The iodine story

Relationship with biological evolution and the possible role on advanced-stage cancer treatment

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Integrated Medical Company, Ltd

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2. What are problems that will cause by iodine deficiency?

3. What is the physical role for human?

4. Is it possible to treat untreatable cancer by iodine?

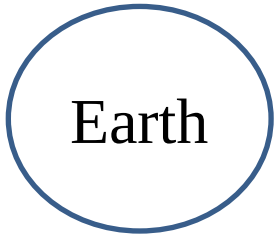
5. Does the iodine treatment carry a risk of side effects?

1. Iodine has taken the essential role for biological evolution as the primordial antioxidant system!

① The creation of oxigen and the start of biological evolution

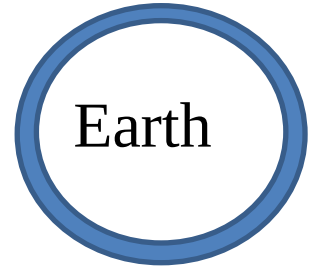
From birth to two billion　From two billion to today

The anearobic Era



Oxigen production via photosynthesis by cyanobacyeria

The aerobic Era



The bacterial world

Development of evolution

The plants and animals world

Low-dose energy is created by ferrmentation under anaerobic condition

A large quantity of energy is created by respiration under aerobic condition

Behind-the-scenes of biological evolution

The first oxigen wielder
-Mitochondria-

Hostile relationship

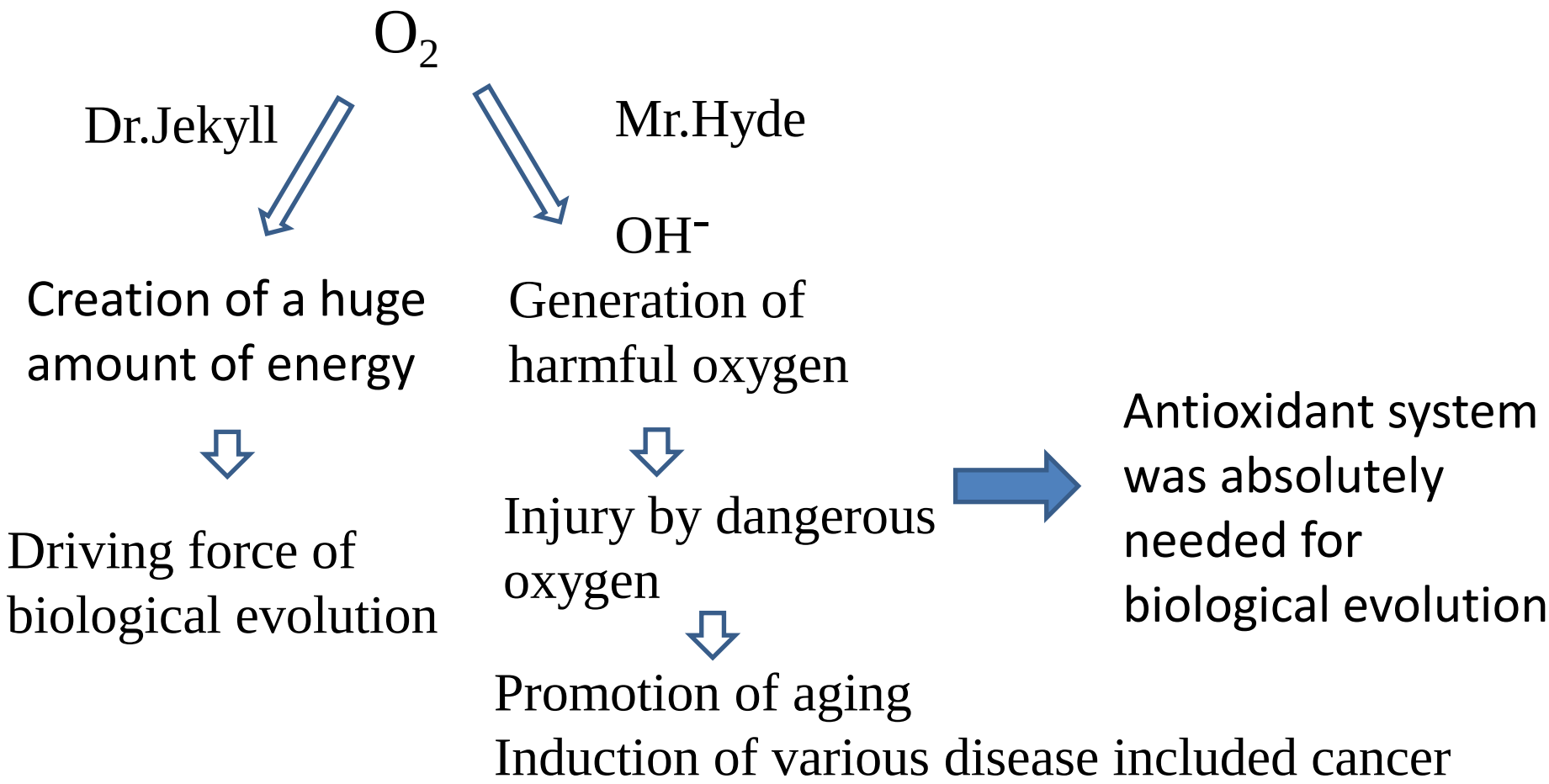
Large thermophilic anerobic bacteria

Symbiosis

The plants and the animals

1. Iodine has taken the essential role for biological evolution as the primordial antioxidant system!

② Oxygen is just Dr.Jekyll & Mr.Hyde



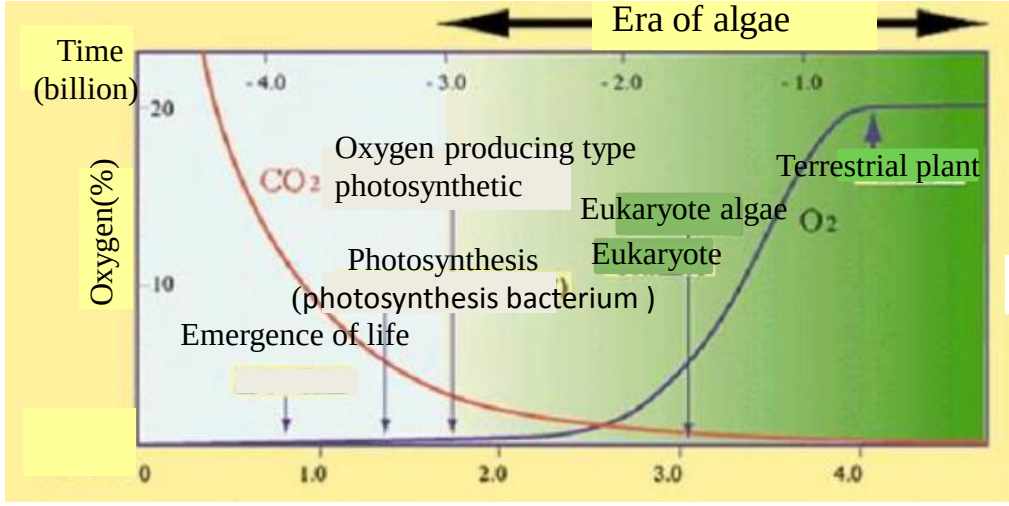
1. Iodine has taken the essential role for biological evolution as the primordial antioxidant system!

③ Iodine is the first and the strongest antioxidant system prepared in life

The first organism that utilized iodine as antioxidant system was eucaryotic algae

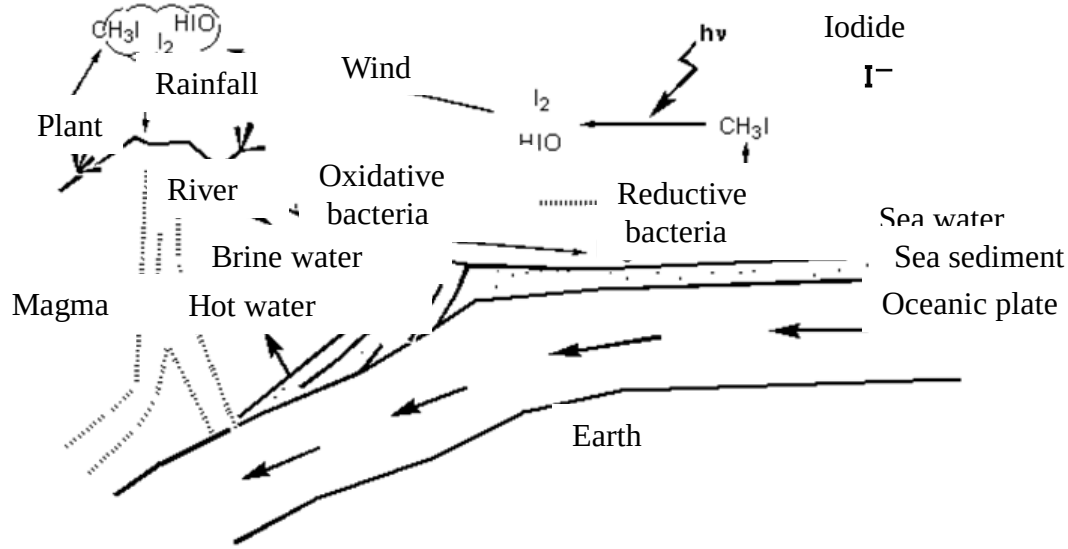
Eucaryote algae is the first successful organism developed a penetration system taken up iodine in seawater

