Evaluation of Essential and Toxic Elements in Blood Samples of Male Smokers Having Different Types of Cancers with Reference to Healthy Male Smokers

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Abstract: Immense epidemiologic studies have been reported about the role of essential trace and toxic elements as risk factors for incidence of different type of cancers in population of developed and developing countries. In present work the levels of carcinogenic, Arsenic, Cadmium, and Nickel (As, Cd and Ni) and anti-carcinogenic, Zinc and Selenium (Zn and Se) elements were measured in blood of male cancer patients (urinary bladder, lung, mouth and esophageal) and healthy referents. The all patients and referents were smoker. The blood samples were analysed with atomic absorption spectrometry after microwave assisted acid digestion. The resulted data indicated that the levels of toxic elements As, Ni and Cd were considerably elevated whereas essential elements, Zn and Se were lower in blood samples of all cancer cases as compared to those values found in noncancerous subjects. As the levels of essential trace elements were low in blood samples of male cancerous patients but difference was highly significant in lung and mouth cancer subjects ($p<0.001$), whereas sequence of decreasing order was not uniform. The levels of Zn in blood samples of different cancerous patients were found in decreasing order as: esophagus< mouth< urinary bladder<lung, whereas in case of Se as mouth<lung<urinary bladder<esophagus.

The study revealed that the carcinogenic processes are significantly affecting the essential and toxic elements levels in biological samples of cancerous patients as related to those obtained for controls/referents.

Keywords: Male, Cancer, Essential and toxic elements, Smoking, Kruskal wallis test, Student's t-test.

1. INTRODUCTION

Worldwide, there are about 10 million new incidences of different types of cancer, appearing each year, and this dreadful disease causes mortality rate around 12% of the entire deaths. Many investigations have been carried out to find the possible risk factors for different types of cancer, among many other factors the correlation of increasing/decreasing toxic/essential elements has received significant consideration [1]. The function of essential trace and toxic elements in the growth/inhibition of cancer is not yet very clear and many studies have been conducted on this subject matter [2].

Many epidemiological studies suggest that Zn deficiency might be enhanced the risk of cancer. Insufficient intake or absorption of Zn, whereas enhanced excretion or metabolic necessities and distorted immune system can caused acute or chronic inflammatory intestinal disorders [3]. Zn supplementation decreases oxidative stress and improve immune function, and may help in the prevention and treatment of cancer. It is also essential for the quenching of free-radical activity of superoxide dismutase [4].

The Se is a vital element required in trace quantity for normal physiological functions of life (animals and humans) which is present in different sources such as vegetables, grains and cereals [5]. It was indicated in literature that in 27 countries, Se intake is inversely proportional to cancer incidence based on different age groups [6]. The correlation among Se contents in forage-crop and cancer mortality rate in USA was studied. It was reported that the mortality rates for cancers of some major forms such as lung, mouth and breast, were found to be drastically elevated in countries having low Se diet [7].

The International Agency for Research on Cancer has declared toxic elements such as As, Cd and Ni, as a Group 1 human carcinogen, which are related with elevated risk of many types of cancers [8, 9]. It was immensely investigated that many toxic elements including Group 1 human carcinogen, catalyse the oxidative damage of biological macromolecules and act as carcinogenic through free radical generations [10]. While anti-carcinogenic elements are those that inhibit the frequently generation of these radicals [11, 12].

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The carcnogenic effects of As is the subject of controversy, different modes of action, which induces cell death and proliferation, inhibit DNA repair, and induce genetic damage, which alter the DNA methylation patterns, act as a co-carcinogen [13]. A population consume As contaminated drinking water might enhanced the risk of lung cancer, over the next 10–20 year mainly due to previous exposures [14]. Recently in Taiwan, incidence of lung cancer in residents of arseniasis-endemic areas were studied for the duration of 8-year [15].

