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< HEALTH AND MOLECULAR DISEASES >

SPECULATING ON THE GLOBAL SPREADING OF MOLECULAR DISEASES:

HOW SHOULD MANKIND REACT ?

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According to biochemistry and biology, all life's systems are run on the same lines of simplicity, as physical phenomena. Man's laboratory is Nature's. Everything obtained by laboratory synthesis can be found in Nature, and everything Nature makes can be obtained synthetically in the laboratory: *Natura enim simplex est* (Newton, 1687).

In this paper we shall review the structural and biogenetic similarities between neurotransmitters synthesised by nerve cells and some psychoactive indole and isoquinoline alkaloids – the former metabolites from the animal world; the latter from the plant world: different origins and targets for structurally similar chemicals, despite their different biological activities. Two worlds – animal and plants – which collide in the brain, causing a whirlwind of effects.[2]

We shall furthermore discuss the brain's ability to synthesise aberrant metabolites of the catecholamines, forming psychoactive compounds which are structurally related to the isoquinoline and indole alkaloids, how these aberrant metabolites affect behaviour and how they are involved in *molecular diseases*.

Chemical and physical agents from our heavily polluted environment can directly or indirectly trigger abnormal chemical reactions – mainly through oxygen free radicals – in our bodies. There follows a cascade of degenerative processes, some of them irreversible, often leading to forms of dementia, psycho- and neuropathies and behavioural disorders.

Today's understanding of the situation suggests that our brain interacts with exogenous and endogenous chemico-physical compounds to give rise to neurochemical alterations, which set in motion abnormal chemical reactions and change our body's functions.

This brings us inevitably to the question of the line between normality and folly, and consequently between acceptable and unacceptable behaviour. The boundaries between normal and pathological

tend to get blurred, unbalancing classic psychiatric patterns and society's traditional rules of good behaviour. This fine line between normal and pathological, between order and disorder – even between good and evil – has a **molecular interface**: a brain swarming with structurally related molecules whose biological functions are sometimes similar but sometimes different – sometimes even opposites.

A ketone group instead of a hydroxyl, a saturated rather than an unsaturated bond, are what underlie the vast gap dividing the sexes; a methyl group, a methoxyl and some other simple constituent can transform normality into madness.

This is the background to the perturbing picture of a changing, plastic brain, a turbine of neurons and synapses churning all the time between past and present – constantly moving and adapting itself in a never-ending chain reaction. The brain exists in a constant state of adaptation, creating the present, memorising the past, planning the future.

In plants, alkaloids are formed in physiological conditions from simple components, by casual, not enzymatic reactions. 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, aberrant dopamine metabolites have been isolated from the urine of healthy individuals, from patients treated with DOPA, and post-mortem from the brains of patients with Parkinson's disease.

Clinical confirmation that in abnormal conditions our brain can form dangerous aberrant metabolites brings us back to the theory of **molecular diseases**. It would be worth checking experimentally to see whether people hit by sudden, irrepressible urges to homicidal violence (*amokläufer*) have in their urine, plasma or post-mortem brain hallucinogenic alkaloids derived from abnormal catecholamine metabolism. According to our hypothesis, such people would be rather patients, suffering of molecular diseases.

Dopamine is involved in the pathogenesis of schizophrenia. Amphetamine and its derivatives, and also the hallucinogen mescaline, are structurally related to dopamine. Hypothetically, therefore, in abnormal conditions the brain might even synthesise these drugs itself, giving rise to pathological symptoms.

Serotonin plays a role in depression. In the brain abnormalities of the serotonin/melatonin metabolism can give rise to hallucinogens related to **armanic** alkaloids. When methylated on nitrogen, serotonin becomes bufotenin, methylation and methoxylation of dopamine convert it to mescaline. Both are powerful hallucinogens. The two reactions can easily be reproduced in the laboratory, and there is no reason why they should not occur in the brain in today's abnormal living conditions.