History of earth atmosphere and oxygen producing type photosynthetic organism



http://www.ecodesign-labo.jp/ozone/ozone/07.php

Circulation of iodine in the earth



http://fiu-iodine.org/studies/

The first organism that utilized iodine as antioxidant system was eucaryotic algae

Eucaryote algae is the first organism developed a penetration system taken up iodine in seawater

1. Iodine has taken the essential role for biological evolution as the primordial antioxidant system!

④ Life advanced from sea to land

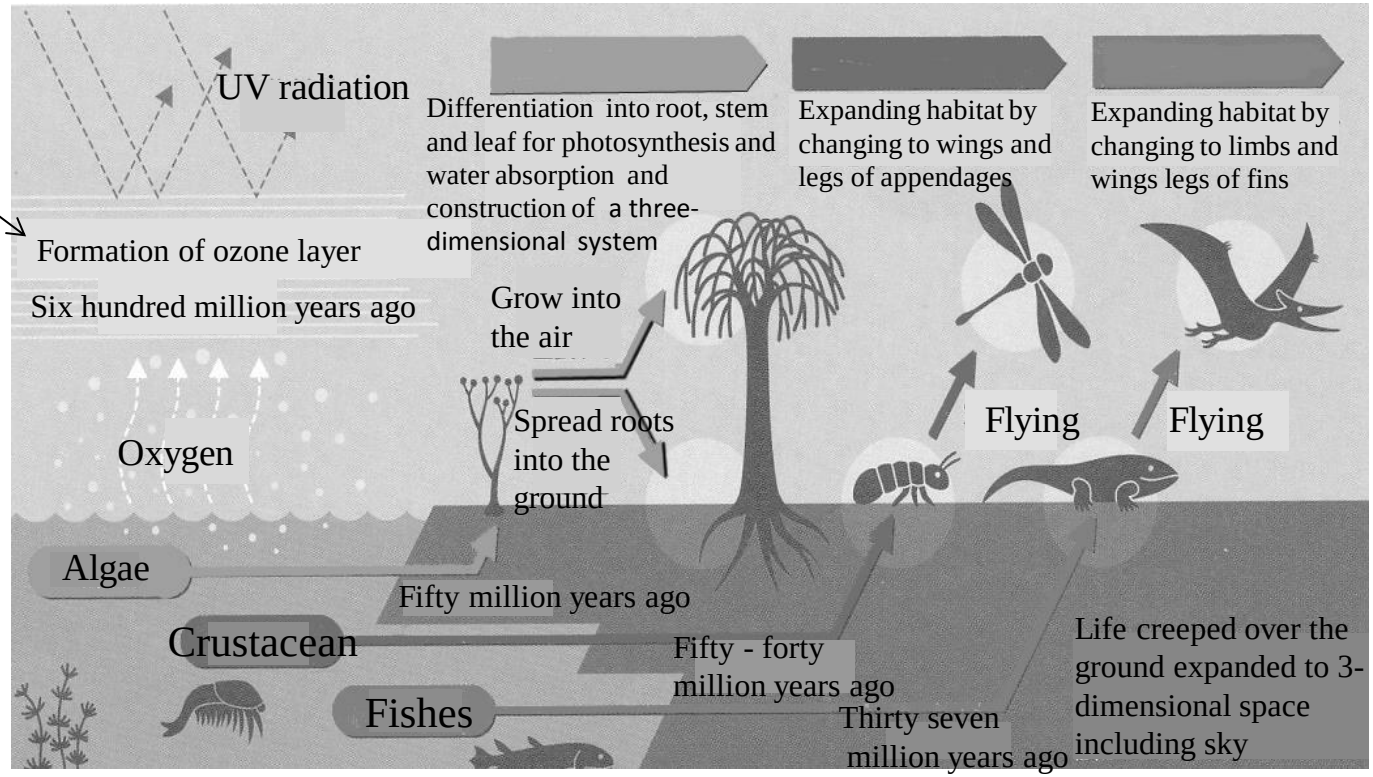
Life was faced with the significant problem that iodine concentration drastically decreased by the advance into land from sea

Oxygen was filled with the atmosphere, and by which ozone layer to prevent dangerous UV radiation that injure DNA was formed.