Cd is a non-essential element having carcinogenic activity. The inorganic toxicants have great environmental concern, mainly due to industrial activity, which is related with different type of cancers in humans [16]. It was also reported that an important risk factor for public health due to Cd exposure by smoking cigarette made of tobacco grown on contaminated agriculture field [17]. It was reported that Cd intake by humans inhibit the enzymes with sulphydryl groups and interrupt the pathways for the oxidative metabolism [18]. The Cd in human system replace some essential trace elements mainly Zn, Se and Cu in some enzymatic and physiological mechanisms [19]. The high exposure of Ni, especially through drinking water, tobacco smoking and industrial pollution can enhanced the tumor capability, through mechanisms such as inhibition of intercellular communication [20].The Ni exposure also causes immortalization of epithelial cells and fibroblasts [21]. It also inhibits the production of DNA-protein cross-links and nucleotide excision repair [22]. Whereas high exposure of Ni enhances the DNA methylation, resulting into inactivation of gene expression [23].

Estimation of trace element exposure are often determined by biological specimens such as whole blood, serum, erythrocytes, excretory products, urine, hair, and nails, which are also representing duration of different types of exposure. To assess the etiology of cancer, plasma and serum measures have increasing interest to evaluate the rate of toxicant exposure for short period of time, whereas the levels of trace element in erythrocytes correspond to long-term exposure [24]. In populations of developed and developing countries, where cigarette smoking habit is very frequent for many decades, 90% of lung cancers and 15–20% of other cancers are due to cigarette tobacco [24, 25]

In Pakistan during first fifty years, incidence rate of cancer in population was not studied and published. In 1995 to 1997 the incidence rate of cancer for population of Karachi south (17 million) was published in international journal of cancer [26, 27]. It was indicated that the occurrence rate of different types of cancers, were 80.5/100,000 [26 27]. The published data about the prevalence of cancers attributed to tobacco smoking and chewing different smokeless tobacco contributing to high proportion of head and neck cancer.

As the mortality rates due to different types of cancer is enhanced in Pakistan, during the last few decades. The wide list of risk factors have been studied for the pathogenesis of this dreadful disease but exposure of toxic metals and metalloids mainly through drinking water, food commodities and tobacco smoke are attributed to be most significant cause of different cancer. Very limited studies have been carried out in Pakistan to show the connection of different cancer with carcinogenic metals. The aims of present study was based on the evaluation of relation among different cancer disease and levels of essential (Se and Zn) and toxic elements (As, Cd and Ni) in blood samples of males having different types of cancers. For comparative purpose, selected elements were also determined in age and socioeconomically matched healthy males as referents. The both patients and referents were smokers and residents of southern areas of Pakistan, consuming contaminated drinking water (surface and groundwater) and locally made cigarette. The organic matrices of blood samples were oxidized with mixture of acids before analysis by atomic absorption spectrometer.

2. MATERIALS AND METHODS

2.1. Reagents and Glassware

Ultrapure water obtained from an ELGA Lab water system (Bucks, UK) was used for experimental work and made standards solutions by stepwise dilution of the stock standard solution of all studied elements (1000 mg/L), obtained from Fluka Kamica (Bush, Switzerland). All reagent used during experimental work are obtained from analytical reagent-grade, E Merck (Darmstadt, Germany), and checked for possible trace metal contamination. All solutions were stored in polyethylene bottles at 4ºC. For the accuracy of methodology, certified reference material, human whole blood (Recipe, Munich, Germany) was used.

2.2. Apparatus

The determination of As, Cd and Ni were carried out by means of a double beam Perkins-Elmer atomic

absorption spectrometer model 700 (Norwalk, CT, USA) equipped with graphite furnace HGA-400, pyrocoated graphite tube, an autosampler (AS-800) and for background correction deuterium lamp was used. While Zn was determined by flame mode. Hollow cathode lamps were used as radiation sources operating at recommended current. The instrumental parameters are shown in Table **1**. Linear graph was obtained for different concentration range of all analytes. Standards of each elements and duplicate of each acid digests were transfer to auto sampler cups, 20 µL of digest and modifier (10 µL+ 10 µL) were introduced to graphite furnace at instrumental parameters of each elements (Table **1**).

2.3. Study Population

The male cancer patient (n=120), admitted in Larkana institute of nuclear medicine and radiotherapy (LINAR) and Nuclear Institute of Medicine and Radiotherapy Jamshoro (NIMRA), residents of different areas of Sindh. The data of patients were collected from hospital records and noted essential information, during study period of 2009-2012. All patients and referents were belongs to southern part of Pakistan, and they consumed contaminated surface and ground water as well as smoking cigarette made of locally grown tobacco [28-31].

