Pharmambíl-Psychonautics

Human Intranasal, Sublingual and Oral Pharmacology of Nicotine

In three prior papers in this series, I reported in turn on human psychonautic models of *caapí*, *yajé* or *ayahuasca* (*pharmahuasca*—oral *N,N-dimethyl*-tryptamine [DMT] plus harmine) [Ott 1999]; *ñopo*, *yopo* or *paricá* (*pharmañopo*—intranasal, sublingual, oral, vaporized and intrarectal 5-*hydroxy-N,N*–DMT [bufotenine or *dimethyl*-serotonine] with harmine and harmaline) [Ott 2001B; Torres & Repke 2000]; and *epéna*, *nyakwana* or *yá-kee* (*pharmepéna*—intranasal, sublingual and oral 5-*methoxy-N,N*-DMT [or O-*methyl*-bufotenine] with harmine and harmaline) [Ott 2001C]—including *data* extracted from my books *Pharmacotheon* [Ott 1993], *Ayahuasca Analogues* [Ott 1994], *Pharmacophilia* [Ott 1997] and *Shamanic Snuffs* [Ott 2001A]. ***Nicotiana tabacum*** L. (Solanaceæ), together with *cocaine*-containing *ahpí*, *hayo* or *coca*-leaves, *Erythroxylum*-spp. (Erythroxylaceæ), are **the central hub** of South American shamanic ethnopharmacognosy—of which these potions, snuffs and other shamanic preparations are among a plethora of **spokes** [Urbina 1992; Wilbert 1972,1987]. *Ayahuasca*, primarily *potions* based-on *liana-stems* and occasionally *leaves* of *Banisteriopsis caapi* (Spruce *ex* Grisebach) Morton (Malpighiaceæ); *snuffs* and other modalities, from *seeds* and (historically) *leaves* of *Anadenanthera*-species (Leguminosæ); and diverse preparations based-on *barks* (and possibly *leaves*; even stingless-bee-honey) [Wilbert 1996], of *Virola*-species (Myristicaceæ): all commonly are commingled—or taken adjunctively—with diverse preparations of *leaves* of ***Nicotiana***-species (Solanaceæ), or **tobacco**. Moreover, triturated tobacco-leaf itself is an important shamanic *snuff*; while tobacco- *potions*, *pastes*, *masticatories* and *fumatories* still widely are used in northwestern Amazonian shamanism [Ott 2001C; Wilbert 1987]. Despite its *post*-Contact introduction there, tobacco has become integrated solidly into an independent and autochthonous African complex of *snuffs*, *fumatories* and other shamanic inebriants [Cremer 2004; De Smet 1998; Hambly 1930; Laufer 1930; Linton 1930]—the same evidently applies to

ill-studied Siberian shamanism [Ott 1993]. Although today *smoking* of industrial *cigarettes* is well-nigh definitive of tobacco-ingestion, only in World War I did that gain ascendancy over tobacco-*chewing* in the United States; while in some Scandinavian countries, only later in the XX century did *smoking cigarettes* overtake tobacco-*snuffing*, as the primary tobacco-use-modality [Goodman 1993].

The large and growing *anti*-tobacco-lobby, inspired and buoyed by the undeniably grave public-health and economic harms accruing from tobacco-*smoking*, even has dared to broach initiatives aimed-at *prohibiting tobacco* (the leading crop, in several Usan States, which is supported by federal subsidies!)—classifying it with DMT, bufotenine and 5-*methoxy*-DMT, as a 'controlled [*sic*] substance'! This surely would be the Waterloo of Prohibition, which arguably has worse public-health, legal and economic consequences, than does *cigarette*-smoking. Besides, this already had been tried, and had failed, *miserably*—no fewer than **28** U.S. States (of, then, a maximum of 48) enacted some form of *tobacco*-Prohibition, between 1897 and 1921; which, together with the disastrous *alcohol*-Prohibition (which began in the States, more than a *half*-century before its national enactment, and *still exists* in parts of several States), shortly and quietly were rescinded [Goodman 1993]. Meanwhile, tobacco- and pharmaceutical companies have embarked-on diffident and largely inconsequential forays into alternative tobacco- or nicotine-products, at times frankly frustrated by the U.S. government [Nowak 1994A] and *anti*-tobacco-activists—such as, for instance, *R.J. Reynolds'* "nearly smokeless" *cigarette*, *Eclipse*,™ withdrawn for more than a decade from test-marketing, after a one-billion-US-dollar-investment [Levin *et al.* 1992; Schelling 1992], but later reïntroduced to market; or when *Phillip Morris* quashed a research-program devoted-to psychopharmacological engineering of safer substitutes for nicotine (2′-*methyl*- and 4′-*methyl*-nicotine, which were as "reïnforcing" as nicotine in rats, but lacked its [potentially deleterious] cardiac effects): as a consequence of a 1988-verdict, in a wrongful-death-lawsuit [Nowak 1994B,C]. *Advanced Tobacco Products*' smokeless *Favor*™ was classified by the U.S. *FDA* as a 'drug-delivery-device,' which mandated ruinously-expensive testing to obtain approval, and so was removed from market. Approved, then shifted to the OTC (Over-The-Counter) drug-market were the best-known nicotine-pharmaceuticals, *Nicorette*™

chewing-gum, and *Nicoderm*™ transdermal patches; although *Nicotrol*™—being a nicotine-nasal-spray and a nicotine-vapor-inhaler—still remained prescription-drugs in the United States.