Underlying Parkinson's disease there may well be a degenerative process of the dopaminergic neurons in the *substantia nigra*, resulting from attack by oxygen free radicals which are formed locally using iron as a catalyst. We believe, that Parkinson's disease is a consequence of disruption of the dopamine-neuromelanine pump, by radical oxidation of dopamine. Once started, the neurodegeneration proceeds by self-catalysis until some unlikely arrival, such as radical scavenger, breaks the chain or the neuron dies:

Is the neuromelanine produced for a purpose or is it trash? It would be worth investigating in detail the bioelectrical properties of neuromelanine and its role in the conduction and modulation of nerve impulses regulating the locomotor system. As a matter of fact, in the *substantia nigra* of newborns, we observe a lack of black pigments, which start to be formed around the end of the first year of age, only. Knowingly, the newborn is unable to coordinate movements. In Parkinson patients again, we observe in the *substantia nigra* a strong deficit of black pigments and an impairment of movement coordination. **Are black pigments and movement coordination maybe correlated,**

due the conducting properties of melanins?

According to the free radical theory, ageing is a consequence of radical chemical reactions which combine with environmental and genetic situations to cause lethal alterations in an individual. Various pathologies are linked to the action of oxygen free radicals.

The brain of a drug addict differs qualitatively from that of a normal person – it uses glucose differently, its gene expression is different, and it responds its own way to environmental stimuli. Drug addiction is basically a brain disease, the mesolimbic dopaminergic system being activated by most addictive drugs. The current “epidemic” of drug addiction is aggravated by other serious public health problems such as AIDS, sexually transmitted diseases, mycobacterial, fungal and viral superinfections. It is also made worse by the regular appearance of newly developed drugs that are even more dangerous for the nervous system.

As if these problems were not worrying enough, we also have to take account of the harm done by environmental pollution (*molecular diseases*).

Many factors contribute to suicide: biological, psychological and cultural. Suicide is peculiar to mankind and crosses frontiers. None of the many interpretations that have been advanced so far gives a satisfactory explanation of the reasons behind suicide.

The suicide rate among the elderly is the highest of all and it has not decreased significantly after the advent of antidepressants. On the other hand, rates among the young have increased sharply in the last twenty years. Social and economic factors (unemployment, stressful way of life, serious family problems, somatic diseases and mental disorders, etc.) augment the risk of suicide but they are not the only causes.

Altered cerebral neurochemistry, low serotonergic and noradrenergic tone, reduced cerebral neurotransmission, with low levels of neuromelanin, increase vulnerability and proneness to suicide, but do not determine it neither singly nor jointly. Drugs and alcohol are important co-causes. All suicides present reduced serotonic tone. However, only a minimum percentage of persons with a low tone commit or plan suicide.

We advanced two hypothesis, to explain the genesis of suicide:

- 1) Suicide is a physiologic event: either a simple casual error, an action planned by the organism to eliminate, analogously to cellular apoptosis, weak individuals that are not very interesting from an evolutionary point of view. The mediator that is thought to trigger suicide is called “LETRA” (Lethal Transmitter).
- 2) Suicide is a pathologic event: at molecular level, it is a casual metabolic error. Rather to be a physiologic transmitter, LETRA is an aberrant metabolite of catecholamines with hallucinogenic properties. It originates in the brain through oxidative radicalic aggression.

“The wind hits those with a light head, the weakest. It gets into their bodies through their nostrils or other orifices; or it sits on their heads. It makes their bodies hot and stiff; it clenches their teeth and gives them a headache. They start to say and do mindless things. If it is not treated it can be lethal. It is not madness but can become it. Spirits are carried along with the wind – not the big wind that precedes the rain, not the sand wind that heralds the end of the dry season, but light, unexpected, insidious breezes: the puffs and whirlwinds that whip across the high plains, across the paths, stirring up the sand and dry leaves. They are home to the woodland spirits, the souls of the dead that know no peace.”

