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# AN ESSAY ON HUMAN AND ELEMENTS, MULTIELEMENT PROFILES, AND DEPRESSION

**Abstract**

The recent development of the analytical techniques offers the unprecedented possibility to study simultaneously concentration of dozens of elements in the same biological matrix sample of 0.5 – 1.0 g (multielement profiles). The first part of this essay entitled "Think globally… An outline of trace elements in health and disease" aims to introduce the reader to the fascinating field of elements, there importance to our nutrition, their essentiality, deficiency, toxicity and bioavailability to the body and their overall role in health and disease, including the genetic metabolic impairments. In the second part of the essay entitled "… and act locally. The multielement profile of depression" we aimed to show the potential of such a hair multielement profile analysis for the study of human depression in a randomized, double blind, prospective, observational, cross-sectional, clinical, epidemiological, and analytical study. The preliminary results of this ongoing study lead us to put forward the hypothesis that the metabolic origin of depression may be due to some "energostat" failure, probably located in the thalamus, and activated by several essential element deficiencies.

**Keywords**

Elements • Essentiality • Deficiency • Toxicity • Food • Environment • Health • Disease • Metabolism • Genetic disorders Hair • Biological matrix • Multielement profiles • Elementome • Depression • Energostat failure hypothesis

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## "THINK GLOBALLY …" AN OUTLINE OF TRACE ELEMENTS IN HEALTH AND DISEASE

*Elements, essentiality, deficiency, toxicity*. Like the Universe, we are all built from the elements that combined in the molecules provides the structure material of all the known living creatures. From the dawn of the human civilization, people tried to elucidate the essential elements of the nature from what all the rest of the forms have been made. Greeks know the four elements of water, fire, earth and air, whereas the Chinese have eight of them but only five were important to medicine, i.e., fire, earth, metal (breath), water, and wood. To be truthful, these elemental schemes were primarily symbolic but, nevertheless essential for the construction of the first visual networks (then called mandala). Today, we live in the real world comprised of 92 stable elements and with the number of those manmade included, this moment the total of elements we know is 118; more than ten of the artificial elements don't have a name as yet. Not all of these elements are essential for the life and human life in particular. The reason for this distinction of being essential or nonessential is a matter of intensive research [1,2]. Some metallic ions were already classified as chaothropic or cosmothropic depending if they help the structure decomposition or formation, respectively [3]; even a spiritual component was involved in search for answer to such a fundamental question [4].

An element is essential if the growth, maintenance, health, and reproduction of an organism is dependent upon it. They are essential since the human body can't synthesize them and hence depends on their regular intake via the food we eat, the air we breathe, and the water we drink. Some twenty plus elements are essential and the heaviest of them is iodine (Figure 1) [5]. Today, there are 28 essential elements considered to be necessary for the human life (element symbol and sequential number in the Periodic table): Hydrogen 1, B5, C6, N7, O8, F9, Na11, Mg12, Si14, P15, S16, Cl17, K19, Ca20, V23, Cr24, Mn25, Fe26, Co27, Ni28, Cu29, Zn30, As33, Se34, Sr38, Mo42, Sn50, and Iodine 53. As evident from their primary function, i.e., essentiality, any impairment of the intake of essential elements would destabilize the homeostatic control of the body functions and hence, by decreasing the adaptive potential of the body, would make it more vulnerable to cope with the unfavorable environmental conditions [6].

Thus, depending upon the available intake, the actual dose of an element received by the body may be whichever deficient, adequate, or toxic. Indeed, if there is a complete lack of an essential element, the poor creature would die; it would gradually strive better and better with gradual increase of the element in the diet until some optimal function is attained. Above that concentration level the pharmacological effects would start to appear until the overt toxicity is induced and the death is incurred (Figure 2). That diagram by late prof. W. Mertz, one of the pioneers of the trace element research is an elegant description of old Paracelsus dictum that "*Dosis sola facit venenum*" (only dose makes

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a poison). Today, the later dictum should be expanded to include the dose rate, to cover for the chronic *vs.* acute element exposure, as demonstrated by the idiorrhythmic dose rate feeding model [7].

*Balance and interaction*. Further experiments have shown that all the essential elements should be present in the body in both right concentrations and proper mutual proportions in relation to one another [8]. If both conditions are not satisfied, the state of imbalance is present; of course there is an acceptable range for such a variability before an imbalance or toxicity could be recognized by analytical (element concentration), enzymatic (target enzyme involvement), or overt clinical manifestation. The first to recognize how the proper mutual relationship between the concentration of the elements are crucial, was a Danish chemist Justus von Liebig who stated that the element in the shortest supply is the growth limiting factor, i.e., even if all the other elements are in optimal supply they can't be used because of the one that was lacking (Liebig's Law of the minimum). Moreover, under the conditions of an element deficiency some other element can act as a provisionally (conditionally) essential element. Indicating that some elements have common, partially overlapping functions, manifested as synergism or antagonism, and what is of vital importance to allow for the adaptation to the changing environment. The elements having similar metabolic properties for the human body may, to some degree substitute one another. Thus, if the body is rendered deficient in iron, the absorption of metabolically alike manganese would be increased [9].

The more complex situation occurs when some elements are deficient whereas the other happens to be excessive at the same time. In such a case the synergy and/or antagonism among the elements gets very important (Figure 3), i.e., it is not the same if the concentration of iodine is low and the concentration of selenium is either low, adequate, or high. If both iodine and selenium are low that would depress the metabolism, if iodine is low and selenium adequate the balance would be further impeded by the presence of relative selenium abundance for what there is no enough iodine to react upon, and if iodine