Misguided public-health-concerns have led to widespread use of ***low***-nicotine-*cigarettes*—nicotine-reduction having been achieved, largely, by the brilliant marketing-stratagem… of *reducing the amount of tobacco per unit!* Prior to World War II, the average Usan *cigarette* contained **1.4 g** of tobacco; by 1980, barely **0.87 g** (62%), of so-called 'tobacco-sheet': literally, a sort of tobacco-*paper*, *en lieu* of shredded leaf; which, moreover, is 'puffed,' to achieve greater volume [Goodman 1993]! Not surprisingly, research shows that smokers of *low*-nicotine-*cigarettes* tend to take more and deeper inhalations *per* unit, compared to *higher*-nicotine-*cigarettes* [Perrine 1996; Russell 1987]. Clandestine attempts, apparently aimed-at breeding *high*-nicotine-strains of tobacco in Brasil, were thwarted, when the U.S. *Department of Justice* fined a small company (consulting for *Brown & Williamson Tobacco Corp.*) U$200,000, for alleged violations of a (since repealed) law concerning tobacco-seed-exports [Marshall 1998]. Of course, from a public-health-perspective, it would be far more sensible to market ***high***-nicotine-*cigarettes*, which smokers would be hard-pressed to smoke voraciously, on pain of falling-into divinatory trances, like so many Warao-tobacco-shamans [Wilbert 1972]!

To many, it seems much more logical to develop *tobacco-free* nicotine-products. In contraposition to the 'organophile'-maxim, that *natural*, or *crude* plant-drugs are safer [Weil 1972], this decidedly is *false*, in the case of **tobacco**, which is **carcinogenic**, however ingested; whereas its major active principle, **nicotine**, is of nominal toxicity [Benowitz 1992], has limited medical utility [Díaz 1999], and appears to be prophylactic against both (neurodegenerative) Alzheimer's, and Parkinson's Diseases, and is one of very few drugs to show modest cognitive improvements, in *some* cases, of the former [Jarvik 1991]. Indeed, the *American Association for the Advancement of Science* (*AAAS*, publisher of *Science*) held a seminar entitled: "Does Nicotine have Beneficial Effects in Childhood and Aging Diseases?— at its annual meeting in 2000. On the other hand, alternative nicotine-products hitherto have been doomed to failure, by their conceptualization as 'medicaments' to 'treat the disease' of 'tobacco-addiction' (imprecisely

called “nicotinism” or “nicotine-addiction”) [West 1992]; part and parcel of the misanthropic pharmacopathological approach to inebriant-drugs—which painstakingly I deconstructed, in *Pharmacophilia* [Ott 1997]. Insofar as *pleasure*, *euphoria*, the so-called ‘reïnforcing’ properties of drugs, *ipso facto*, thus are classified as *adverse side-effects*, and such happen to be the motive force behind tobacco-use; not surprisingly, nicotine/tobacco-replacement divagates from one dead-end *cul-de-sac* to another—*half-baked*, *hit-or-miss*, *barely serviceable*, *overpriced* and *inferior* succedanea for **tobacco**: designed merely *to wean* stalwart habitués from their beloved *cigarettes*… ‘heaven’ forbid, they should become habitués, of **nicotine** itself!

Already I have reviewed in detail [Ott 1997] the defects of this approach, as pertain specifically to nicotine, and refer the reader to *Nicotine Replacement* [Pomerleau & Pomerleau 1992A], a comprehensive review of human nicotine-pharmacology—albeit doggedly ensconced in this pharmacopathological mindset. This psychonautic study aims to point the way to a more sensible approach to tobacco-replacement, *via* what I have dubbed “psychopharmacological engineering” and “psychonautic posology” [Ott 1997]. After all, we are dealing here, with one of the most *extensive*, and *deeply-rooted* habits in the world, and only by offering *viable* alternatives—which perforce must be *superior in euphoric efficacy*, to each of the extant tobacco-ingestion-modalities—reasonably might we expect to be able to *influence* (much less *reduce*; never mind *stop*) tobacco-consumption… especially, tobacco-*smoking*.

Wilbert [1987] masterfully and comprehensively has reviewed the historical, botanical and ethnographic aspects of South American shamanic tobacco-use—whether as *fumatories*, *snuffs*, *potions*, *masticatories* or *clysters*—while Cremer [2004], Hambly [1930], Laufer [*et al.* 1930] and Linton [1930] have made far less detailed surveys of its African counterpart. The history of Western tobacco-use well has been reviewed by Brooks [1953], Goodman [1993] and Gately [2003]. Regarding South América, where *Nicotiana*-species originated, as well as diverged [Goodspeed 1954], and their use clearly is archaïc, tobacco-*snuffs* are second only to *fumatories* in prevalence (after updating Wilbert’s *Tables*); followed by *potions* and *masticatories*; with but a few reports of tobacco-*enemas*… even of *intraocular* application (literally, ‘disembodied eye-

drops); [Samorini 1996; Wilbert 1987]; and *one* citation, of tobacco-*bougies*, or intranasal suppositories [Antonil 1711]! *Bougies* are obsolete in modern pharmacopœiæ, but Martindale [1886] described *Buginaria Cocainæ* for hay-fever—with 1/6 grain (~10.8 mg) of cocaine-*hydrochloride*. Not surprisingly, the bulk of Peoples who take tobacco-*snuffs*, *also* employ shamanic *snuffs* of *Anadenanthera*- and/or *Virola*-species—and, frequently, take these conjointly. Tobacco-*snuffs* may be *powders*, *liquids* or *solids—liquid snuffs* (infusions of tobacco-leaf) do not differ essentially from tobacco-*potions*; and *bougies* or solid tobacco-*errhines*, 'tobacco-*pellets*' (as *yiaqualli*, also employed in Mesoamérica), more than likely represent an alternative ingestion-modality for tobacco-*linctuses* or lambitive 'tobacco-*pastes*.'