It is easier to live in sea because UV rays do not reach and also gravity is low, however

Many competitors with the food chain predation relationship emerged

Formation of ozone layer

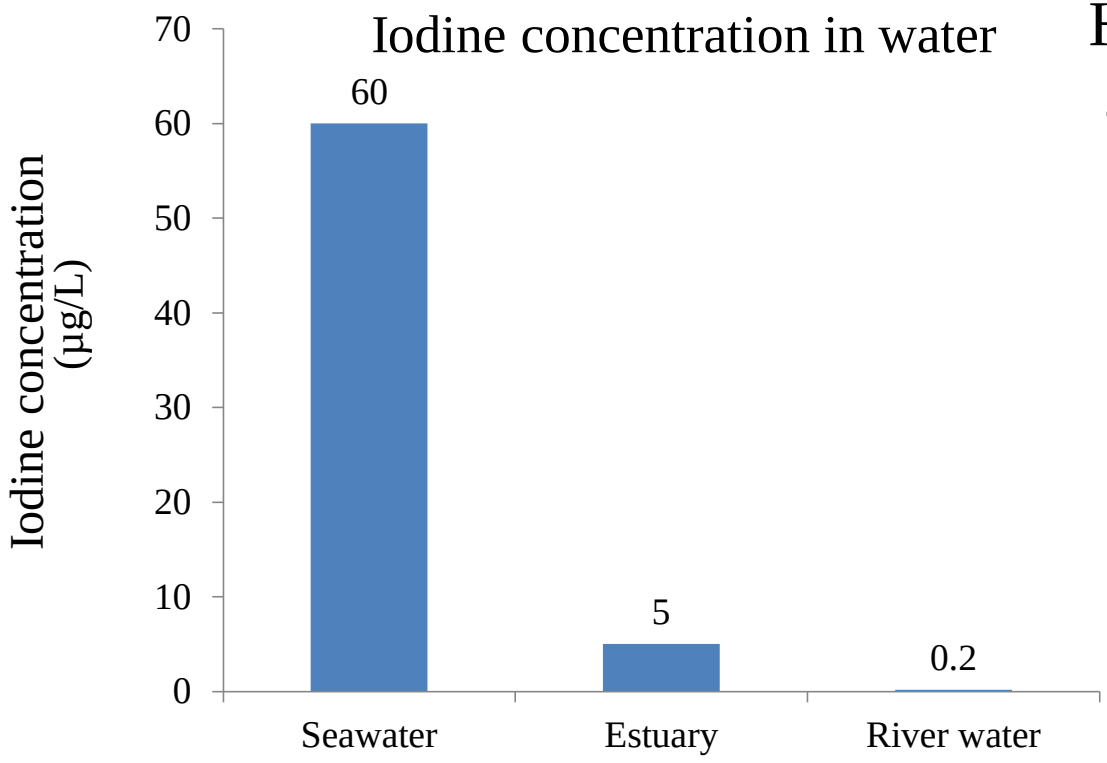


http://www.saltscience.or.jp/symposium

By ozone formation, life advanced into fresh water from shallows and into land from fresh water securing rich minerals in sea by hard bone osteogensis

1. Iodine has taken the essential role for biological evolution as the primordial antioxidant system!

⑤ How did life solve the problem of iodine lacking associated with advance to a land environment ?