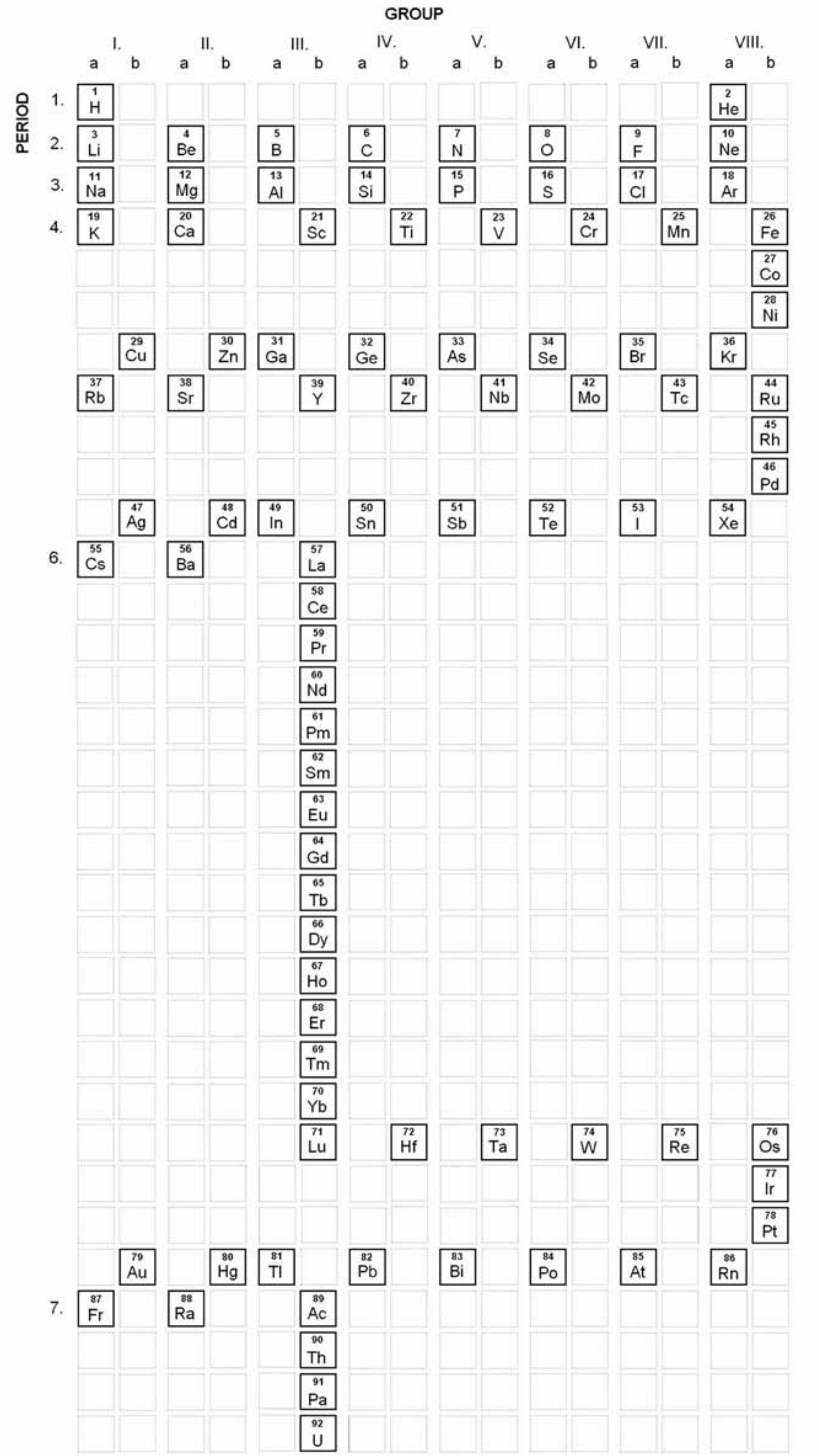



Figure 1. The Periodic system of elements (Elementome).

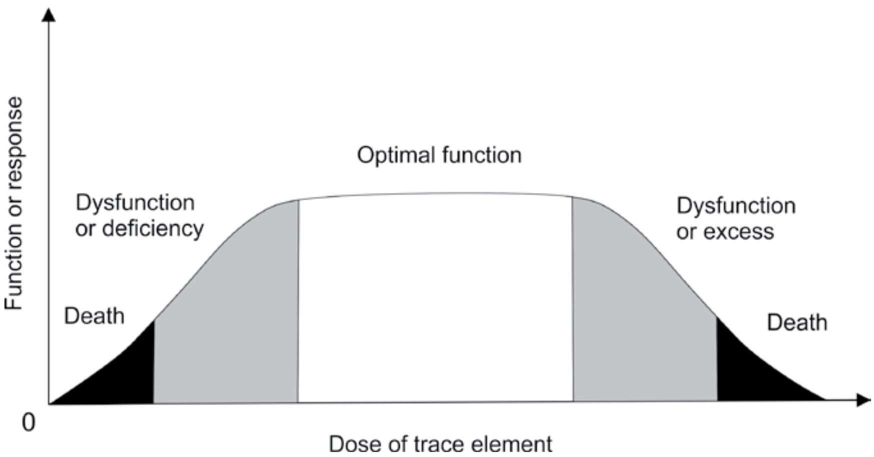



Figure 2. Biological function of an element depends upon its concentration.

is low and selenium is high then the dangerous "burn out" of the thyroid metabolic function may occur. Or even worse case scenario, if the concentration of mercury is increased, whereas that of iodine and selenium is decreased, that would additionally compromise the already low metabolic performance of the thyroid. Such combinatorial situations are numerous in multielement profile data interpretation, and they are currently beyond the analytical capacity of any available computer software available today. The existing software can identify the lack or excess of some element of the multielement profile, but it needs the expert hand to identify multiple interactions, especially if they are of diverse deficiency/excess type. A note of warning is needed here as interaction maps like this shown in Figure 3 are inherently limited, since not all the possible interactions has ever been studied. Indeed, some element interactions were studied to a much greater extent than the other, depending upon the time of their discovery when their essentiality (or toxicity) have been recognized, and also about their total amount in our diet and/or chosen biological matrix of the body; what rendered them more accessible to the analysis owing to their greater mass in the studied biological matrix. Thus, such interaction maps are subjective to qualitative and quantitative expansion by including of the new facts about who is reacting with whom and at what dose concentration such interaction occurs. The map envisaging the totality of the quantitative aspect of elemental interaction hasn't yet been reported since it would need infinite number of concentration of one element to be compared with the infinite span of concentrations of some other elements and so on.

*Food and bioavailability*. The majority of elements enter human body via food. Now, food itself is not some imaginary homogenous stuff; every natural member in our food chain, from apple to meat, is a distinctive genetic package that is more or less available to our digestive capability. Indeed, human cannot prosper on grass since we do not have enzymes in our gastrointestinal tract to digest cellulose, whereas grazing cattle has such enzymes and get sugar from the cellulose to sustain their metabolism. Moreover, elements from the different food sources are of different biological availability (bioavailability) to our digestion, i.e., some food items may have the same amount of some element by chemical analysis, but the amount that could be absorbed to the human body from such a food source may be quite different. The saga of the popular cartoon character "Popeye the sailor" was based on the analytical data showing exceptionally high amount of iron in the spinach; however, less than 1% of that iron can be absorbed in the human body what renders the iron bioavailability of spinach as one of the lowest known to all the food items comprising the human diet (blood iron is of the highest bioavailability).

*Requirements*. Thus, the amount of elements in our diet depends upon the specific food sources available for diet composition, the quality and quantity of such foodstuff in our living environment, and their bioavailability to our bodies. The dietary needs for the essential elements are different in their quantity, e.g., the required amount of calcium is much higher than that for selenium, and so on. Special food tables have been established on how much of an element should be presented daily in our food, what are the upper limits for such element intake, are there specific sex and age restraints, what are the specific requirements of an element in pregnancy, lactation, and newborn [10,11]. Not surprisingly, the rate of absorption of any element in the human body, the kinetics of their tissue distribution, possible target organ deposition, and elimination from the body varies from element to element, and may be dependent upon the age and sex, and different in health and disease. Many elements have entire books devoted to describe their whereabouts to a great extent. Modern armies are especially interested on how much of an element would be present in the military food ratios so that the solders can stand longer the heavy duty physical tasks and at a lesser health risks, including on how to improve the possible wound healing processes. Indeed, if you are zinc deficient, your wounds would also heal at a slower rate [12].

