

< FROM BUTTERFLIES TO PSYCHOTROPICS, A CHEMICAL ODYSSEY>[1]

Bruno J.R. Nicolaus

Bruno J. R. Nicolaus, chemistry researcher and educator, born in Naples, Italy, to Oscar and Rosa Bipper Nicolaus, on June 1928; PhD Organic Chemistry University of Zurich, Switzerland (1954); Assistant to Nobel Price Laureate Prof. Paul Karrer University of Zurich (1949-1953); Lecturer of Organic Chemistry University of Milan, Italy(1962-1972); Pharmaceutical Industrial Advisor United Nations, Mexico City, ME (1966); Conferring of the Dr. Title University of Bologna, Italy (1979); Contract Prof. of Pharmaceutical Chemistry University of Perugia, Italy (1987-1988); Senior Scientist and Vice President Research and Development at various multinational Corporations (1954-1991); Freelancer (1991-to now).



Contributed to more than 150 articles to professional publications and international patents. Main scientific interests: natural and synthetic pigments, antibiotics and infections, chemical pathology of the brain, ageing, learning and memory, neuropsychopharmacology, molecular diseases, aggressivity and suicide, astrochemistry and origin of life.

The roots of my family can be found in a sunny and friendly village of the Swiss Alps (Müstair, GR), from which my ancestors emigrated almost 150 years ago. I grew up in Italy, where I received a multilingual education, with the opportunity of combining Italian creativity with Swiss accuracy. As a high school student, I had more interest in the humanities than in science, my favourite subjects being philosophy, history of arts and ancient Greek. After I received my BA in Italy, I decided to pass the Rubicon and devote myself to chemistry and biology. I returned to my fatherland, Switzerland, to get my degree in chemistry from the Faculty of Sciences at the University of Zurich. This happened shortly after the end of World War II and my decision had been strongly influenced by the desire of new frontiers, the spirit of <new age> fluttering in Europe, as

well as by the impressive boom of science of that time.

I learned that chemistry, besides being science and art, is a good key for understanding many of the mysteries of life and how a thin chemical thread binds the elements of nature in a wonderful net, from the very distant stars up to the mind.

The same thread accompanied me during the whole life, connecting in a logical sequence many of the topics I treated in my scientific career.

In the 1950s, Swiss chemistry played a key role in the international arena. This gave me the unique opportunity to meet outstanding teachers, as well as to develop close friendships with colleagues from all over the world.

Among my various teachers, I feel very grateful to Nobel Laureate Prof. Paul Karrer, who taught me, besides organic chemistry, accuracy, patience, a humble and honest style of life, which are, as he used to say, the three main virtues of a scientist. I also feel very indebted to him, because he appointed me in 1949 as his assistant. In 1954, I received my PhD, after submitting my thesis on the chemistry of butterfly pigments (pteridins) and developing an original method for the chemical synthesis of biologically active polyamines from polypeptides [2].

The colour of the pteridin pigments may shift from white to yellow, orange, red and blue by chemical manipulation. I was able to point out some years later, that colour and biological activity might be related, displaying important roles in nature [3].

The focus of my attention focussed, years later, to another class of natural pigments, the melanins. Neuromelanin, the black pigment mostly located in the *Substantia Nigra* of human brain, occurs in different settings, depending on whether its biological precursor is L-dopa, adrenalin, serotonin, and so forth. I was involved in the debate, whether these mysterious <blacks>are produced in the body on purpose and I suggested that it would be worth while to study the bioelectrical properties of neuromelanin, and its conduction and

modulation of nerve impulses in regulating the loco motor system [4].

Today, chemists are spoiled by the availability of physical methods, which allow the accurate purification and analysis of almost any chemical compound. This was not the case 50 years ago, when experimenting with natural products, often created insurmountable difficulties to any chemist. Because of this, the discovery of Thin Layer Chromatography (TLC) was highly welcomed and by my group, developed it in the fields of pteridins and antibiotics. Its application to antibiotics was very fruitful, leading to an original and very sensitive microbiological assay.

This new methodology contributed to the investigations on rifamycins, a class of antibiotics, which is still widely used against infections caused by the mycobacterium of tuberculosis and leprosy. [5].

In plants, alkaloids are formed in physiological conditions from simple components by casual non- enzymatic reactions. I pointed out, that in the human brain the biosynthesis of alkaloids, identical to the natural plant products, could also happen casually, by non-enzymatic pathways. As a matter of fact, some aberrant dopamine metabolites were isolated from the urine of healthy individuals, from patients treated with L-dopa and from the post-mortem brains of Parkinson's patients [6].