These tobacco-*pastes* or -*syrups* are known as *ambíl*, *ambirá* or *yera*, at times contain *B. caapi*-(*ayahuasca*-) liana [Candre 1996; Shepard 1998] and, like tobacco smoked, snuffed and chewed, at least nominally have escaped the shamanic context, as *chimó* or *chimú*—a citified, *semi*-industrial version—used sublingually in Venezuela and Colombia, and regulated like other tobacco-products [Kamen-Kaye 1971,1975]. I had occasion to mention tobacco-*linctuses* in the context of sublingual *Virola-pastes* [Ott 2001C], and these clearly are kindred inebriants. Apart from sharing *ayahuasca*-admixture, both have other plant-additives and ash-sources in common: indeed, the Witoto-name for shamanic *Virola*-species is *úkuna* (or *oo-koó-na*); *viz.*, 'jungle-tobacco' [Urbina 1992], and Witotos may *smoke* tobacco and *ayahuasca* together; while the Tukano may *snuff* them conjointly [Ott 2001A]. Both *Nicotiana*- and *Virola*-species have been reported to be admixtures to various *ayahuasca*-potions [Ott 1994].

Based on our insipid, and less-than-inspiring experiences, with 'puffed-up,' 'tobacco-paper'-*cigarettes*, we habitually fail to classify tobacco as *a drug*, much less *a psychoptic drug* widely used as *an entheogen* or *shamanic inebriant* (like *coca* or *Erythroxylum*-species, which we also tend to exclude from the *entheogen*-category). Suffice it to note that, the *American Society of Pharmacognosy* held its 1992-annual meeting—one of two *Symposia* of which was devoted to "Drugs of Abuse"—under the sponsorship of *Phillip Morris USA!* Forsooth, tobacco hovers in a nebulous regulatory limbo in the U.S.A.: somewhere between *food* and *drug*; overseen by the

Bureau of Alcohol, Tobacco and Firearms (the common denominator of these three Macbethian "weird sisters" would appear to be *fire—fire*-water, *fiery* brands, and *fire*-arms)! In linguistics, kindred confusion reigns: obfuscatory "Drugspeak" [Dally 1995] admits of "alcoholism and drug abuse" (as if there were some substantive difference): not yet, of "alcoholism, *tobaccoism* and *other* drug-*use*." But we have only a nodding acquaintance with **tobacco**, and almost *none* with **nicotine**: however intimate it might be, with depauperate, exsanguinate, industrialized succedanea. Tobacco is *the* shamanic inebriant: no well-known American shamanic/psychoptic drug exists independently of some intimate connection with tobacco, which likewise is the only shamanic inebriant which (possibly) stands alone, in any culture. At once tobacco became available, late in the XVII century, shamans in Siberia, Africa and elsewhere adopted it, for purposes strikingly similar to South American prototypes (generally: as a 'spiritual shield' or 'animistic ægis'). For some Peoples—such as the Warao of Venezuela [Wilbert 1972], and the Matses of Perú [Gorman 1993]—tobacco unquestionably is their *primary*—if not their *only*—divinatory entheogen. A psychonautic bioassay [Gorman 1990] of *nu-nu*, being the Matses shamanic **tobacco-snuff**, attested to its vatic and visionary potency:

> When *nu-nu* hits, it seems to explode inside your face. […] Soon you fall to the ground: you close your eyes and the visions begin. Out of the blackness animals appear—tapir and peccary, monkey and jaguar, even animals you may never have seen before. They are vivid, almost holographic.

The *nu-nu* tobacco-snuff evoked a vision of wild boars stampeding, and when our psychonaut returned to his senses, he was interrogated by his hosts, as to *where*, and *when* in the day, he had 'seen' the boars; whence they all repaired the following morning; and, within an hour: "hundreds of boars charged into the river in front of us… it was exactly like my vision."

Materials and Methods

While there exists a copious literature on human nicotine-pharmacology—including some intranasal *data*—this is bedeviled by its pharmacopathological bents and bias. With an eye to improving the "psychonautic posology" of nicotine, I resolved to model shamanic tobacco-*snuffs* and *linctuses*, employing reagent-grade nicotine-*free-base* and its *hydrogen-tartrate*-salt (*Sigma Chemical Co.*, St. Louis, MO); sometimes combined with procaine-*hydrochloride* (*Sigma*); and likewise to bioassay the pharmaceutical preparations, *Nicotrol NS*™ and *Nicorette*.™ I am the sole author, and likewise the only test-subject: these drugs *were not* administered to anyone else, thus obviating any ethical concerns. All of this research was *self*-financed, independent of any institution, so having it blessed by an *Ethical Review-Board* was not germane, nor did such exist.

Pharmanunu-Psychonautics: Intranasal Nicotine-Pharmacology [NN]

I commenced modeling ***pharmanunu***, or ***intranasal* nicotine**, with the pharmaceutical preparation *Nicotrol NS*,™ a pump-sprayer calibrated to deliver a mist of **0.5 mg** nicotine *per* spray, into each nostril (**1.0 mg** basic dose)—this is sold by prescription only, and is absurdly overpriced, at some U$50.00 for 100 mg (10 ml @ 10 mg/ml, or **U$500.00/g**: reagent-grade-nicotine then sold for **~U$1.00/g**!). In **NN-I** and **NN-II** (separated by several hours) I insufflated **1.0 mg**, then **2.0 mg** of nicotine. Not only is this product no bargain, but is so irritating withal, as to provoke repeated sneezing—such that I was unable to absorb sufficient nicotine, to enjoy its effects. I highly recommend this, as *a sternutatory*, but as *a nicotine-delivery-device*, it is quite worthless. With a refillable pump-sprayer that had contained an asthma-medication (which can be calibrated simply: by adding a known amount of water, and counting the number of sprays yielded), I prepared my own stock-mixtures of nicotine-free-base (which is a light oil, insoluble in, but miscible with water). For **NN-III**, I found insufflating 1.0 mg bilaterally (**2.0 mg**; 0.028 mg/kg) to give negligible results; whereas *doubling* the dose, in **NN-IV** (**4.0 mg**; 0.057 mg/kg) was quite satisfactory—eliciting a rapid (25-30 seconds) nicotine-rush, which peaked in 2–3