*Genetics and disorders*. Today, there is the well-defined clinical pathology of some health conditions associated with the elements and their metabolism in the human body. Hemosiderosis and Wilson's disease are the well- recognized clinical conditions related to the respective excessive tissue accumulation of iron and copper. Dermatitis enteropathica and the Menke's disease are the well- defined genetic disease of impaired zinc and copper absorption, respectively. Many parts of the world are endemic for their nutritional deficiency or excess of some elements - Iodine deficiency disorders are the huge world-wide problem in Asia, Africa, and Australia (aborigines), and now on rise in the Western Europe (Italy, Germany, UK); fluorosis and arsenic overexposure are common in under the Himalayan region of India and Pakistan, and from the water wells (arsenic) in Bangladesh, respectively. The iron deficiency anemia is the most common metabolic impairment of an elementome member in the world, a special form of cardiomyopathy was discovered in

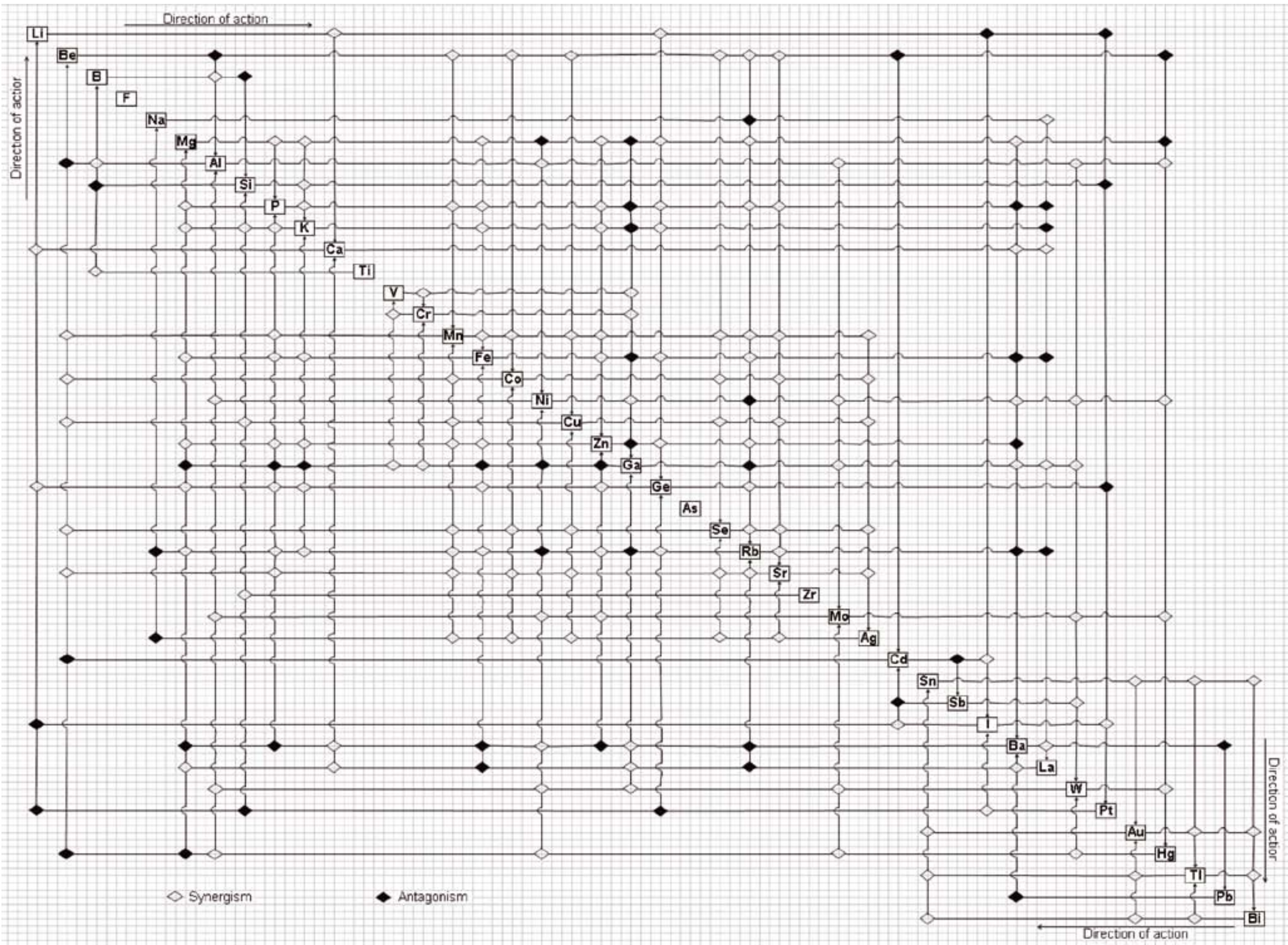



Figure 3. Reported elemental interactions (®2008).

China, and is now known as Keshan heart disease due to the selenium deficiency. The impaired body growth and delayed sexual maturation observed for the first time in Iran, has been proved to be the consequence of chronic zinc deficiency. Some forms of human alopecia areata totalis were proven to be the result of dietary zinc deficiency, perhaps due to the increased individual requirements of the body for that element. At Medical schools we all learned about the rickets, a bone disease associated with the impairment of the calcium and vitamin D metabolism, respectively. Evidently, dietary deficiencies of some essential trace elements are a world- wide phenomenon of great public health importance. Moreover, any high physical performance demands may aggravate the underlying trace element deficiency, e.g., our two most prominent sport women in skiing and high jumping underwent the thyroid surgery due to the most likely unrecognized iodine deficiency [13-15].

*Toxicity*. On the opposite side of the element deficiency is the element toxicity. Likewise, the fact that dose high enough can make every essential element toxic, there is the group of elements that under the normal, i.e., habitually observed, concentrations appears to be indifferent to the function of our metabolic machinery (non-essential elements), whereas some elements are overtly toxic to our body even at a very low concentrations. The most notorious are the so called heavy metals of notably lead, cadmium, and mercury with their profound effects to the impairment of the cognitive capacity and nerve, blood, and kidney damage. Elemental arsenic, molybdenum, beryllium, gallium, and antimony are also considered to be toxic to the body at a very low concentration. Similar holds for the naturally occurring environmental radon, a radioactive mother to the chain of the poisonous heavy element daughters of bismuth, polonium, and lead. The majority of elements heavier than iodine are toxic to the human at a very low concentration. Naturally, simultaneous combined exposure to several toxic elements would result in a more severe form of element poisoning than if they were administered separately; the same principle of multiple targeting is used for cancer therapy where different drugs acts simultaneously upon the different stages of cell cycle division [16]. As a matter of fact, lead was attempted for cancer treatment in the 20-eth of the last century, evidently with not much of a success.

The ill effects of metal and metalloid overexposure to Al, Sb, As, Ba, Be, Bi, B Cd, Cr, Co, Cu,Ga, In, Ge, Au, Fe, Pb, Li, Mn,Hg, Mo,Ni, Nb, Ta, Pt, Pd, Ir, Rh, Os, Ru, Y, La, Se, Ag, Te, Tl, Sn, Ti, W, V, Zn, Zr and, Hf are well known in the industrial setting of the occupational medicine. Today, the metal and metalloid elemental contamination has spread from the industrial backyards into the entire human environment and thus presents a constant threat to human health and well- being. It has been documented that the increase of the environmental lead is directly proportional to the reduction of the IQ in children – and there are so many other elements comprising the environmental pollution exposure of which we know nothing about. It should be noted that quite a number of quoted industrial toxicants is essential at a low concentrations [17,18].

*Allergy*. It's interesting that some essential elements like Ni > Cr >Co in dental metal alloys, iodine in contrast enemas, Pt in anti-cancer drugs, As in taxidermists, and Be in metal workers, can induce serious allergic skin and organ system sensitivity. How is that possible that the essential elements like Ni>Cr>Co can induce allergic response (presumably as haptens), and at the same time be essential for life, remains to be elucidated [19]. Thus far, no common denominator was identified which may explain such apparently paradoxical outcomes [20].