Different types of cancers classified, on the basis of anatomical sites, such as, mouth (34), lung (38), urinary bladder (30) and esophagus (18). The age range of selected patients was 40 - 65 years, with median value of 55 years. The main criteria of inclusion for the present study were histologically confirmed cancer, at initial and advanced stages such as primary diagnosed tumor before any treatment. The occupational, residential areas, and smoking histories were acquired from the patients themselves and their attendants. As all patients have smoking habit, the patients were grouped according to different types of cancer. For comparative purposes noncancerous male referents (n=110), were mostly the relatives of patients have same age and residential areas (2 region of province Sindh, Pakistan), socioeconomic status, occupations (farming, fishing and laborers) and smoking habit, whereas none of patients/referents are industrial worker. Nonsmoker cancer patients and referent were excluded from this study. Prior to blood sampling the referents have undergone a routine medical examination.

Consents were taken from all referents and cancer patients and also administering a performa indicating the aim of the study. Physical examinations were performed in the cancer hospitals to measure participant's weight, height, and other biochemical data carried out in diagnostic laboratories of hospitals.

Table 1: Measurement Conditions for Determination of Trace and Toxic Elements by Atomic Absorption Spectrometry

	ETAAS				FAAS
Parameters	**As**	**Cd**	**Se**	**Ni**	**Zn**
Lamp Current (mA)	7.0	8.0	12.5	30	7.5
Wave length (nm)	193.7	228.8	196	232.0	214
Slit-width (nm)	0.7L	0.7	2.0	0.2	0.7
Argon flow (mL/min)	200	200	250	200	Oxidant (Air L/min= 17.0) Fuel (acetylene L/min) = 2.00
Heating programme for ETAAS: temperature ^{o}C [ramp time (s), hold time (s)]					
	As	**Cd**	**Se**	**Ni**	
Drying 1	80-120 [1, 30]	100 [5, 20]	100 [5, 20]	100 [5, 20]	
Drying 2	300-600[10, 20]	140 [15, 5]	140 [15, 15]	140[15, 5]	
Pyrolysis	1150 [5,10]	850 [10, 20]	1100 [10, 20]	1000 [10, 20]	
Atomization	2200-2400 [0, 5]	1800[0, 5.0]	2100 [0, 5]	2300 [0, 5]	
Cleaning	2400-2800 [0, 2]	2600[1, 3]	2600 [1, 3]	2600 [1, 3]	
Chemical Modifier	$Mg(NO_3)_2$+ $Pd(NO_3)_2$	$Mg(NO_3)_2$+ $Pd(NO_3)_2$	$Mg(NO_3)_2$+ $Pd(NO_3)_2$	$Mg(NO_3)_2$	

Among study groups, more than 70% patient's condition appeared to be worse in terms of chronic illnesses, mainly due to poverty, malnutrition, and lack of knowledge about disease for long period of time. During study period 38 patients (32% of total) were died, among them lung cancer (18), mouth cancer (12), bladder cancer (5) and esophageal cancer (3). This study was approved by ethnic committee of institute, working under the auspice of higher education commission. The histological distribution and biochemical data of cancerous patients were also collected simultaneously but not shown in present study.

The whole blood samples were collected from patients and referents. Venous blood (10 mL) was sampled by using metal-free vacutainer EDTA tubes (Becton Dickinson, Rutherford, NJ). About 5 ml of blood samples of each study subjects was sent for biochemical test, and 5 ml was stored at −20 ◦C till further analysis.

2.4. Microwave Induced Acid Digestion Method

For digestion of biological samples, duplicate samples of whole blood samples (0.5 ml) of each referent, patients and six replicate samples of CRM, were directly taken into Teflon flasks. To the contents of flasks added 2ml of a freshly prepared mixture of concentrated HNO_3–H_2O_2 (2:1, v/v), and kept them at room temperature for 10 min. The all flask were heated in a microwave oven at one-stage digestion program at 80% of total power (900 W). The decomposition matrices of blood samples required 2 - 4 min. The contents of flasks were heated to avoid extra quantity of acid then diluted to 10 ml in volumetric flasks with 0.1 mol/L of nitric acid.

A blank acid digestion (without samples/standards) was carried out through the complete procedure [32].