minutes, conferring a fine cerebral stimulation, for about one hour. Albeit much less irritating than the *Nicotrol NS*,™ this still effected noisome nasal irritation—a transient burning-sensation akin to that of the piquant *chile*- (*Capsicum*-spp., Solanaceæ) alkaloid, capsaicine. For **NN-V**, I added the local anæsthetic procaine-*hydrochloride* to the nicotine-mixture, such that each spray delivered 10.0 mg procaine (**20.0 mg** dose; 0.28 mg/kg) and 2.0 mg nicotine (**4.0 mg** dose; 0.057 mg/kg). This largely ameliorated the nasal irritation, especially during repeated applications, and other local anæsthetics likewise have been tried with great success. Intranasal nicotine-mixtures result-in peak blood levels commensurate with those of *cigarette*-smoking, perhaps slightly more swiftly (less than 7 minutes) [Russell 1992].

The crystalline *bitartrate*-salt of nicotine proved all-but-useless, as a medium of nicotine-delivery, only being effective, when solutions were basified sufficiently with sodium-*bicarbonate* ($NaHCO_3$), so as to neutralize the tartaric acid. Procaine is psychoactive in its own right, possibly a monoamine-oxidase-inhibitor (MAOI), and is a prototypical 'smart drug,' in the Romanian *Gerovital*,™ or GH-3 [Dean & Morgenthaler 1990]. Given the putative prophylactic effects of nicotine, against grievous neurodegenerative diseases, here we have the makings of a 'noötropic smart-snuff.' Given in high intravenous doses, procaine appears to possess visionary properties—of 32 human subjects, *all* had *auditory* 'hallucinations,' and 9 reported *psychoptic* effects. Although 9 subjects experienced only fear and anxiety, another 9 rather were treated-to "intense euphoria" [Perrine 1996]!

It appears a start-up-company has been developing a novel, dry-powder, *pulmonary* snuff-inhalation-technology, which has been shown to effect *sustained time-release*, *through the lungs*: both of *high*-molecular-weight, water-soluble (insulin), and *low*-molecular-weight, lipid-soluble (testosterone) compounds—this most surely would work with nicotine (not to mention *cocaine*, *morphine*, *THC*, *etc.*), and the "large porous particles" mixed, then inhaled with the drug, likely could be engineered, to minimize or obviate local irritation [Edwards *et al.* 1997; Inhale 1999].

Pharmambíl-Psychonautics: Sublingual Nicotine-Pharmacology [NS]

Again employing standard mixtures of nicotine-free-base in distilled water, I commenced modeling ***pharmambíl***, or ***sublingual* nicotine**. In **NS-I**, a **1.0 mg** (0.014 mg/kg) sublingual drop had negligible effects; while **NS-II**, **2.0 mg** (0.028 mg/kg) barely was perceptible. On the other hand, **NS-III**, **4.0 mg** (0.057 mg/kg) virtually was identical, both as to euphoric potency, and pharmacodynamics, to the same dose *intranasally* (**NN-IV**): a swift (25–35 seconds) and quite satisfying nicotine-rush, peaking within 3 minutes, with a good hour of cerebral stimulation (in both cases, and with nicotine in general, there is no dramatic *physical* stimulation—save for a slightly-elevated cardiac rhythm). When I ingested **NS-IV**, **8.4 mg** (0.12 mg/kg), first thing in the morning, it proved excessive, causing vertigo: leading me to expectorate and rinse my mouth *post haste*—although I readily have tolerated doses as high as **15.0 mg** (0.21 mg/kg), in the course of repetitive applications, bespeaking a rapid development of tolerance (this is typical of *cocaine* and other stimulants, is ephemeral, and resets within several hours). For **NS-V** and **NS-VI**, I spaced two, **8.4 mg**-doses (0.12 mg/kg), by exactly one hour; the second of which was noticeably weaker in action, signaling the persistence of tolerance. In **NS-VII** and **NS-VIII**, I repeated the experiment, with a 2.25-hour interval. This time, the second dose was *almost* as potent as the first, suggesting that nicotine-tolerance persists for approximately 3-4 hours. This jibes with the metabolic half-life of nicotine—roughly 2 hours (that is, roughly 75% would be metabolized, after 4 hours) [Russell 1992].

Next, I confected *ambíl* or *chimó*: steeping fresh ***N. tabacum***-leaves from my garden in water, periodically heated near to boiling over several days, following which those tough leaves were wrung-out thoroughly, and the filtered extract inspissated by simmering on low heat. During this lengthy process, I added about *one-fifth* of the extract-volume, of wood-ash-leachate (roughly equal weights of ashes and water steeped for several days, then filtered); as flavorings: pods of *Vanilla planifolia* G. Jackson (Orchidaceæ); crushed, dried leaves of *Justicia pectoralis* Jacquin var. *stenophylla* Leonard (Acanthaceæ); and dried flowers of *Quararibea funebris* (La Llave) Vischer (Bombacaceæ); lastly, sweetening with commercial *Apis*-bee-honey, prior to the final