*Multielement profiles*. Until recently, the analysis of elements in various biological matrices was a hard task for many elements, especially those that can be found in the human body tissue in minuscule concentrations of few micrograms per gram (Engl. *trace elements*, Franc. *oligoelementes*, Germ. *spurenelementen*). The situation was additionally complicated by the fact that elements can be analyzed only separately, one after another, that in many cases they should be concentrated prior to the analysis, and not the least, that the amount of the available biological sample (biological matrix) is not without the limits. The new era in element research came to being with the development of advanced analytical instrumentation, notably the inductively coupled plasma mass spectrometry (ICP MS), what allowed for the simultaneous determination of tens of elements from the same biological sample of less than a gram and at the same time. Thus, after an era of a single element concentration measurement in whatever biological matrix, we entered the era of multielement profiles (MP) that became accessible to the general medical practice. Even the more so, since previously some elements were very hard to assess, and there was a small chance that the obtained results would ever leave the research laboratory, or have an impact beyond the scientific paper addressed to a very limited audience. Today, some of the elements are, so to speak, in a search for their biological function – they were quantitatively analyzed, but there are no data on their possible biological effects. The other problems associated with the suddenly available plethora of multielement profile data is how to meaningfully analyze them, considering the antagonistic, neutral, or synergistic mutual affinity of the elements under the condition of fluctuating concentrations due to the innate biological variability. Until now, our common reasoning would concentrate on one element vs. another, and almost all the developed statistical methods are tailored to solve such dose/response or yes/no problems. Now, we confront the network type of reactions where a group of elements at different concentrations are mutually related, better say entangled in a metabolic life web, and new statistical methods are needed to study such complex situations. Perhaps, bioinformatics developed to handle the huge data sets from the genome and epigenetic research would help us to generate the adequate software packages to solve the problem of simultaneous multifarious, i.e., multielment, interactions and what is now left to the decision making capacity of the researchers.

*Indicator tissues*. Evidently, any biological matrix can be subjected to the multielement profile analysis and any of them would provide us with the valuable data about the functional metabolism in the various parts of our body and in various medical conditions. However, not all the tissues are accessible for sampling and analysis, notwithstanding the ethical reasons. Taking biopsy tissue samples, or any other invasive medical procedure, can be both painful to the patient and laborious for the doctor, and it is still an open question how valuable it would be for the diagnosis and treatment of the involved subject condition. However, Mother Nature endowed us with an easily accessible bio-indicator biopsy tissue (biological matrix), and that is hair and nails, the omnipresent skin appendages (save for alopecia that is already a disease condition). Most commonly, we studied the changes of some parameter in the blood, or watch its excretion via the urine and feces. However, concentration of any element in the blood is subjected to the ceaseless dynamic homeostatic equilibration between the various biochemical and structural compartments of the body, i.e., their kinetics and organ targeting, with the end result that any element in the blood is in the state of the permanent flux, and it depends upon the circumstances if you are lucky enough to pick up any moderate element time dependent change. The urine is notorious for its poor reliability starting with composing the daily urine collection, whereas the fecal content contains both absorbed and non-absorbed dietary ingredients (plus the inconvenience in handling the human excreta). In contrast to that, and what tentatively may be called "historic" bio indicators, hair (nails) is a memory tissue. Starting from the hair follicle, any element or substance that enters the hair is deposited there irreversibly and would grow for approximately seven year at a reasonably constant velocity of 0.3 mm per day (longer for nails); after that time the follicle degenerates and it's time for a new one to get formed (baldness excluded). It is pertinent to note here that the cells of the hair follicle are the second most active in the body after those from the bone marrow [21]. Such activity may explain, at least in part, why the concentration of the elements in the hair is for the most of the elements much higher than that in the blood. Hair, indeed, is an accurate biological matrix for the imaging of the metabolism of the elements in the body, a true time log [5].

*Hair.* That hair is an attractive, easy available, no-risk sampling biological biopsy material, has been recognized as such for years. A lot of discussion went on over the last three decades about the merits and pitfalls of the mutielement hair analysis. How to wash (or not to wash) the hair, the external contamination problems, observed differences in replicate analyses within the subjects and between the subjects, and the different results in cross-comparing of the different laboratories. These have been the evident technical questions necessary to be solved before multielement analysis can became the part of a regular diagnostic armament in the daily clinical practice. Fortunately, many of these analytical problems were overcome over the years and, indeed, the high quality ISO certified commercial laboratories for multielement analysis (and numerous other analyses of different biological matrix, the enzymes, and chemical compounds), appeared in the USA (The Great Plains Laboratory, Inc., KS, USA), Western Europe (Toxiba, Basel, Switzerland), and Russia (CBM, Moscow, Russia), to name a few. The existence of such laboratories, that strictly follow the established high analytical practice standards, [22] is a real savior since they can provide services for what would be too expensive to run occasionally even for a large hospital; you may need some special type of analysis only few time in a year and commercial laboratories provides for that gap in "orphan" diagnostic tests (analogous to diagnosing, treating and monitoring of the orphan diseases). Indeed, hair has a potential to be routinely used in clinical practice as an essential part of a metabolic status [23,24]. An innocent bystander may conclude that although the absolute concentration of an element in the hair may vary from laboratory to laboratory to a certain extent, the analytical error within the same ISO certified laboratory is reasonably constant (in-built error), so that any observed comparative difference in the analytical value between some health conditions is essentially real. As a matter of fact, the greatest disfavor to the multielement hair analysis did not came for analytical reasons, but from the fact that people who dealt with it, try to make it all inclusive so that it can diagnose if not everything, but then certainly almost everything. Indeed, like any other indicator tissue, or enzyme, or staining/labeling technique, the multielement hair analysis may prove right on target for some, but not for all of the health impairment conditions. Hair multielement profile is certainly not a diagnostic golden bullet, but is a reliable diagnostic tool for detecting deficiency, normality, and toxicity of elements in health and disease, and in various physiological states like pregnancy and lactation, physical activities like sport and exercise especially at their high professional end and, perhaps, even for assessing emotional states. Today, in our opinion, the main issue with the hair multielement profile analysis is both on the "giving" and "receiving" end, respectively. This is a highly sophisticated analytical technique that, on the "giving"" end, left the analytic chemist with a lot of data he don't know what to do with, and lack of educated practicing MD's on the "receiving" end [25,26]. To be honest, there is some downplaying of the importance of such analysis at the "receiving' end, due to the lack of already existing knowledge about the element metabolism in health and disease, plus the fact that the preventive medicine lacks the lure of the clinical one. Whoever would find on how to make money on human empathy would solve the problem on how to pay doctor when healthy instead of waiting to get diseased.