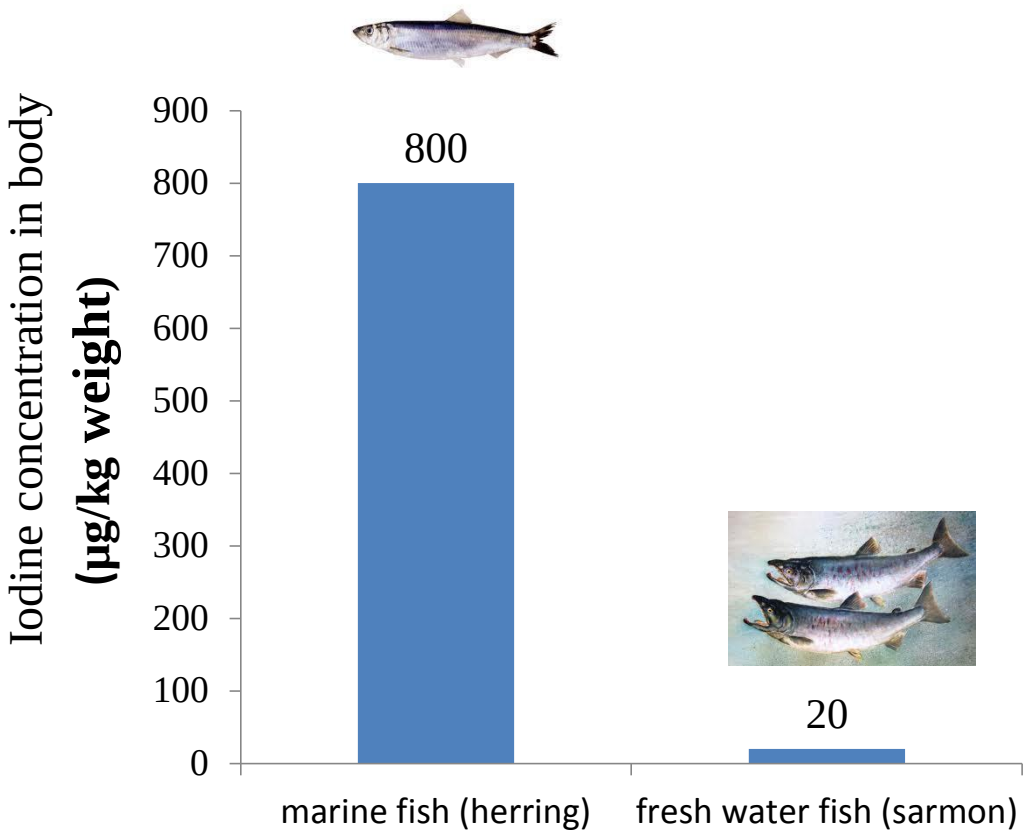


How do life maintain iodine lacking associated with advance to a land environment ?

Thyroid and tyroid hormone is the system equipped in life to take in iodine actively from food and accumulate

2. What is the problem to cause by iodine deficiency？

① Fresh water fish is subject to a variety of diseases in comparioson to marine fish



Joint committee on marine research in the US Senate/ House of Representatives made a statement that a significant low incidence of cancer was recognized in marine shark.The physical role of iodine in fish is not well known. However, the committee clarified that fresh water fish lacking iodine is vulnerable to infection and has a high risk of developing atherosclerosis and cancer in comparison to marine fish.

Venturi, S. and Venturi, M. (2007) Evolution of Dietary Antioxidant Defences. *European Epi-Marker,* 11(3), 1-12.

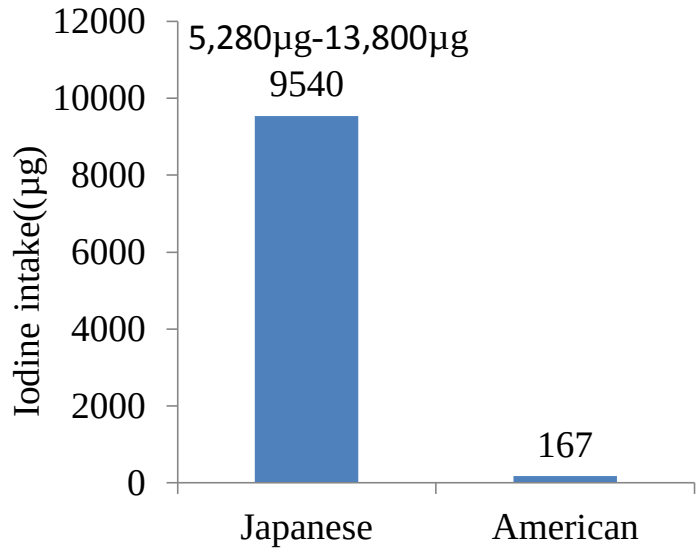
2. What is the problem to cause by iodine deficiency？

② One-third of the world is iodine insufficient state

Dunn JT. Seven deadly sins in confronting endemic iodine deficiency, and how to avoid them. *J Clin Endocrinol Metab* 1996;81:1332-1335.

Iodine lacking area: Africa, southeast Asia, central Asia and European countries including Germany, France, Belgium

The average intake of iodine a day in Japanese and American



The mean intake level of iodine in Japanese is 5-14 fold higher than acceptable daily intakes (1mg/day) of iodine in USA

Japanese can take 7000 μg of iodine a day from only Kelp

Fuse Y, Saito N, Tsuchiya T, et al. Smaller thyroid gland volume with high urinary iodine excretion in Japanese schoolchildren: normative reference values in an iodine-sufficient area and comparison with the WHO/ICCIDD reference. *Thyroid* 2007;17:145-155.