concentration, to the consistency of hard taffy when cooled. Even absent these condiments, my fresh tobacco-concentrate had a delightful taste of caramel—coumarin-like, even 'though I had been careful neither to burn, nor allow the filtrate to boil, lest steam-distillation of nicotine ensue. *Coumarin* itself has been found in dried tobacco-leaf, along with *scopoletine* (another coumarin), as well as the volatile oil, *myristicine*—all putative psychoactive compounds [LaVoie *et al.* 1985; Ott 1993]. In **NS-IX**, a **2.0 g** *bolus* of this *ambíl* stuck inside my lower front-teeth readily would dissolve under my tongue, but this barely elicited any sublingual nicotine-effects. Accordingly, I enriched a **15.0 g** aliquot to **5%** nicotine, triturated with **15.0 g** of *Hershey's*™ cocoa, *Theobroma cacao* L. (Sterculiaceæ)—to facilitate handling and weighing (now, at minimum, **2.5%** nicotine)—such that **200 mg** of *ambíl*, *per se* containing negligible alkaloid, would deliver ≥ **5.0 mg** of nicotine. In **NS-X**, *sublingually* I ingested **200 mg** (≥ **5.0 mg** of nicotine; ≥ 0.07 mg/kg), of this ***pharmambíl***. Although this dry *bolus* would dissolve slowly, it proved extremely effective for nicotine-delivery; as did **NS-XI**: **400 mg** of ***pharmambíl*** (≥ **10.0 mg** of nicotine; ≥ 0.14 mg/kg).

Oral Nicotine-Pharmacology [NO]

I describe bioassays of *Nicorette*™ chewing-gum as ***oral***, rather than sublingual, insofar as its use for effective nicotine-absorption needs involve *vigorous* chewing (right from the start, I was ignoring the warnings of the *Prospectus*), leading to swallowing a goodly portion of the nicotine (which will occasion a transient *singultus*, or hiccoughing). This peculiar product is sold in the form of *Chiclet*™-squares, containing **2.0** or **4.0 mg** of nicotine-*polacrilex* (nicotine is linked to an ion-exchange-resin, to slow its release), and is known to be a *slow* and *inefficient* method of nicotine-delivery in human beings: the **2.0 mg** is only about ***one-third*** as effective as depauperate industrial *cigarettes*; the **4.0 mg** around ***one-half***; particularly, should one attend to instructions (which I *did not*) to ruminate it only sporadically [Henningfield & Jasinski 1992; Russell 1992]. In **NO-I**, I found one, **2.0 mg**-piece (0.028 mg/kg), gave barely-perceptible effects—even with rapid and vigorous chewing. **NO-II**, a single **4.0 mg**-piece (0.057 mg/kg), once again, ruminated rapidly, evoked a *mild* nicotine-stimulation; although swallowing the bulk of the nicotine elicited

singultus lasting one minute or so. Finally, in **NO-III**, fierce mastication of **two**, **4.0 mg**-pieces (**8.0 mg** of nicotine; 0.11 mg/kg), afforded me a decent nicotine-stimulation, which manifested too slowly to elicit a pleasurable 'rush.' I might mention that when *Nicorette*™ was moved to the OTC-market in the U.S.A., this applied only to the **2.0 g**-formulation: the **4.0 g**-gum remained available by prescription only; and both—like *Nicotrol NS*™—are *exorbitantly* overpriced.

Ruminations and Conclusions

It is well and widely known that *the smoke* of industrial tobacco-*cigarettes* contains substantial concentrations of **carbon-*monoxide***, **CO** [Budavari *et al.* 1996]; roughly in the range of **3–6%** (30,000–60,000 ppm): which is about ***double*** that found, in the most polluted urban vehicular traffic-conditions; and some ***eight-fold*** the **carbon-*monoxide***-levels permissible, in industrial environments, in the U.S.A. [Gossop 1996]. Moreover, purportedly 'safer' filter-*cigarettes* generally deliver ***higher*** smoke-concentrations of **carbon-*monoxide***, than do their *non*-filtered equivalents [Schelling 1992]! Parenthetically I note that an early filter-*cigarette*, bombastically hawked on television, when I was a lad—the *Kent*™ "Micronite Filter"—was made of 100% **asbestos**! Generally, it is taken for granted—indeed, has become a tacit ***axiom***—that **tobacco-*smoking*** is equivalent psychopharmacologically to the inhalation of *vaporized* and/or *particulate* **nicotine**. Careless scientists habitually refer to **tobaccoism** (particularly, tobacco-*smoking*, which by far is the predominant ingestion-modality) as '**nicotine-addiction**,' or '**nicotinism**'; the while overlooking; aye, passing-by in silence, some potential contributions from, or psychoactivity of, **carbon-*monoxide***. On the other hand, **carbon-*monoxide*** arguably is psychoactive—particularly in the *mild* context, of *quite feeble* subjective effects, of smoking industrial tobacco-*cigarettes*—more than likely, owing to partial and progressive *hypoxia*, occasioned by its binding to serum-hæmoglobin (**carbon-*monoxide*** has greater binding-energy, to *iron*-centered heme-sites, than either molecular *oxygen* [O_2] or carbon-*dioxide* [CO_2]). The *percentage* of available *oxygen*-binding-sites upon hæmoglobin, preferentially occupied by **carbon-*monoxide***, is denominated ***carboxyhæmoglobin***-levels (**COHb**), and is used as an index of **carbon-*monoxide***-poisoning. At

COHb-levels sufficiently high, *death from hypoxia* supervenes; and inhalation of **CO**-rich automobile-exhaust is a not-uncommon method of suicide. Our autonomic regulation of breathing-rhythm is a function, not of *oxygen*, but of carbon-*dioxide*-concentrations in the lungs.