*Nutritional status Croatia*. At the beginning of 20th century, Vinogradsky was the first to report that elements in the body may reflect the geochemical composition of the region where the subjects actually live. Today, the fact that human body and hair multielement profile depends upon the local geochemical characteristic is less important for the developed countries where there is much more social mobility as people are mobile looking for a job, and/or the food supplies came from various parts of the same country and from countries across the world. However, the problem still exists in the developing countries where people are trapped in the same place and have to eat on what is locally available. We also studied the hair multielement profile in a large random sample population in Croatia. Our hair multielement profile was comprised of 23 elements in a random sample of 929 adult Croatian men and women and only the highlights are shown here. The results showed a considerable number of cases of manganese > iron > selenium > zinc > chromium deficiency (Table 1). Later we learned that iodine should

Table 1. Hair multielement profile ("Short" list) showing adequate, deficient, and excessive elements in the random sample of 929 adult Croatians of both sexes (* no known lower limit).

| Element | Adequate | Deficient (D) | Excessive (E) | D+E (%) |
|---|---|---|---|---|
| Manganese (Mn) | 459 | 459 | 11 | 50.6 |
| Sodium (Na) | 463 | 52 | 414 | 50.2 |
| Magnesium (Mg) | 489 | 135 | 305 | 47.4 |
| Potassium (K) | 500 | 162 | 272 | 46.2 |
| Iron (Fe) | 510 | 376 | 43 | 45.1 |
| Selenium (Se) | 516 | 369 | 41 | 44.5 |
| Zinc (Zn) | 601 | 280 | 48 | 35.3 |
| Chromium (Cr) | 618 | 201 | 110 | 33.5 |
| Silica (Si) | 633 | 110 | 186 | 31.9 |
| Copper (Cu) | 660 | 87 | 182 | 28.9 |
| Calcium (Ca) | 669 | 24 | 236 | 28.0 |
| Phosphorus (P) | 729 | 99 | 101 | 21.5 |
| *Aluminum (Al) | 817 | 0 | 112 | 12.0 |
| Tin (Sn) | 868 | 16 | 45 | 6.56 |
| *Lead (Pb) | 887 | 0 | 42 | 4.52 |
| *Vanadium (V) | 887 | 0 | 42 | 4.52 |
| *Cadmium (Cd) | 888 | 0 | 41 | 4.41 |
| *Nickel (Ni) | 894 | 0 | 35 | 3.77 |
| *Arsenic (As) | 904 | 0 | 25 | 2.69 |
| *Titanium (Ti) | 906 | 0 | 23 | 2.47 |
| Cobalt (Co) | 916 | 8 | 5 | 1.40 |
| *Lithium (Li) | 922 | 0 | 7 | 0.75 |
| *Beryllium (Be) | 928 | 0 | 1 | 0.17 |

be also included to that CBM, Moscow "short", i.e., standard list of elements comprising the multielement profile (the "'long" list is comprised of 40 and more elements and can be expanded as needed). We also detected an increased number of cases with the high concentrations of calcium and magnesium reflecting the presence of osteopenia and osteoporosis in our predominantly middle age population of women. Accidental lead poisoning is also still with us; 42 cases of that well known environmental heavy metal poison were identified (about 4.5% of the studied population). The increased aluminum concentrations were also high in our population amounting to 12%. Of the essential elements the consumption of salt appears to be notably increased [27]. It should be noted that the observed concentrations were considered to be increased at a very broad margin; the more scrutinized standard reference values would only make the situation worse.

*Supplementation*. The entire multibillion dollar business arose around the various dietary supplements, including minerals and other elements over the last two decades. Today we read about the necessity to take this element, tomorrow to take that element, the day over tomorrow the next mineral, and then the first acclaimed mineral may be already declared not to be so beneficial or even damaging, and so on, and so forth. Well, nothing is wrong with having the minerals (and vitamins and other supplements) available on a supermarket shelf. The problem is when the people read that they may need such and such dietary supplement; they buy them, and consume them not knowing if they, indeed, really need them. Recently, the first author reported a case of a chiropractitioner who get poisoned with molybdenum after his doctor suggested him to use it to diminish his allergy to the perfume odor of some of his patients, but without looking if, indeed, my dear chiropractitioner really need molybdenum or not [28]. The right way to go is to check the element level in some indicator tissue of yours, and that specific finding would tell you what, indeed, may be lacking or is too high in your body. Such assessment of your personal mineral status with your own multielement profile is the only right way to go. It may be surprising to many what few milligrams of some mineral can do for you and your well-being. Indeed, all the US standard textbooks of internal medicine provide a large chapter on nutrition and nutritional deficiency and excess of the number of elements since it is much more economical to support yours own health with necessary supplements than with the expensive drugs. You may check your copy of Merck manual, a common textbook digest in our country, for a proof.

*Elementome*. There are three major objectives for the science today: (1) the immensely small (atom), (2) the immensely large (the Universe), and (3) the complex (living systems). Since the ultimate complex includes in itself all the three major objectives, it is questionable if the final solution of such a system can ever be reached. However, it is possible to study complexity by selecting the context of interest and one of such contextual approaches is the concept of Elementome. Indeed, Elementome is the contextual subject frame to include all the elements in all of their possible combinations in any possible matrix set sample in physics, chemistry, biology/medicine, or psychology, and in health and disease. The need for such defined term Elementome and its introduction became necessary after the new analytical techniques allow us to determine 40 and more elements simultaneously in any possible biopsy matrix sample. The biological matrix set samples may come in many disguise by reflecting various environmental conditions and contamination, dietary exposure to various food concentrations, and in various functional states of the body and its parts in health and disease. The vibrant area of element research in all its available forms is now dispersed among too many disciplines what renders their results inaccessible to the wider audience. Terms Elementome and hair multielement profile were used interchangeable in this text, as the reader may already have noted.

## "… ACT LOCALY". THE MULTIELEMENT PROFILE OF DEPRESSION

*Depression*. For all the enumerated reasons the idea we developed was to study the changes in the hair multielement profile in depressed and apparently healthy subjects. Depression is the most frequent mental impairment in human where it is more prevalent in women than men in about 2:1 ratio, respectively. For mostly financial reasons the US medicine treats depression as a health impairment, not the disease. However, it is a highly prevalent human condition and, believe it or not, one half of all the medical conditions found in the medical wards today are regarded to be depression [29]; the symptomatology of depression is protean, indeed [30]. Here, we aim to show our preliminary results on hair multielement profile difference between the depressed and control subjects; we would skip all the analytical ICP MS and technical details of this randomized, double blind, prospective, observational, cross-sectional, clinical, epidemiological, and analytical study since they have been heralded earlier in a more specialized journal [31]. We followed the Helsinki Declaration on human subject research, and other national and international by-laws and regulations; the diagnosis of depression was handed down by a board certified specialist in psychiatry following the DMS-IV-TR criteria [32].

The first author "long" list hair multielement profile, i.e., his metabolic image, is shown here as a working example (Figure 4). In brief, the analytical method is highly sensitive since it was capable to detect slight increase in already trace concentration of gold coming presumably from the earlier dental fillings; the lead is most likely associated with the large amounts of black tea he have consumed. However, the increased magnesium values that were followed by calcium increase (albeit still within the normal range), indicated initial impairments of bone metabolism leading towards the osteopenia in this then 65 years old man. On the deficient side there is a light deficit of iodine and zinc, indicating decreased metabolic activity and impaired tissue regeneration, respectively. Cobalt and iron on the boundary normal to low level decreased authors capacity for hard physical work (iron) and may herald some nerve conduction nuisance (cobalt). Just to mention that cobalt (Vitamin B12) deficiency is common in the old population and vegetarians.