2.5. Statistical Analysis

The resulted data of triplicate of each composite sample were expressed as mean ± std. The resulted data of each element in different types of cancer were compared by a Kruskal Wallis test. The level of statistical significance was $p<0.05$. The Spearman's correlation analysis performed for data of each element. All relationships were significant at 95% confidence interval ($p<0.05$), unless otherwise noted. Statistical analyses was performed using Statistical Analysis System (SAS) software (release 801; SAS Institute, Inc, Cary, NC, USA).

2.6. Merit and Demerit of Methodology

The resulted data of each element in certified samples were closed to the certified values, confirming the consistency of our methods. The percentage recovery of selected elements in the certified reference material of Clincheck human whole blood, was varied between 98.5 to 99.2 % (Table **2**). The microwave assisted digestion method require less time (< 5 min) as compared to classical wet acid digestion. The coefficient of variation deviated <2% for all elements.

Table 2: Determination of Elements in Certified Samples of Whole Blood by Microwave Assisted Digestion Method (n=6)

Elements	Certified Values	Experimental Values	% Recovery[d]
Zinc[a]	2.27±0.06	2.25 ± 0.0.12 (5.33)[c]	99.1
Selenium[b]	70± 14.8	69.2± 3.50 (5.05)	98.9
Cadmium[b]	1.2±0.4	1.19± 0.09 (7.58)	99.2
Arsenic[b]	8.83	8.72±0.621 (7.12)	98.5
Nickel[b]	1.74	1.72±0.102 (5.93)	98.8

Key: [a] mg L^{-1}
[b] µg L^{-1}
[c] Values in parenthesis ( ) shown % Relative standard deviations
[d] % Recovery= Experimental Values - Certified value. ×100

3. RESULTS

The mean and standard deviations of essential trace and toxic elements in whole blood of males cancerous and healthy referent, are presented in Table **3**. The resulted data indicated that the levels of anti-carcinogenic elements (Se and Zn) were considerably lower in blood of cancer patients as compared to healthy referent, while reverse in the case of carcinogenic elements (As, Cd and Ni).

The Zn in blood samples of the mouth and esophagus cancer patients were 45 to 50%, respectively, lower than healthy referents. While, 30-40 % lower levels of Zn was observed in blood samples of bladder and lung cancer patients respectively, as compared to referents.

The other essential trace element Se was found to be significantly lower in all four types of cancer subjects as compared to healthy referent at 95 % confidence intervals [C.I: 170 to 178] µg/L. The levels of Se in

Table 3: Concentration of Essential and Toxic Elements in Blood Samples of Male Cancer Patients and Referents

Study Subjects	Zn	Se	As	Ni	Cd
	mg /L	µg /L			
Referents	10.15±1.01	175±12.0	1.75±0.55	0.552±0.15	4.24±1.3
Esophagus	5.08±0.41	120±5.46	3.65±0.85	0.897±0.39	11.7±1.16
Lung	7.12±0.46	105±4.32	5.73±1.48	1.032±0.68	13.5± 2.59
Mouth	5.63±0.59	95.9±8.48	7.56±2.15	1.069±0.40	11.9±1.42
Urinary bladder	6.74±0.70	115±9.97	7.62±1.16	0.946±0.18	10.59±1.2

esophageal, mouth, lung, and urinary bladder were found to be 32 - 45 % lower than healthy referents. In the case of mouth cancer patients significantly low values of Se was found in blood samples [C.I: 90.5 to 98.2] as compared to results obtained for other types of cancer patients ($p<0.01$).

The levels of As were significantly higher at 95% confidence interval in blood of esophageal, lung, mouth and urinary bladder cancer patients [C.I: 3.22 to 4.03], [C.I: 5.15 to 6.11], [C.I: 6.85 to 8.11], [C.I: 7.16 to 8.04] µg/L respectively, than healthy referents [C.I: 1.63 to 1.86] µg/L ($p= 0.01 – 0.02$). The level of As in blood of cancer patients were 2-4 fold higher than referents. The levels of Cd and Ni were 25 -32 and 16 - 2 times higher than the both elements in referent blood samples. The difference was more significant in lung and mouth cancer patients ($p<0.01$).

