the data prove to be exactly the opposite of your predictions, and the simpler the hypothesis the better. Inspiring creativity consists in asking

questions or proposing hypotheses that fail in interesting ways, opening unexpected leads, which in turn can initiate paradigm shifts.

Mimo's interest in studying single neuron activity after specific drug treatments, in the experiments he did with Salmoiraghi and me, led him to move beyond measuring brain levels of amines and their metabolites, to methods to estimate the turnover of the transmitters (Costa, 1972; Neff et al., 1969). This was the era when Norton Neff was in the Costa lab. Turnover was later a strategy Mimo and colleagues applied to neuropeptides as well (Costa et al., 1978). When methods to measure what he wanted to measure proved insensitive, Mimo started the use of mass spectroscopy and mass fragmentography to get the data precisely.

When the emphasis moved beyond what a neurotransmitter did at its receptors, Mimo asked what happens when a transmitter raises or lowers intracellular cyclic AMP, and how did that change influence the longer term adaptation of the neuron's gene expression—the era when Sandro joined the Costa Lab (Biggio et al., 1976; Guidotti et al., 1975; Uzunov et al., 1976).

During the interval between leaving the Brodie lab and returning to the NIMH Intramural Program, Costa and his younger colleagues such as Ben Weiss applied their curiosity and analytic skills to the pineal gland as a means to manipulating afferent signals and evaluating changes in receptor sensitivity. In these studies they showed that denervation of the beta-adrenergic receptor-cyclic AMP system in the pineal gland causes a super-sensitive response to the effects of norepinephrine, thus providing the biochemical basis for noradrenergic super-sensitivity (Ebadi et al., 1970; Weiss and Costa, 1967). These experiments (also see (Strada and Weiss, 1974)) ultimately led to the biochemical explanation for the up- and down-regulation of adrenergic receptors.

When Mimo moved to University of Illinois-Chicago's Department of Psychiatry he resolved to work on schizophrenia—a quest we had shared when we had both moved back to St. Elizabeths in 1968. But this time Mimo did it: starting with the discovery of an unexpected linkage between the expression period of reelin, linking that persistent expression to GABA neurons, that can regulate the dendrites and dendritic spine synapses of cortical pyramidal neurons (Costa et al., 2001; Grayson et al., 2006; Tueting et al., 2006).

2.4. Reason 2: he followed through in depth

Good questions and good targets are good starting material, but to make contributions that are substantive requires persistence and dissatisfaction with minor advances that do not provide insight into the bigger issues.

Mimo was never one to publish shallow studies; he consistently strived for reproducibility and using novel approaches to develop converging lines of evidence to test his hypotheses.

But if we look at Mimo's accomplishments in the translational neuroscience of schizophrenia, we see a continuously evolving and refined productivity of more than 30 first rank publications since the first one in 1998. One could see a similar productive and substantive theme in the work done to isolate the neuropeptide originally identified on the basis of its ability to block the binding of benzodiazepines to their brain receptor (Costa, 1991; Costa et al., 1994; Costa and Guidotti, 1991), and to the equally lengthy story of the brain neurosteroid allopregnenolone and its regulation by antidepressant drugs and stressors (Pinna et al., 2004; Puia et al., 1992; Uzunova et al., 1998).

2.5. Top reason 1: he blazed a trail

As Barney Carroll has noted (Carroll, 2006) in the course of one's career progress towards an eventual tribute, it never hurts to record

some “firsts”. Our Mimo has recorded many firsts. He was the first to show that the expression of serotonin in the brain was regionally selective (Costa et al., 1960), that—based on the effects of LSD—there were likely multiple 5-HT receptors (Costa, 1956), the first to apply steady state kinetics to measure the turnover rates of 5-HT, NE and DA with isotopic and non-isotopic methods (Neff et al., 1969, 1971), the first to measure acetylcholine dynamics with mass fragmentography (Costa et al., 1983; Eva et al., 1987), and to assay the indoleamine content of single rat pineal glands (Cattabeni et al., 1972), the first to establish that an allosteric amplification of GABA-mediated receptors underlies the action of benzodiazepines (Costa and Guidotti, 1991; Guidotti et al., 1979), and all of the themes previously mentioned from DBI (the diazepam binding inhibitory peptide) to allopregnenolone and depression to reelin and schizophrenia. He was lastly one of the first to pursue epigenetic regulation as a source for mental illness (Guidotti et al., 1976) and his colleagues in Chicago have taken up that line of investigation (Costa et al., 2002, 2007, 2009).

3. Concluding remarks

Let me now close by sharing with you a brief excerpt from one of my favorite scientific statesmen, Dr. Vannevar Bush. After World War II, Bush almost single-handedly led the conversion of the academic scientific community from its contributions to the war effort into a peacetime in which Science was to be the endless frontier for the good of the public. Among other achievements, he also accurately predicted computerized information handling, hyper-text, and desktop computers.

In his book of essays “Science is not Enough”, Bush ((Bush, 1967)) wrote a short essay that he titled “The Builders” that seems to me quite pertinent to thoughts of scientific tributes. He wrote:

“The process by which the boundaries of knowledge are advanced, and the structure of organized science is built, is a complex process indeed. It corresponds fairly well with the exploitation of a difficult quarry for its building materials and the fitting of these into an edifice...”

“...the edifice (organized science) itself has a remarkable property, for its form is predestined by the laws of logic and the nature of human reasoning. It is almost as though it had once existed, and its building blocks had then been scattered, hidden and buried, each with its unique form retained, so that it would fit only in its own peculiar position, with the concomitant limitation that blocks cannot be found or recognized until the building of the structure has progressed to the point where their position and form reveals itself to the discerning eye of the talented worker in the quarry.”

Bush went on in this very short essay to describe the nature of the workers; to mention a few you will recognize:

“Those content to dig away, unearth odd blocks, pile them up for others to view and caring not whether they fit in now;”

“Those who watch carefully until some industrious group digs out a particularly ornamental block, whereupon they fit it into the structure with much gusto and bow to the crowd;”

“...groups (that) do not dig at all but spend their time arguing about the placement and fit of earlier additions;”

“...those who sit by and give advice, and those who just sit.”

“On the other hand there are those men of rare vision who can grasp well in advance just the block that is needed to advance construction rapidly and can tell by some subtle sense where it will be found. For each of these masterworkmen there will be many who chip and delve industriously... with little grasp of

what it is all about but (who) nevertheless make the great steps possible.”

“There are also those ... men, whose days of vigorous building are done; they have built a wall here and there, and lived long in the edifice and learned to love it, and who have even grasped a suggestion of its ultimate meaning, and who sit in the shade and encourage the young workers.”

“There are those who can give the structure meaning, can trace its evolution, and describe the glories that are to be to inspire those who work and enjoy.”

In closing, I salute Erminio Costa as one of the true masterworkmen of neuroscience who has long inspired us while he enjoyed his craft. I wonder what he would have explored had he had the chance to get his next new set of tires.

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