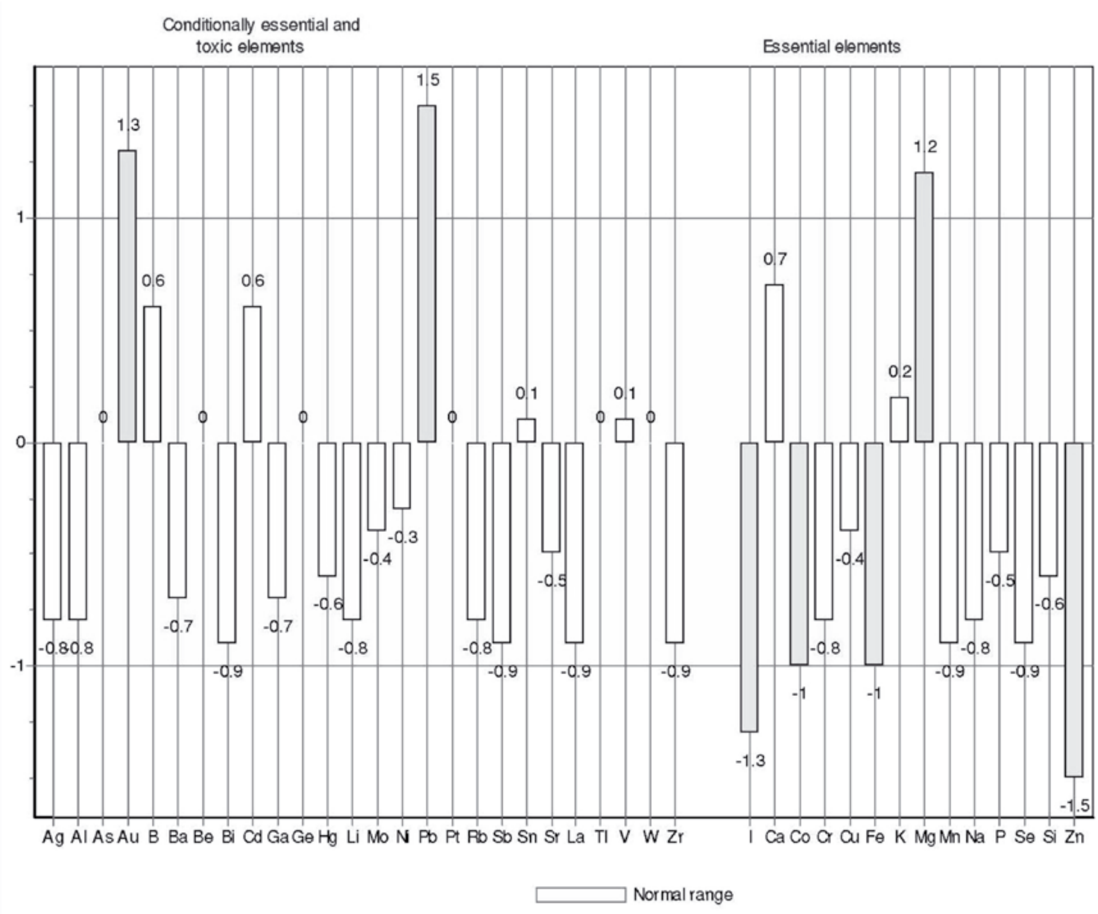
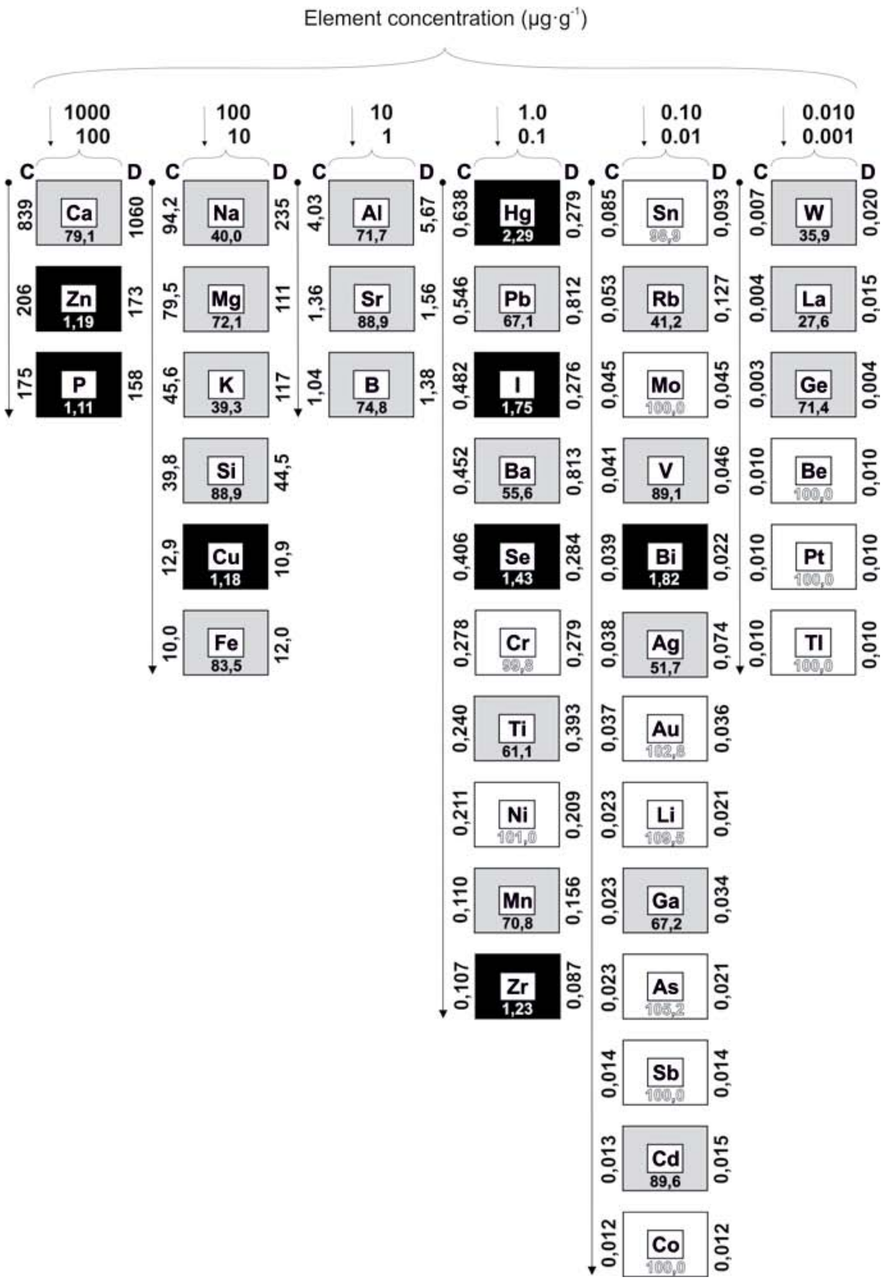



Figure 4. The hair multielement profile of the first author. Normal boundary is between 1.0 and (-1.0). The y axis division is based on percentiles.

*In search of a pattern*. The overall spectrum of what we got is shown in Pictogram 1 (term pictogram was chosen since it simultaneously comprises the elements of a classical figure and table). First what amazes is the wide range of element concentrations observed in the hair. The elements were arranged in columns such that each neighboring column denotes one range of magnitude difference starting from calcium (Ca) down to thallium (Tl). Indeed, the concentrations ranged from about a thousand micrograms (one milligram) per gram of hair for the most abundant element of calcium, down to the 0.001 microgram per gram for platinum and thallium. This is the range of about seven orders of magnitude, i.e., ten million time is calcium more abundant in the hair than platinum or thallium (NB. none of the people was occupationally exposed to the metals or metalloids). The name of the element is in the middle of the either black, gray, and white frame where the color shade indicates that the respective hair median concentration of an element in the control subjects was, respectively, either lower, higher, or neutral in comparison with the depressed subjects. On the left side of the frame under the column heading C are the hair median concentrations of a particular element for the control subjects, and on the right side of the frame under the column heading D are the hair median concentrations of a particular element for the depressed subjects. Within the frame and below the chemical symbol of the element is inscribed the element ratio of Control/Depressed subjects. The next impressing thing was that since some elements were higher in the depressed than the control subjects, the other elements behave in opposite way, i.e., they were higher in control than in the depressed subjects, and some were not affected by the fact of being from depressed or control subjects. The later (white frames) did not exceed the pre-set ±10% difference of the Control/Depression ratio of the hair median concentration of the element in question between the control and depressed subjects.