2. What is the problem to cause by iodine deficiency？

③ The relationship between iodine deficiency and a risk of developing the diseases such as cancer

The incidence of both benign and marignant diseases of the breast in Japanese women who eat traditionally seaweed everyday is much lower than those in American women

Pisani P, Parkin DM, Bray F, Ferlay J. Estimates of the worldwide mortality from 25 cancers in 1990. *Int J Cancer* 1999;83:18-29.

⇕

The incidence of fibrocystic disease and breast cancer in Japanese women who live in USA or eat more regularly a Western meal with insufficient seaweed ingestion is high as well as USA women

LeMarchand L, Kolonel LN, Nomura AM. Breast cancer survival among Hawaii, Japanese, and Causcasian women. Ten-year rates and survival by place of birth. *Am J Epidemiol* 1985;122:571-578.

Minami Y, Takano A, Okuno Y, et al. Trends in the incidence of female breast and cervical cancers in Miyagi Prefecture, Japan, 1959-1987. *Jpn J Cancer Res* 1996;87:10-17.

Iodine concentration in blood is insufficient in Alzheimer's patients

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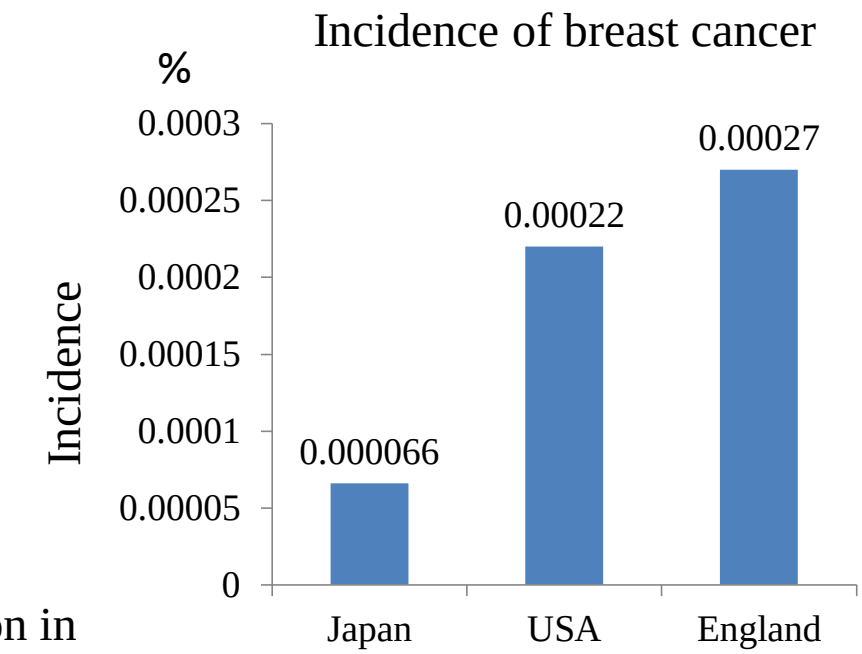
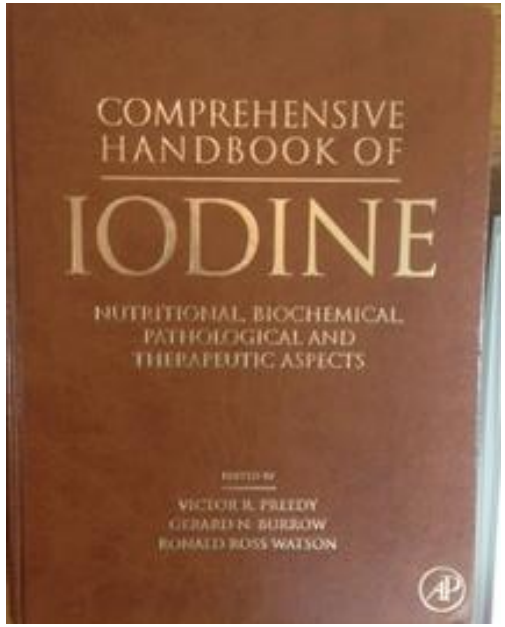


Parker SL, Tong T, Bolden S, Wingo PA. Cancer statistics, 1997. CA Cancer J Clin 1997;47:5-27

Iodine concentration in blood is insufficient in Alzheimer's patients



Andrasi E. & Pali N.