As a rule, **COHb**-levels above **50%** usually are fatal, although levels as low as **~35%** have caused death, and the symptoms of **CO**-poisoning supervene, at **COHb**-levels above **~10%**. Above 1,000 ppm (0.1%) in air, concentrations of **carbon-*monoxide*** may be fatal within *one hour* (this was the principal complication in the famous *Apollo XIII*-rescue of 1970) [Martindale 1984]. Pure *oxygen* (O_2) is given in therapy for **CO**-poisoning, which treatment is continued until **COHb**-levels have fallen below **~5%**, which is considered to be the danger-threshold. Now, **4% CO** in tobacco-smoke (40,000 ppm) led to smokers' **COHb**-levels of **5.9%**; and typical, one-pack-*per*-day smokers of industrial *cigarettes* will evince **COHb**-levels in the range of **3–10%** ('normal' levels in *non*-smokers are approximately **0.65%**) [Levin 1992]! Effects of **CO**-poisoning include: dizziness; visual disturbances; mental dullness and confusion; weakness; lethargy and nausea [Budavari *et al.* 1996; Leikin & Paloucek 1995; Martindale 1984]. **COHb**-levels around **3%** have adverse effects on 'visual threshold'; levels near **5%** may alter 'time-discrimination' and 'visual vigilance' [Gossop 1996]. Given the low levels of nicotine *delivered* by *smoking* industrial *cigarettes*—typically **~1.0 mg** and frequently lower (dosages listed on the pack are the amounts *delivered* by *eight* inhalations, as quantified by a 'smoking-machine'; but some smokers might extract up to **3.0 mg**, from one '**1.0 mg**'-*cigarette*) [Russell 1992]—and the negligible subjective effects of **2.0 mg** of nicotine *intranasally* (**NN-II**) or *sublingually* (**NS-II**)—so swiftly absorbed, that a 'rush' accrues within *one-half*-minute and effects peak within *three* minutes—it seems obvious to me, that the so-called 'nicotine-rush' or 'nicotine-buzz' perceived, particularly after smokers' first *cigarettes* of the day, or after 8–12 hours of abstinence (following a lengthy flight, for instance), obtains partially, if not exclusively, from the *hypoxia* occasioned by the **carbon-*monoxide*** in the inhaled smoke. To be sure, smokers experience this 'buzz,' after *two or three* inhalations, whereas peak-plasma-concentrations of nicotine are not attained, until roughly ***one minute following the smoking of that cigarette****!* Moreover, one expert [Russell

1992] on human nicotine-pharmacodynamics, commenting on the ingestion of **2.0 mg** of pure nicotine, in the form of that crappy chewing-gum, stated:

> …*it is* ***relatively ineffective at reducing the craving or urge to smoke****… it* ***does not provide the almost instant gratification and relief from craving*** that is obtained from a *cigarette* [emphases mine].

Such "instant gratification" ***cannot*** obtain from **nicotine**; **carbon-*monoxide*** is a much likelier source of this "relief from craving," during a smoker's first *cigarette*, following some protracted abstinence… if indeed this be a *pharmacological* effect, which cannot be taken for granted. As it happens, remarkably, the subjective effects of **carbon-*monoxide***—at least: dizziness; visual disturbances; weakness; lethargy; nausea—likewise are subjective effects of **nicotine**! Whereas nicotine, *per se*, demonstrably is 'reïnforcing' in animal-models (which is to say: rodents locked in 'NIDA-*coke*-cages'), **carbon-*monoxide*** appears not to have been tested systematically in this regard. Moreover, significant reïnforcement and subjective satisfaction (*viz.*: "gratification") in human tobacco-smokers clearly has been shown to be *independent* of the concentrations, both of **nicotine** and **carbon-*monoxide*** in the smoke [Rose 1992]! When—over ten days—'blinded' smokers surreptitiously were switched to ***ultra-low***-nicotine-*cigarettes*, they experienced no strong cravings: despite **a 60% drop** in their peak-plasma-nicotine-levels [West *et al.* 1984]! Much the same result obtained, when abstinent smokers were given **tobacco-free-*cigarette***-analogues, the 'smoke' of which contained *neither* **nicotine** *nor* **carbon-*monoxide***: they reported these to be "satisfying." The key to ensuring smokers' satisfaction, had been optimizing the *temperature* of the gas, and the *size* of its suspended particles (nicotine in tobacco-smoke exists as suspended *particles*, not *vapor*); that is: in emulating those factors in the genuine smoke of tobacco-*cigarettes* [Rose 1992]. Summarizing such results, Rose remarked [emphasis is mine]:

> ***Smokers' craving for*** **cigarettes** ***is satisfied more effectively by irritation from smoke in the upper respiratory tract than by nicotine's direct pharmacological effects on the***

> ***central nervous system***. […] …the ***flavor*** of the *cigarette* smoke and ***the throat impact*** accompanying each puff ***produce immediate satisfaction***…

Meanwhile, another researcher [West 1992], commenting on high *intravenous* doses of nicotine **having failed** to eliminate smokers' cravings to smoke *cigarettes*, concluded:

> …this finding suggest that ***nicotine plays only a minor rôle on cigarette craving***, and that the ***failure of nicotine gum to affect craving was due to the relative unimportance of nicotine*** rather than to inadequate nicotine replacement. […] …the weakness of any effect of high intravenous nicotine doses on craving… seems to set smoking apart somewhat from classic drugs of dependence… Relief of craving in the case of these other drugs seems to be controlled primarily by obtaining a high dose of the drug… […] [**Nicotine**] ***probably does not fit the classic model of drug addiction***. […] …***non-*** **pharmacological factors seem to play a greater *rôle* in the addictiveness of *cigarettes***.

Studies of nicotine-gum [Henningfield & Jasinski 1992], given to smokers, found this to be a:

> …***very weak reïnforcer***… possibly even… ***mildly aversive***… [emphases mine];

and smokers' "liking"-ratings of that gum ***increased***, *in proportion as its* ***nicotine-content decreased****!* Nevertheless, the editors of the anthology in which the above-cited research was published [Pomerleau & Pomerleau 1992A], characterized the *anti*-smoking-movement as: "combat [against] **nicotine addiction**" [emphasis mine; Pomerleau & Pomerleau 1992B]! *Marion Merrell Dow* advertised *Nicorette*™ as treating: "your body's **addiction to nicotine**."