Tale of the African people Mali

It must have been a century ago that Sigmund Freud, the “father” of psychoanalysis, announced categorically that [there is]: “...only one cause of all mental illness, even the most severe: an inadequate upbringing. Everything depends on how one was treated as a child.” Many decades were to pass for a more balanced view to take hold. Giovanni Cassano summarized it as follows: “...melancholy, moral suffering and mental distress have always been attributed to mankind’s higher spheres – the spirit, heart and soul. Our humanistic training, our idealized concepts of the individual, are repelled by the idea that chemicals, be they substances found in the brain, or drugs, can change our view of the world, our way of being.”[3]

Most people are well aware that our organism suffers wear and tear, that our heart, intestine, liver, kidneys, lungs, eyes, etc. can all break down even to the extent of needing replacement, when this is possible; still, though, most of us are unwilling to accept the idea that the brain is an organ just like all the others, and that mental illness has biochemical roots. Many patients thus fail to recognize the real causes of their disease in time, and waste efforts on hopeless therapies or even illegal drugs in vain attempts to free themselves of suffering and nightmares.

This brief “background” led me to formulate a chemical interpretation of the many afflictions involving our brain. This approach gave rise to a fascinating hypothesis: various psycho- and neuropathies, and behavioral disorders, can be grouped in a new class, with similar etiopathogenesis - I call them **molecular diseases; most of them being caused by undue action of exogenous chemical and physical agents on our bodies.**

To explain the plague that had devastated Athens, Lucretius maintained that contagious material and rotting things gave off tiny germs, which he called *semina*, that infested the air, water and food and caused illness in anyone who came into contact with them. Fracastorius of Verona, the physician who gave syphilis its name, picked up the threads from Lucretius, concluding that the germs that caused these ailments were capable of reproducing themselves (*seminaria consimilia sibi alia generant et propagant*).^[4] In 1840 Jakob Henle suggested that “*the infective material is not only organic, but viable, with its individual life, and has a parasitic relationship with the diseased body*”.

Lucretius, Fracastorius and Henle are three of the steps in naturalistic thinking that developed through Koch, Pasteur and other microbiologists, evolving towards modern theories on the etiopathogenesis of infections.

The environment we live in today has undergone biochemical changes. We have only to compare the composition of the biosphere a century ago and today: it pulses with billions of molecules, most of whose structure and biological activity we know nothing about. Another factor to be borne in mind is the action of man-made radiations on our central nervous systems and other vital organs. The planet’s water reserves are increasingly polluted with heavy metals, toxic wastes, pesticides and other chemicals used in agriculture, and industrial by-products. The air is filled with smoke and fumes from the chimneys of millions of homes and factories, and the emissions of our combustion engines, while the oceans are fast becoming a cemetery for the flora and fauna of the water.

This vast bio-ecological aggression on our brains involves a huge variety of pathogens, and their interactions, while our organisms grow more vulnerable as they become older.

In the first century before Christ, Pliny had already grasped how poisonous lead could be, and tried to persuade his fellow citizens not to use the “*sugary Saturnian crystals*” to sweeten their food and drinks. The crystals that formed when wine fermented in lead-glazed jars were no less than pure lead acetate – sweet and delicious, but lethal to the kidneys and brain. Lead poisoning, or “*plumbism*”, gradually decimated the aristocracy and legions of ancient Rome, contributing to the fall of the Empire. Pliny certainly would never have imagined that despite the hard lesson learned from Saturn, man would have persisted in poisoning his world with lead, but this time with tetraethyl lead, the “*sweetener*” of petrol.

Another threat hangs over the food chain. Every time we eat fish from lakes or streams fed by acid rain or polluted with industrial waste waters, we are exposed to excessive concentrations of lead, aluminum, mercury, cadmium, nickel and other heavy metals. The acid waters can also dissolve the lead still used for many water pipes, which becomes another source of “**Saturnism**”. Epidemiological findings indicate that high lead levels in the blood, common in many cities, are correlated with a significant lowering of the intelligence quotient (IQ) among school children.[5]

Today, we have access to an unprecedented variety of mood-altering drugs. We also have ample understanding of the harmful effects of alcohol, cocaine, amphetamine-like substances, heroin and other opiates, hashish, nicotine, LSD and other alkaloids.