Brain iodine and other halogens of control and Alzheimer's disease patients:Brain iodine deficiency in Alzheimer's disease

A comparison of iodine concentration in each brain area between Alzheimer's patients and healthy persons

Table 69.5 Iodine concentrations in brain regions of five German control and five AD patients (mean ± SD; ng · g^{-1} dry weight) and results of statistical treatment[a]

Each brain area

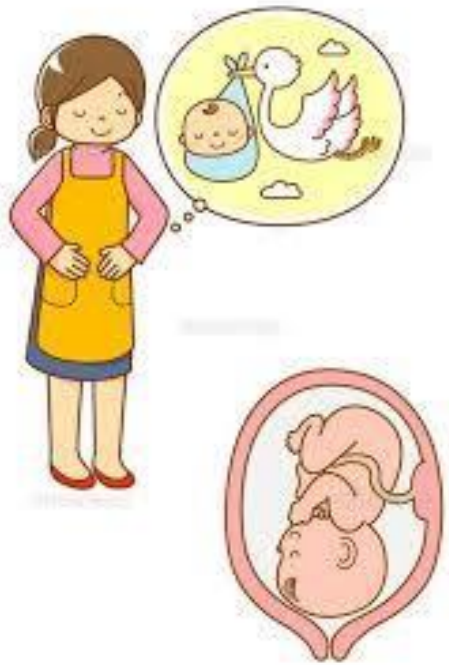
Brain region	*Control group (mean±SD)*	*AD group (mean±SD)*	*p value*
Ammon's horn	(52)	(22)	–
Cortex entorhinalis	(94)	89 ± 45	–
Cortex frontalis parasagittalis	104 ± 33	36 ± 19	0.05
Cortex frontalis basalis	100 ± 37	42 ± 26	0.05
Area occipitalis	74 ± 25	71 ± 26	n.s.
Parietal lobe	108 ± 14	39 ± 12	0.001
Thalamus	83 ± 23	46 ± 7	n.s.
Caput nuclei	(86)	63 ± 35	–
Putamen	159 ± 137	63 ± 13	n.s.
Globus pallidus	54 ± 16	(44)	–

[a]Results of iodine determined by radiochemical neutron activation analysis for control and AD subjects are summarized in this table. Applying statistical treatment to the data sets, mean, SD, confidence interval and significance (*F*-test, *t*-test) were calculated. Where a trend is indicated to be significant the *p* value is ≤0.05. Mean values cannot be given if we have only few data (parenthetic values); therefore, statistical treatment is not possible (–). n.s.: there is no significant difference between the control and AD values.

2. What is the problem to cause by iodine deficiency？

④ Iodine is essential for embryogenesis

Iodine deficiency in pregnant women may have a miscarriage or a stillborn baby with various damage in embryogenesis and further cause a deformation of face even if survived



Thirty six % of pregnant women in USA are insufficient for iodine ingestion and in the the 16%, iodine concentration in urine is ≤ 50μg /L

Definition of iodine deficiency：urinary iodine concentration is ≤ 100μg /L

Caldwell KL, Jones R, Hollowell JG. Urinary iodine concentration: United States National Health and Nutrition Examination Survey 2001-2002. *Thyroid* 2005;15:692-699.

http://image.search.yahoo.co.jp/search?rkf=2&ei=UTF-8&p=%E8%83%8E%E5%85%90

2. What is the problem to cause by iodine deficiency？

⑤ Iodine deficiency affect a fetus

Fetal thyroid starts to function from 11 weeks after pregnancy and iodine (thyroid hormone) works for the development of the nervous system

Iodine deficiency in pregnant women may link with an underactive thyroid gland in fetus, and even if it was borned, it is a risk that other neuropathy such as brain damage, decrease of IQ, convulsions and dyskinesia will occur

*Iodine concentration needed to newborn is insufficient in 47% of lactating women targeted according to the research of Boston, USA

Pearce EN, Leung AM, Blount BC, et al. Breast milk iodine and perchlorate concentrations in lactating Boston-area women. *J Clin Endocrinol Metab* 2007;92:1673-1677.