This research more clearly outlines and signals a 'tobacco-***smoking***-addiction' (*sic*, ***habituation***), and calls into question some contributions of **nicotine**, to its 'reïnforcement.' In all events, it is imprecise, simplistic and reductionistic—perhaps even entirely unwarranted—to characterize 'addiction' ***to*** **the habit *of smoking*** industrial *cigarettes*, as "**nicotine-addiction**" (we forget that

an ‘addiction,’ or *devotion*, is to *the habit* of performing some behavior; *not* to ***some substance*** involved in said behavior); and most *cigarette*-smokers decidedly *are not* ‘**nicotine-fiends**’… although the majority quite fairly and aptly might be described as ‘**smoking-fiends**.’

As for the so-called ‘**nicotine**-withdrawal-syndrome,’ with regard to *cigarette*-smokers: in my view, this is a misnomer, for a ‘**smoking**-withdrawal-syndrome.’ It is more than strange to be told by two experts, that **nicotine**: “when present in tobacco-formulations… shows ***marked*** abuse [*sic*] liability”; whereas **pure nicotine** in chewing-gum: “appears to have ***low*** abuse [*sic*] liability” [Henningfield & Jasinski 1992; emphases mine]. Ordinarily, the more concentrated or purified is a given drug, *the greater* is a liability to become habituated to its use. This rather is a statement, that **smoking** (or inhaling particles and/or vapors of pure bases) is more strongly habituating than **oral**/**sublingual** ingestion of any given compound. The rule is: *the closer* is the temporal connection, between an ingestion-behavior, and the consequent ‘reward’… *the more* **habituating** is that behavior. My extensive personal experience with nicotine (I consume approximately **0.35 g** of nicotine daily—equivalent to some **17 packs** of *cigarettes*)—*every day*, and have done so for more than a decade) demonstrates clearly that ***there is no*** palpable *physical* ‘nicotine-withdrawal-syndrome,’ in any case (as a daily user, for the past 40 years, of *opiüm*, *Papaver somniferum* L.; [Papaveraceæ] and/or other opioids—particularly the opiates *codeine* and *morphine*—I am well-familiar with a *genuine* withdrawal-syndrome).

Drugabuseologists list the following, as so-called ‘***cigarette***- (not a few dare say **nicotine**-) **withdrawal-symptoms**’: irritability; inability to concentrate; depression; insociability; restlessness; dizziness; discomposure in company (how does this differ, from *insociability*?); and “feeling at a loose end.” It will be observed that (with the possible exception of *vertigo*), these all are *mental*/*behavioral*, and not *physical* symptoms: as I stated categorically, **there is no *physical* withdrawal-syndrome** upon ceasing prolonged, heavy use of nicotine (with regard to *smoking*, I cannot say). However, it appears to me that smokers tend to be somewhat nervous, anxious types [Escohotado 2024], and rather than being *stimulated*—as one should expect, if smoking were in fact **nicotinism**— smoking *relaxes* and *calms* them! Well… **smoke** *does* that… is becalming,

stupefying—as is well-known to bee-keepers! So-called 'junkies' likewise tend to be nervous, anxious types, and when withdrawing from *physical* dependency on *opioids*, they will suffer from *all* of the above… *but*, accompanied by *physical* withdrawal-symptoms: piloerection and perspiration (while one always feels that one is cold, however warm the weather); extreme physical weakness, want of energy, weariness, always being tired (but with insomnia by night), "feelin' 'bout half-past dead"; diarrhœa; twitching of the legs; a sort of hollow, whole-body-ache —as if one's 'center,' 'the seat of the soul,' suddenly were vacant. *Nothing* like this occurs in the case of **nicotine**… **just nothing** (neither, in the case of ***cocaine***—these two drugs have much in common, and combine seamlessly: in South América, shamanic cultures that use ***coca***, *always* accompany it with **tobacco**; as do the Bolivian Aymara *acullicadores*, or '*coqueros*').

Having done so a few times, I tell smokers that *it is easy* **to quit**: what *is difficult*, it **to continue** smoking! One has repeatedly *to procure*, then *pay through the nose for*, *cigarettes* (besides *work*, to earn the money to be able to do so); 20, 30, 40… even 60 times a day, *seize one*, *light it* (it might be, *after looking for the lighter*—maybe even for *the cigarettes*); *smoke* the filthy thing; then *clean-up the 'god'-awful mess*—the ash-trays, the fine dust over everything, when those smoke-particles settle; the films on the insides of all of the windows… by quitting, one does **just nothing**, does **none** of that—in the process, saving an hour or more each day, and a Hell of a lot of money! Sooth, 'tis **a lot of work**, *to continue* smoking; *quitting*… means lazing-off, on Easy Street! During some three years, endeavoring to understand the habituation to tobacco-smoking —hypothetically and, as it happened, *mistakenly*, as a **drug**-habit—I forced myself to become a one pack *per* da*y* smoker, for one full year; then, I quit, 'cold turkey'—there was **absolutely no withdrawal-syndrome**! At the outset of straight-nicotine-use, I was ingesting **100–150 mg** of nicotine daily (equivalent to **5–8 packs** of *cigarettes*), over periods of several months, frequently interrupted by foreign trips, for lecturing. While on-the-road, I ceased using nicotine altogether. Following several such abrupt cessations of nicotine-habits *far in excess* of those of any smoker, anywhere… **never** did I experience **the slightest** withdrawal-syndrome! As a rule, habitual use of *stimulants* (*amphetamines*, *cocaine*, *etc.*), although they *do* provoke a transient and short-term-tolerance, *is not* associated with any *physical* withdrawal-syndrome, upon abrupt cessation of a