*The Question*. Well, is there any meaningful pattern here? Evidently, searching for a meaningful pattern in such a huge combinatorial network matrix, where potentially every one of 41 analyzed elements can react (interact) with any other element or group of elements over the range of seven orders of magnitude of concentration, and under the probability constraints of sample




Pictogram 1. The elementome pattern of depression. From left to right the elements are arranged in columns in decreasing order depending upon their concentration in the hair. The direction of decrease is shown by the down pointing arrow Black frame: Concentration of element decreased in depressed subjects, Gray frame: Concentration of element increased in depressed subjects, White frame: Concentration of element is unchanged within the ±10% of the median, C: Element concentration in controls, D: Element concentration in depressed, Inscribed in the frame and below the chemical symbol is the ratio of Control/Depression concentration of elements.

size, is a formidable task. Thus far, and with only the basic statistic at hand for such a complex task, we managed to "decode" some segments of this multielement "Rosetta stone", to allow us to dwell deeper into the metabolic underpinnings of depression, and to look at the depression from a new prospective.

*Elements increased in depression*. It was not a small surprise to realize how the two major electrolyte elements of the human body, i.e., sodium and potassium, are more than two times higher in the hair of depressed than the control subjects. Indeed, even the sodium and potassium respective "sputnik" elements lanthanum and rubidium were proportionally increased. Well, the depressed people in this study didn't consume excessive amounts of sodium and/or potassium rich food, or were taking the supplements of these elements, neither do they show some ECG or kidney impairment, but still, they managed to deposit over two times more Na (La) and K (Rb) in the hair. However, in the overwhelming number of cases they were physically less active. Meaning that they had less need for the potassium rich muscles and the apparent loss of the muscle mass was reflected in the increased potassium levels of the hair. Remember that deposition of any element in the hair is unidirectional, whereas that of potassium in the blood is under the strict homeostatic control next to that of sodium [33]. Similar condition may arise in sarcopenia, the involute loss of muscle mass in older people (NB. Older people are also known for the depressed mood). It is reasonable to assume, that such conditions associated with the muscle inactivity, would appear in the cases of cast immobilization in bone fractures and, perhaps, in the space mission crews. There is also the possibility that the function of ion channels, pores and gates in depression is impaired. In support of this view on the depression induced metabolic changes in trace element profile, are the increased values of calcium and magnesium, both bone and muscle physiology related principal elements. When weight unloaded, the bone mass is decreasing, as shown by the loss of bone mass in astronauts/cosmonauts of the manned space orbital stations. In summary, hair appears to be a very sensitive biopsy tissue to assess the calcium and other osteotrophic elements metabolism; we observed the changes in calcium and magnesium metabolism leading to osteopenia much earlier in the hair than they would show up on a dual x-ray absorptiometry; todays golden standard for osteopenia/ osteoporosis diagnosis [34].

Yet, another member of elements that can be categorized to fall under the "Use it or lose it" principle family, was iron. And for the same reason as sodium and potassium, and calcium and magnesium, since the reduced muscle mass needs less oxygen for support so that iron found its way out via the increased deposition in the hair. Indeed, manganese, an element that is metabolically closely related to iron, was also increased in the hair of depressed subjects. Essentially, the "sputnik" pairs of elements Na (La), K (Rb), and Fe (Mn) can be regarded as an internal control for the quality of measurement of the concentration of these element pairs in the hair. The question arose if depression affects, respectively, more potassium increase from muscle deterioration, or from sodium increase that affects more presumably ion channels, pores, and gates. The study of Na/K ratio of the hair points to the somewhat stronger preponderance of potassium than sodium involvement indicating muscle as a principal reservoir of potassium that is available for hair deposition (Figure 5). Calculating the ratio between the pair members of the elementome (like the Na/K ratio) is a promising analytical approach to monitor the metabolism of elements, although the sound principles on how to do the paring is now mostly left to the interpreter since the stoichiometry of the hair, unlike that of ecological one, is still not well understood [35].

*Elements not changed in depression*. The elements that were not changed in both control and depressed subjects, form an interesting group comprised of mostly metallic elements having the allergy inducing potential (in descending order): Ni > Cr > Co > Pt ≈ Tl ≈ Be ≈ Mo ≈ Au ≈ As ≈ Li (?). That puts in question theories about the allergic nature of depression, at the least as far as the enumerated metals are concerned. As mentioned earlier, the first three of them are definitively essential and have some blood glucose lowering potential Cr > Co > Ni. Platinum is used in a powerful anticancer drugs, thallium is involved in the Tl·S·Se sub-cycle of element interactions, beryllium is overtly toxic to human, arsenic can impede bone remodeling processes but was reported recently to be beneficial in some forms of the leukemia, gold is potent anti-inflammatory agent in the treatment of the autoimmune rheumatic diseases and suspected week allergen, whereas lithium is of questionable allergic potential, but well known for its blocking of thyroid function [14]. At the same time, this data provides some indirect evidence that the velocity of hair growth hasn't changed with the depression. Indeed, if the velocity has changed then it would not be possible to have elements concentrate in the hair to the same extent. Hence, the observed difference in either increase or decrease of the other hair trace element concentration is real or, in the worst case scenario, the difference may be of too small a magnitude to be distinguished between the two groups of subjects.