Diseases like the plague, syphilis, cholera, smallpox, German measles, scarlet fever, tuberculosis, malaria and poliomyelitis have decimated humanity at various times. The molecular diseases have taken their place – or perhaps only flanked them. The combination of live germs, pathogenic molecules, and free radicals is not merely formal, but is significant from all viewpoints. Chemical infection, just like bacteria and viruses which attack us orally and topically, through our skin, mucous membranes and conjunctiva, enter our bodies in the air, water, soil, food and drinks.

Like many germs, pathogenic molecules and free radicals can often be inactivated by heat (sterilization), by molecular filtration (ultrafiltration), or by contact with other active substances (disinfectants). There may, however, be some synergism of action between live germs and their “chemical” counterparts.

Heavy drugs frequently cause immune system impairment, and can speed up the progression to AIDS in HIV-positive patients. Heavy smokers suffer chronic inflammation of the respiratory tract caused by the toxic action of tobacco combustion products. These people are susceptible to bacterial, viral and fungal superinfections, which can even sometimes be fatal. Many of the molecules and free radicals in the air of our cities (SO_2 , SO_3 , ozone, NO, NO_2 , and others) are irritants for the conjunctiva and respiratory tract, predisposing to bacterial and viral infections. Some of the pyridine derivatives found in pesticides are toxic for the dopaminergic cells in the brain and may contribute to the onset of Parkinson’s disease. An excess of aluminum reaching the brain can cause structural alterations to certain proteins, facilitating the subsequent development of Alzheimer’s disease.

Another widespread problem is passive smoking, which can cause serious illness in non-smokers. The toxic chemical in this case is transferred from the smoker to the people around him, in a sort of process of contagion through the respiratory tract, traveling in much the same fashion as airborne bacterial and viral infections like influenza and tuberculosis.

These poisons we absorb with the air we breathe, in the water we drink and food we eat, harm our bodies; they make their way to the brain and other vital organs, interacting with other substances,

and triggering true “molecular diseases”, caused not by living microorganisms, like those discovered by Koch and Fracastorius, but by chemicals, or by both.

Four particular classes of chemicals merit our attention here:

1) heavy metals (Pb, Al, Cd, Ni, Hg, Sn, Zn, Fe, etc.)

2) various natural and synthetic organic molecules widely used in or as medicines, pesticides, food additives, legal and illegal drugs, etc.

3) organic fragments from the combustion of fossil fuels (coal, oil, etc.), tobacco and other organic products, such as refuse

4) prions (proteins with no genome).

For thousands of years humanity was periodically afflicted by pestilences, that seemed to have become a thing of the past: conquered, routed for ever. But that was not to be – they have reappeared, in modern guise, possibly even stronger and certainly more treacherous than ever. Disease is manifest in the myriad ailments afflicting living things: plants, men and animals. There is no life without ailments: life and disease seem to share roots, inexorably linked to the same fate. With our ailments, the future is already written clear in our genome. Life is a series of happy and less happy events, many of them apparently “predestined”, others the result of pure chance.

Our forefathers rejected the idea that man had been afflicted with illnesses since he first appeared on this earth. Hesiod maintained that “*the human race lived on the earth apart, and sheltered from suffering, from hard fatigue, and from the painful diseases (noùsoi) that bring death to men*”. Then came Pandora’s box. Plato rationalized the myth of the Golden Age, explaining that most of the afflictions were caused by luxury, laziness and too much rich food.

In modern times the myth of historical decadence is being replaced by the idea of progress, interpreted in absolute terms, and certainly no less of an illusion. In the beginning, Man, freed of Prometheus’ bonds, started on his long and tortuous path: from tribal life to the Neolithic era, to the cities of classical Greece; from the provinces of the Roman Empire to the primitive medieval hospitals – burning witches along the way, medicine men, charlatans, healers, philosophers and self-proclaimed scientists, all lumped together trying to exorcise pain and disease.

So what’s new today ? It was almost two thousand years later, in 1715 at Leiden, when Boerhaave confirmed it was time to turn over a new leaf: “*We must consider illicit those metaphysical reasonings where so many philosophers have lost their way, and confine ourselves to*

results obtained and confirmed by experimentation. Let us abandon metaphysics and move towards physics. This is the only way to find out the true characteristics of nature that we have overlooked so far.”