lavish habit, and nicotine is no exception to this norm. There *is* an exception to every rule: lavish *caffeine*/*xanthine*-habits can occasion a ***physical*** **withdrawal-syndrome** [Dreisbach *et al.* 1943; Goldstein & Kaizer 1969; Goldstein *et al.* 1969; Ott 1985; White *et al.* 1980]. Over the years, I have offered straight nicotine (either in the form of *sublingual* drops, or when triturated-into ***pharmambíl***) to *hundreds* of friends and even conference-attendees, and found, in general, that **nicotine** ***is not especially popular***; moreover, that *cigarette*-smokers, if anything, were ***less likely*** than *non*-smokers, to enjoy its effects! *Cigarette*-smokers, obviously, like **smoking**… only some few of them, it would appear, also are fond of **nicotine**. Be that as it may, the often-commented "ambiguïties" of the widespread habit of *smoking* tobacco-*cigarettes*, would seem to bear a direct relationship, to the stubborn and illogical, ill-informed insistence, on characterizing this habit, as "**nicotine-addiction**," rather than what it so obviously is—a '**smoking-addiction**' (or, far more precisely, **smoking-*habituation***)!

As Johannes Wilbert quite thoughtfully established, pharmacology *does* "corroborate the nicotine therapy and practices of South American shamanism" [Wilbert 1991]. These psychonautic bioassays of nicotine—***pharmanunu***, as **tobacco-*snuff***-analogue, and ***pharmambíl***, as **tobacco-*paste***-analogue—substantiate his conclusions. Having bioassayed numerous South American shamanic tobacco-*snuffs*, and been an *habitué*, for more than one decade, of commercial tobacco-*snuff* (*McChrystal's Original*,™ by far the best product), I can attest that my *intranasal* sprays of nicotine-free-base mixed with water model effectively *insufflated* shamanic tobaccos, as well as their still-common citified derivatives. Likewise, I have bioassayed several shamanic tobacco-*pastes*, along with commercial and artesanal ***chimó***, and aver with confidence, that my home-made drops and ***ambil*** (or rather ***pharmambíl***, with nicotine-enrichment), faithfully model *this* less-common shamanic tobacco. Indeed, merely by removing the tobacco from an industrial *cigarette*, adding a pinch of ash or sodium-*bicarbonate* and moistening it, will elicit *far stronger sublingual* or *intranasal* [Plotkin *et al.* 1980] nicotinic effects, than the *smoking* of said *cigarette*. Nicotine *does not* vaporize at the temperature of a lighted *cigarette*-tip; and, in any case, is absorbed *far less* efficiently in the lungs—despite their much greater surface-area—than in the buccal or nasal cavities [Wilbert 1987]. Drugabuseologists seem convinced it is the converse.

Experiments with *R.J. Reynolds' Eclipse*™ (in which hot air from a lighted charcoal-tip would be sucked-through **tobacco**); and *Advanced Tobacco Products' Favor*™ (with a similar tip, but hot air would be sucked through *a wick saturated with* **nicotine**), showed that the great majority of the nicotine was being absorbed *in the mouth and throat*. Moreover, even with 10 inhalations of *Favor*™ *per* minute, only about *two-thirds* of the peak blood-levels from smoking a *cigarette* could be attained—and that took 30 minutes, as opposed to the *cigarette*'s 7–8 minutes. Only *intranasal* nicotine-solutions could equal the serum-nicotine-rapidity of *cigarette*-smoking [Russell 1992].

Nicotine clearly is the main active principle of shamanic tobaccos, but it may not be the *only* one. Originally, I had planned to extend my psychonautic bioassays, to the natural tobacco-analogues **anabasine** and ***nor*-nicotine**, which are little-tested in human pharmacology: but the vicissitudes of life intervened, and this project ended-up on the 'back burner, 'til it fell-off o'the stove! Doubtless, tobacco-companies have conducted research on anabasine and *nor*-nicotine, but such remains a proprietary 'trade-secret,' and they always have been loath, so much as to *intimate* that tobacco-smoking could be harmful, might lead to some 'addiction'; or that there were any reasons to search for *safer* alternatives (which, *ipso facto*, would be an admission that tobacco-smoking is deleterious).

In this psychonautic program, swiftly I established the grave deficiencies of the *half-baked* and *exorbitantly-priced* pharmaceutical nicotine-products: the *Nicotrol NS*™ nasal spray; and the *Nicorette*™ chewing-gum (both of which I was able *dramatically* to improve, after somewhat less than fifteen minutes in the laboratory!). The main reason 'nicotine-replacement-therapy' has been such a miserable failure, is that physicians and pharmacologists have been barking-up the wrong tree: tobacco-smoking *is not* a case of so-called '**drug-addiction**'… it most definitely *is not* so-called '**nicotine-addiction**.' Not only does nicotine *not* occasion a *physical* withdrawal-syndrome… but industrial tobacco-*cigarettes* deliver doses of nicotine *well below* the threshold to perceive its effects! The medical, pharmacological and pharmaceutical establishments have yet to perceive that, in reality, they are dealing with the recondite phenomenon, of '**smoking-**

addiction'—***what*** is being smoked, possibly, is all-but inconsequential! **Smoking**, *per se*, for reasons which mystify me (I find the practice *distasteful*; besides being *messy* and *dirty*: even for some *half-way* punctilious housekeeper), is **extremely habituating**. Alas!, **nicotine** has suffered considerable reputational harm, by its irrefragable association, with **tobacco-smoking**. Nicotine is an invaluable *mental stimulant* (one of the "ambiguïties" of the *cigarette*-smoking-habit, is that smoking *sedates*, rather than *stimulates* the smoker): together with ***opiüm***, ***caffeine*** and ***cocaine***, is an imprescindable ally for writers like me. The fact that nicotine likewise is *neuroprotective*… well, that's just *icing on the cake*, as I have embarked-upon my *fourth* quarter-century of life!

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