During study period 38 patients (~32%) were died, among them lung cancer (18), mouth (12) bladder (8) and esophagus cancer (3) corresponding to 47%, 35%, 26.5% and 16.7% of each type of total patients. The multiple logistic regression analysis was applied to evaluate the mortality rate due to different types of cancer in males. The odd ratio for lung and mouth cancer mortality among total different types of cancer patients were higher at 95% confidence interval, 1.49 [C.I: 0.77 to 2.92] and 1.11 [C.I: 0.52 to 2.36] respectively as compared to bladder and esophageal cancer patients 0.526 [C.I: 0.191 to 1.45] and 0.526 [C.I: 0.147 to 1.88], respectively ($p< 0.05$).

The difference between mean values of elements in blood samples of referents and different types of cancer patients were significant ($p = 0.01 - 0.001$), calculated by unpaired Student's t-test at different degrees of freedom. Our calculated t-values exceeds that of $t_{critical}$ value at 95% confidence intervals, which indicated that the difference between means values of each element in blood samples of referents and different types of cancer patients were significant ($p = 0.01 – 0.001$). The correlation of resulted data for Se and Zn with toxic elements have negative values in cancerous patients, ranged as ($r = -0.55$ to -0.867). The higher odd ratio of toxic with essential elements was observed in cancer patients as compared to referents (Table **4**).

DISCUSSION

This study was conducted on cancerous and referent male residents of two different areas of Sindh, Pakistan. The resulted data in Table **3**, indicates that the levels of essential and toxic elements were varied in whole blood of lung, mouth, bladder and esophageal

Table 4: Odd Ratio of Toxic Elements Versus Essential Elements in Blood Samples of Referent and Cancerous Patients

Study Subjects	As/Zn	Cd/Zn	Ni/Zn	As/Se	Cd/Se	Ni/Se
Referents	1.5×10^{-4}	2.4×10^{-4}	6.0×10^{-5}	$1/05\times10^{-2}$	1.68×10^{-2}	4.25×10^{-3}
Esophagus	6.3×10^{-4}	1.34×10^{-3}	2.0×10^{-4}	$2/08\times10^{-2}$	6.847×10^{-2}	1.01×10^{-2}
Lung	7.0×10^{-4}	1.10×10^{-3}	1.6×10^{-4}	18.4×10^{-2}	28.9×10^{-2}	4.34×10^{-2}
Mouth	1.17×10^{-3}	1.23×10^{-3}	2.1×10^{-4}	17.3×10^{-2}	18.2×10^{-2}	3.13×10^{-2}
Urinary bladder	9.9×10^{-4}	9.1×10^{-4}	1.6×10^{-4}	7.65×10^{-2}	7.08×10^{-2}	1.21×10^{-2}

male cancer patients than healthy subjects of similar age group and socioeconomic status.

The studied elements Se, Zn, As, Cd, and Ni, are found naturally in the environment, and human exposure derives from a variety of sources, including drinking water, air, food commodities and cigarette. It was indicated in literature that an increasing concern has been occurred due to interactions between toxic and essential trace elements in an organism. These interactions are multifarious and engage essential elements such as Zn, Cu, Fe, Se, Ca and toxic elements (As, Cd, Ni and others) [33]. The Cd toxicity is due to its negative influence on enzymatic systems of cells, which replaced the essential elemental ions such as Zn, Cu and Ca in metalloenzymes and its very strong affinity to biological compounds containing –SH groups, such as proteins, enzymes and nucleic acids [34]. The importance of Cd–Zn interactions should be considered in general population at high exposure of Cd [35] and insufficient amount of available Zn, due to nutritional factors in the world [36].

An immense investigation has been carried out about the possible role of essential trace and toxic elements to enhance or inhibit the incidence of cancer, but it is still unclear [37]. The most important mechanism to induced carcinogenicity and oxidative stress by metals are well studied factors [38]. It was reported in literature that blood and tissues of the cancerous patients have altered values of essential trace and toxic elements as compared to healthy subjects [39, 40].

It was reported that over two billion subjects in the developing world, have nutritional deficiency of Zn, which creates different physiological disorders such as growth retardation, immune dysfunction and cognitive impairment [41]. The Zn enhances the tumor size and progress in cancer incidences which is especially implicated in the management of patients with head and neck cancer [42]. An epidemiological study indicated that content of Zn in serum of tumor patients was lower than in healthy persons [43].