Does he mean we must forget Hippocrates ? In our anxiety to reach the future we risk neglecting the past. But, as Carlo Levi wrote, “*the future has an ancient heart*”. Even if we forget them, we still trail those old habits along with us, deep-rooted in our culture.

The pain stimulus is universal even though it causes different levels of distress in every individual. Hence the centuries of efforts to relieve it. Sedation and self-medication are closely linked in the past and present, including the use of heavy drugs. Self-medication, sedation for pain and suffering, and artificial paradises are all dictated by our neuronal structures; they are just one of the outlets for man’s culture of deception, built up by *homo sapiens* to cheat himself.[6]

In the industrialized countries most deaths after the age of 30 are due to pathologies related to aging, which brings us back to the theory of free radicals. Aging is viewed as a consequence of chemical reactions which, combined with environmental and genetic circumstances, induce lethal alterations in the body. It should therefore be possible to prolong life expectancy by delaying the start of these radical reactions, or shortening the chain reaction by reducing oxidative stress. Free radicals come from normal enzymatic and non-enzymatic reactions, and they can react in biological fluids, cells and tissues. Their high level of reactivity means they tend to react with a wide variety of structures, such as nucleic acids, proteins and carbohydrates, etc., present in the organism: this is why they are so dangerous.

Some examples illustrate the range of diseases, many of them life-threatening, believed to originate in the free radicals [7]:

- **various malignant tumors (due to the mutagenic effects of free radicals on DNA);**
- **arteriosclerosis (due to the interaction of endothelial cells with low-density lipoproteins – LDL – oxidized by free radicals);**
- **essential hypertension (due to the action of the O_2^- radical on the endothelium);**
- **amyloidosis (due to radicals causing oxidation of amyloid precursor protein – APP);**
- **senile immune deficiency (due to weakening of the immune defences);**
- **Parkinson’s disease (due to peroxidation of membrane lipids, and deficit of dopaminergic neurons in the substantia nigra).**

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The brain has a high concentration of lipids, high oxygen consumption, and limited amounts of antioxidant enzymes. The brain also has a substantial supply of iron in the form of various protein complexes: ferritin, neuromelanin, etc. If this is released inappropriately it can catalyse the production of oxygen free radicals, the cause of oxidative stress.[8] The brain is a chemical laboratory where thousands of compounds, some of them highly reactive, are formed, transformed, and excreted, apparently incessantly. Chemicals with all sorts of structures are processed continuously, for numerous highly specific purposes, under the watchful eye of tiers of enzymes. The whole system is a model of order.

The brain, however, is the organ with the highest oxygen consumption, and the highest turnover of free radicals, which can lead to unpredictable, unexpected reactions – sometimes producing aberrant metabolites. Chemical and physical agents from our polluted environment can trigger anomalous chemical reactions in the body. These in turn can set in motion cascades of degenerative processes, sometimes irreversible. Alcohol, smoking, coffee, drugs, environmental pollutants, exhaust gases, industrial fumes and smoke, incorrect eating habits, and medicines taken over the years all contribute to the involution of the brain and the onset of psycho- and neuropathies: parkinsonism, maniac-depressive states, schizophrenia, Alzheimer's disease – and molecular diseases.

In plants alkaloids such as morphine, cocaine, mescaline, etc. form in physiological conditions from simple components. Alkaloids identical to these natural products can be synthesized in the human brain too, by chance, by non-enzymatic pathways.[9]. Here we have the clinical confirmation that in abnormal conditions dangerous aberrant metabolites can form in our brains, taking us back to the theory of the origin of molecular diseases: “**the chemical plague of the third millennium**”[10].

LITERATURE AND NOTES

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[9] M. Sandler et al. <*Tiq alkaloids: in vivo metabolism of L-DOPA in man with Parkinsonism and in DOPA treated Parkinsonians*> Nature 241, 439-443 (1973);

[10] **It might be worth checking, whether the urine, plasma or brain of individuals who < run amok > and commit violent homicides, contain hallucinogenic alkaloids derived from the aberrant metabolism of catecholamines. If so, these would be patients with molecular diseases, not murderers in the usual sense of the word.**