The symbiotic approach to drug design involves the fusion of two mutually complementary biological activities into one single entity by medicinal chemical hybridisation (MCH). The main advantage of MCH is pharmacokinetic, i.e. reduction of unwanted side effects and production of bivalent therapeutic action. We developed, with the employment of MCH, various new products that combine vasodilating and beta-blocking activities and suggested applications of MCH in the development of new products, acting on the central nervous system (CNS) [7]. The pyridazine system has two adjacent nitrogen atoms and shows aromatic properties. This proved to be useful for the

preparation of new pharmacological agents. The pteridins contain a pyrimidine ring, which, in some instances, is an isoster with the pyridazines. My team synthesized a large number of 3-hydrazinopyridazines and studied their vasodilating and antihypertensive activity. *Cadralazine*, one of the substances we studied, was developed for clinical use and marketed after extensive pharmacological, toxicological and clinical investigations, under the trademark *Cadragen*. The mechanism of action of cadralazine is not fully understood so far, although there is stringent experimental evidence that it is acting as precursor of NO, formed by oxidation [8].

The hydroxyl and the amino group proved to be in some cases bio isosters. In view of this, we prepared and tested pharmacologically a large number of hydroxylamine derivatives in which an amino group was substituted by an oxygen atom [9]. Several sedative-hypnotics, like the barbiturates, have in their ring a quaternary carbon atom, substituted by aromatic, aliphatic or heterocyclic chains, which are expected to monitor potency, liposolubility, duration of action, toxicity and other biological parameters. With the aim of preparing new compounds acting on the CNS, we synthesized many 4-,5- and 7-membered heterocyclic compounds with a quaternary C-atom. However, because of the therapeutic advantages of the new benzodiazepines we abandoned this program [10].

Nootropics are an heterogeneous class of substances. They enhance learning and memory and prevent impairment of cognitive functions, induced by brain insult and diseases. We were involved in the preparation and screening of oxygenated 2-pyrrolidinones (cyclic derivatives of GABOB), that led to the development of *Oxiracetam*, which was thereafter marketed in various countries under the trademark *Neuromet*. We also developed new pharmacological models, with the aim of getting more insight into the mechanism of action of this class of drugs. Although oxiracetam has one asymmetric C-atom in its structure, we did not succeed in showing a significant difference in the activity of the two isomers [11]. In so far as the therapeutic activity of oxiracetam is concerned, we

found that some of some of those patients who responded well, reported a marked enhancement of sexual drive. In my view, 4-oxy- 2-pyrrolidinones deserve to be further investigated, with special attention paid to the separation of responders from the non-responders.

Returning to neuromelanin and brain metabolism, we suggested checking , whether those people, hit by a sudden irrepressible urge to commit homicidal violence, *<Amokläufer>*, have hallucinogenic alkaloids derived from abnormal catecholamine metabolism in their urine, plasma or post-mortem brain. Our hypothesis is that *<Amokläufers>* suffer from a *<molecular disease>* , with altered cerebral neurochemistry; and that decreased serotonergic and noradrenergic tone, reduced cerebral neurotransmission, and low levels of neuromelanin, increase vulnerability and proneness to suicide, even if none of these factors alone or jointly determine suicide. There is a decreased serotonin tone in all cases of suicide. Yet only a small percentage of those with a low serotonergic tone commit or plan suicide. To explain the genesis of suicide, I have emphasized in my work, that: *< suicide might be a pathologic event>* and, at the molecular level, it is *a casual metabolic error*. The mediator that possibly triggers suicide we called LETRA, the Lethal Transmitter, and suggested that LETRA is an aberrant metabolite of catecholamines with hallucinogenic properties, which originates in the brain through oxidative *< radical aggression >* [6,12].

Senile and pre senile dementias, Alzheimer's disease and other neurodegenerative diseases are increasing as the population ages. I believe that we shall be faced shortly with *<NEW ATYPICAL DEMENTIAS> (NAD)*, with behavioural changes resulting from environmental changes, i.e. the combined action on the brain of pathogenic molecules, new *<free radical species>* and longer lifetime exposure to radiation [13].

The chemistry of carbon, the main component of living matter, that started in the stars with formation of various hydrocarbons, is almost the same which we encounter on our planet, confirming the universal character of chemistry. Biochemistry and molecular biology show that all life's systems are run on the same lines of simplicity as physical phenomena: <Man's laboratory is Nature's >.

As Newton stated, < *Natura enim simplex est* >.

The adventurous trip from the Big Bang to the human brain, shows how exceptional is life within the global universe economy and how wonderful is consciousness, within the economy of life itself. Life and human consciousness offer a steady growth of organisation and information against the global increase of cosmic entropy. In some way, we are going to find in the human brain, the matter lost at cosmic level: an admirable virtual reversed image of our surroundings [14,15].

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From the left: Luciano Dorigotti, Eliana Pepeu, Giancarlo Pepeu and Bruno J.R. Nicolaus at the 14th CINP Congress in Florence, 1984



From the left: Stefano Majnoni, Ted Watanabe and Bruno J.R. Nicolaus at the 17th CINP Congress in Kyoto, Japan, in 1990



Bruno J.R. Nicolaus (left) and Turan Itil at the 15th CINP Congress in San Juan, Puerto Rico, in 1986



Dietrich Lehmann and Jasmine Itil at the 15th CINP Congress in San Juan, Puerto Rico, in 1986