The anti-carcinogenic nature of Se has been investigated for several decades. However, researchers found that there is an inverse association among Se content and cancer risk. It was reported that Se doses at 100–200 µg/d, inhibit the genetic damage and cancer development in human subjects [44, 45]. The antagonistic effect of Se on arsenic toxicity has been gradually accepted by the public. In recent years, *in vitro* research showed that Se can alleviate arsenic toxicity by modifying cytotoxicity, genotoxicity and oxidative stress [46, 47]. This is confirmed by a study carried out by Sah and Smits (2012), who suggested dietary Se at 0.6 mg/ kg, improved the antioxidant capacity and counteracted chronic as toxicity in rats [48]. It was also demonstrated that Se at 0.3 mg/kg in diets can improve immunity to counter As-induced immunotoxicity [49].

Numerous reports support the perception that toxic metals such as As, Cd and Ni, hinder the important step of repairing of damage DNA [50, 51]. Some heavy metals might also inspire the cell proliferation, by activation of early response of genes or by interference regulate the normal cell growth [52]. Now a day, millions of people worldwide suffer from chronic arsenic poisoning [53, 54], largely due to utilizing As-contaminated drinking water and food commodities. Since cancer is a complex process, arsenic induces carcinogenesis by multiple mechanisms. The evidences have shown that arsenic interferences with a series of gene proliferation process (*e.g*., DNA damage and repair, and cell cycle and differentiation) and alter signal transduction pathways [55, 56]. The reactive oxygen species induced by As also play a crucial role in triggering cancer [57]. Smoking tobacco cigarettes have adverse health impact. It delivers hundreds of toxicants including toxic metals, which are not limited to active smokers. In indoor environments, the toxic metal and other organic carcinogens are effected passive smoker from side stream smoke [58, 59]. Toxic elements exposure from smoking cigarettes may be a more serious health concern than their levels in food. Smokers may enhance the daily intake of Cd compared with nonsmokers. Tobacco smoke has been related to an elevated risk of bladder and lung cancers [60]. Tobacco smoking is causally associated with laryngeal and esophageal cancers. In most of the epidemiological studies, the risk for all types of esophageal cancer increased with numbers of cigarettes smoked daily and duration of smoking [61]. Cigarette smoke contains >4000 chemical components, including over 30 heavy metals [62]. Environmental exposure to cigarette smoke has been epidemiologically related with different types of cancers [63, 64]. It was reported in our previous studies that toxic elements were significantly high in whole blood of smoker referents as compared with nonsmoker referents [64].

It was reported in many studies that smoking tobacco significantly enhanced the risks of lung cancer, might be due to inhaling high Cd [65]. The resulted

data about the levels of toxic elements in blood samples of smoker cancerous patients are consistent with the hypothesis that exposure to fumes of Cd oxide by smoking enhances the risk of mortality rate in lung cancer [66]. It was found that mortality from lung cancer was considerably enhanced by high intake of As from different routes [67]. In addition, As and other toxic metals in cigarette smoke have synergistic effects, thus enhancing the risk of cancers especially of lung [68].

The resulted data indicated that the mortality rate was higher in lung and mouth cancer patients, which is consistent with other studies carried out in Taiwan and Argentina [68]. It was studied that the incidence of some cancer are correlated with high levels of arsenic in drinking water [67, 69]. Exposure to might cause different types of cancers, (bladder, lung, skin, kidney, prostate and liver). The study carried out in Chile confirmed that the elevated cancer rates (lung and bladder cancers, along with skin cancer) were likely to be attributable to As contaminated water and food items [70].

CONCLUSION

The present resulted data about the levels of essential and toxic trace elements in blood of different types of cancer patients varied widely than those observed for noncancerous referents. The increasing/decreasing incidences of the carcinogenic processes are drastically affecting the balance of carcinogenic and anti-carcinogenic elements in humans. It was confirmed that essential trace elements, Zn and Se, which have anti-carcinogenic activities were considerably lower in blood samples of different types of cancers especially mouth, lung and esophageal. Therefore, in addition to other routine biochemical tests, evaluation of essential (Zn and Se) and toxic element (As Cd and Ni) could also be carried out in patients with different types of cancers as for the management of health protocol. Whereas additional research is desired to clarify the mechanisms of carcinogenesis by metals and metalloids.

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