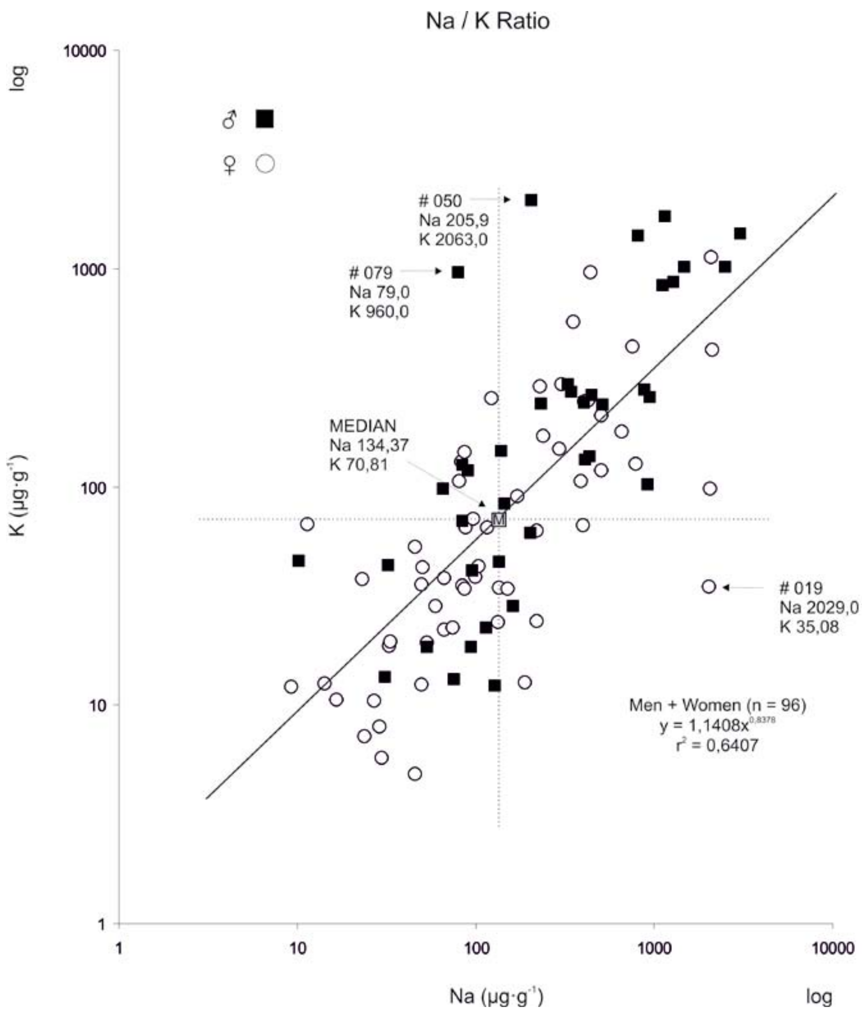



Figure 5. Comparative hair Na/K ratio.

*Elements decreased in depression*. From the nutritional point of view, the lack of the essential elements (in the decreasing order of concentration): zinc, phosphorus, copper, iodine, selenium and bismuth is of great importance. Any lack of these elements in the diet would impede the growth, development, and wellbeing of humans. The immune defense capacity would be decreased; the cognitive capacity of especially young children would be retarded, the more so if several of the essential elements would be deficient simultaneously. The observed low concentrations of mercury and zirconium may simply follow the already low levels of iodine and selenium to which they appear to be strongly bound [36]. In a way, the fact that iodine deficiency was so more prevalent in both the depressed and, albeit to a lesser extent in control subjects, have come as a surprise; apparently our diet in Croatia is not so well iodine supplemented as we thought. Further exploration revealed that it is possible to have serum T3, T4, and TSH values to be normal by our current standards, but to be iodine deficient by hair analysis. That would be somewhat paradoxical finding if we do not know that lower dietary iodine levels stimulates the hormone synthesis independently of TSH [37]; hence measuring the thyroid hormones is not identical with the actual iodine status of the body and, consequently, there is no such a case as a euthyroid struma – the euthyroid struma is the product of a sustained level of T3 and T4 production under the conditions of the low iodine intake [38]. In the same paper, we analyzed separately three thus far the most likely candidate elements to be implemented in depression: iodine due to its crucial role of metabolic energy regulation by the thyroid, selenium as a key element in several enzymes regulating the uptake of iodine in the thyroid, and copper because of its involvement in the noradrenaline production in the body what was supposed to be reduced in depression. The analysis demonstrated that the key player among these three element ingredient associated with the depression was the lack of iodine (Figure 6). The two last articles we received reported diminished contrast discrimination [39] and reduced olfactory sensitivity [40] in depressed patients. Since zinc is mostly abundant in the retina and essential for olfactory function [41], these results support our view on zinc deficiency as an important dietary factor in the etiology of depression. It would be great if Bubl at al. and Negoias et al. (2010) did the hair multielement profile of their subjects. *Metabolic Energostat failure hypothesis of depression*. Evidently, the collected data shows that the physical activity of depressed subjects is mostly reduced, that such inactivity is accompanied by the loss of muscle and bone mass, and reduced need for oxygen. The condition is further engraved with the lack of the essential elements iodine (essential for thyroid body energy maintenance), zinc (essential for growth, development and regenerative processes in the body), copper (essential for fat oxidation and elastin formation of the blood vessels), selenium (essential for the selenases enzymes in thyroid iodine transport and in glutathione peroxidase anti-oxidant body defense), phosphorus (essential ingredient of the bone calcium phosphate crystal), and bismuth having a protective role in gastric mucosa. Both the excess of some elements and the lack of other reflect the reduced physical and metabolic activity in depressed subjects. That activity decrease may be genuine, starting as a failure of some thalamic structure involved in energy homeostasis and here, tentatively, named "energostat'. Such a hypothetical "energostat" may be secondarily impaired by the lack of the essential element ingredients necessary to support its activity; the epigenetic role of the elements excess and/or deficiency appears to be greater than now anticipated. In conclusion, metabolic imaging of elementome function by the hair multielement profile in depression showed depression to be the multifactorial syndrome of decreased overall metabolic body activity where the respective deficit of essential element nutrients may be either the initial trigger or a secondary consequence to inadequate "energostat" function.

## FUTURE PROSPECT OF MULTIELEMENT PROFILES

The multielement profile availability of hair, blood, or some other biological matrix, offers a new possibility to study the complex dynamics of entangled metabolic changes in the human body in health and disease. Such studies would also allow for the better interpretation of the proteomic results, since all the protein synthesis has to be nurtured and the elements are the essential part of any such activity. Depending upon the nature of the examined matrix, multielement profile analysis provides the research clinician with a valuable "snap shot" over the range of already entangled metabolic systems operating in the body concomitantly. And what can be further scrutinized by more specific tests. At this moment the multielement profiles are the unsurpassed method for quick detection of overall nutritional status, and their deficiency and/or toxicity to the body, especially under the condition of the increased or decreased physical activity; notwithstanding the old fashioned single element metabolic impairment identification. Essentially, the hair multielement profile should be a regular part of any clinical status exam where, at a reasonable cost of about 100 €, a profound metabolic insight could be obtained and millions of wasted money on unnecessary expensive diagnostic procedures and un-adequate drug treatment could be spared. Moreover, the proposed analysis of the multielement profiles may be tried for a study of a number of other health conditions of uncertain etiology, like schizophrenia and autism, where an early environmental insult may affect the specific gene expression at various developmental points in the postnatal life [42]. The personalized medicine implication of such knowledge is expanding rapidly.

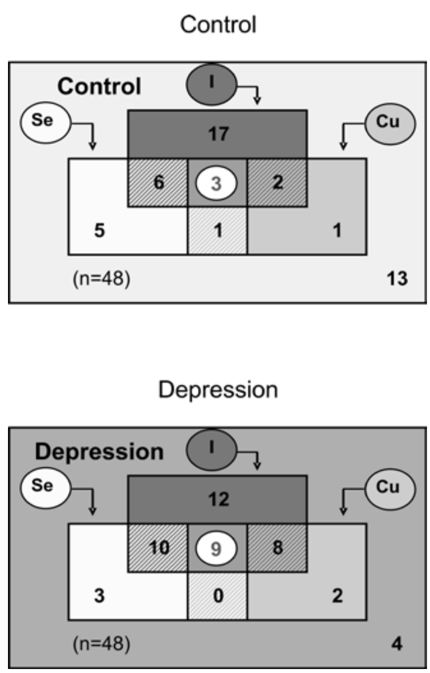



Figure 6. The cluster frequency distribution of iodine, selenium, and copper (Venn diagram). Only the iodine cluster ( I, I+Se, I+Cu, I+Se+Cu) differed significantly between the control and depressed subjects (p<0.01).

## NOTE TO THE READER.

Except for the authors genuine research work, only the comprehensive key references were provided. Today, it would take the book library to cover for the entire area of elementome research.

## ACKNOWLEDGMENTS.

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