3. What is the role of iodine in the body?

For example, in the thyroid gland

Iodine in sea weeds or the related foods

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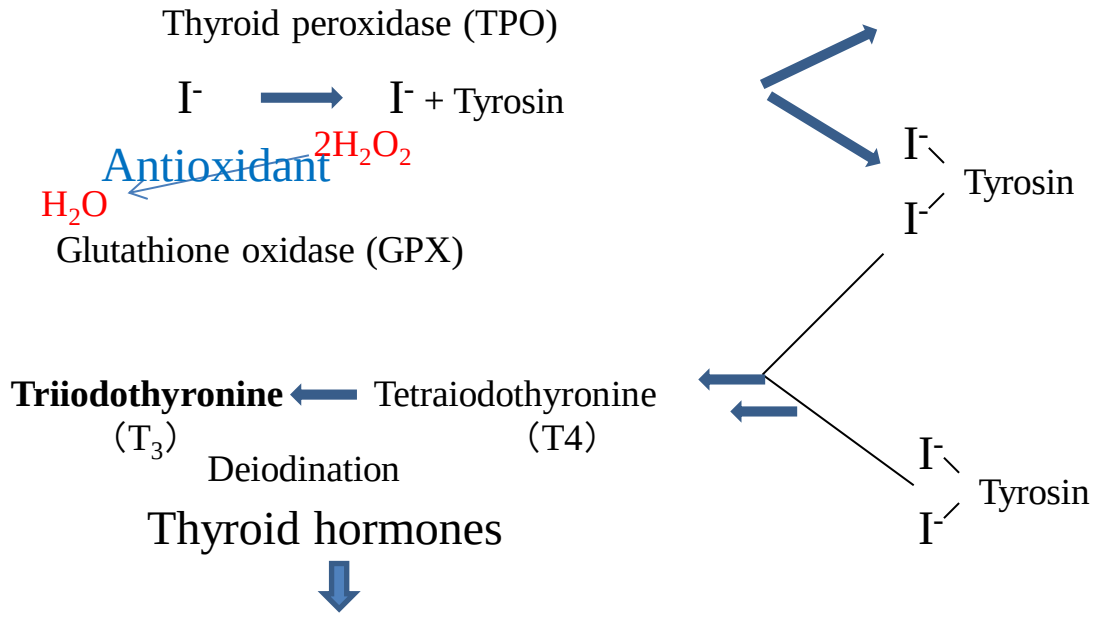
Molecular iodine (I_2) is uptaked by the facilitated diffusion system in small intestin mucosa and iodide (I^-) is internalized by the specific sodium iodide symporter(NIS) in gastric mucosa

⇩

These are utilized in the thyroid gland, the salivary glands, gastric mucosa, lactating mammary gland, the choroid plexus, ciliary body of the eye, lacrimal gland, thymus, skin, placenta, ovary, uterus, prostate, and pancreas, and they may either maintain or lose this ability under pathological conditions



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Regulation for growth and metabolism

Iodine uptaked

⇩

30% Concentrated in thyroid gland and utilized as thyroid hormones

70% Concentrated in extrathyroid tissues and utilized as probably antioxidant

Antioxidant ⇨ Anticancer therapy

4. Possibility of Iodine as curative medicine

① History of treatment using iodine

10% Lugol solution had been used for tubercular lymphadenitis, scrofula in 1829, and the 40 years later for anthrax. In the early twentieth century, it had been widely used for various diseases including goiter and Graves' disease and many clinical trials had been performed in 1932

Even 1952, 0.1-0.3mL of 5% Lugol solution(corresponding to 12.5-37.5mg as molecular iodine) had been applied as therapeutic medication for goiter

Gennaro AS. Remington: The Science and Practice of Pharmacy. 19th ed. Easton, PA: Mack Pub Co.;1995:1267

4. Possibility of Iodine as curative medicine

② A case of clinical trials aiming iodine treatment

Fibrocystic disease
(Intractable disease)

⇩

Water soluble molecular iodine (I_2) was dosed 5mg a day for 7 months and the therapeutic value was evaluated by scoring breast tenderness, node, fibrosis , irritation and macrocyst and adding each point

Administration of water soluble molecular iodine for fibrocystic disease patients with breast pain and the therapeutic effect

Subject	Treatment group	Base score	Score after treatment	Changing rate
All	I_2 treatment (46)	37.3 ± 16.4	13.5 ± 12.7	23.9 ± 18.1
	Placebo（46）	35.3 ± 16.4	32.7 ± 16.7	2.6 ± 8.9
Therapy group	I_2 treatment group (23)	42.0 ± 14.4	12.9 ± 12.6	29.1 ± 18.2
Therapy cessation group	I_2 treatment group (23)	32.7 ± 17.2	14.0 ± 13.1	18.7 ± 16.7

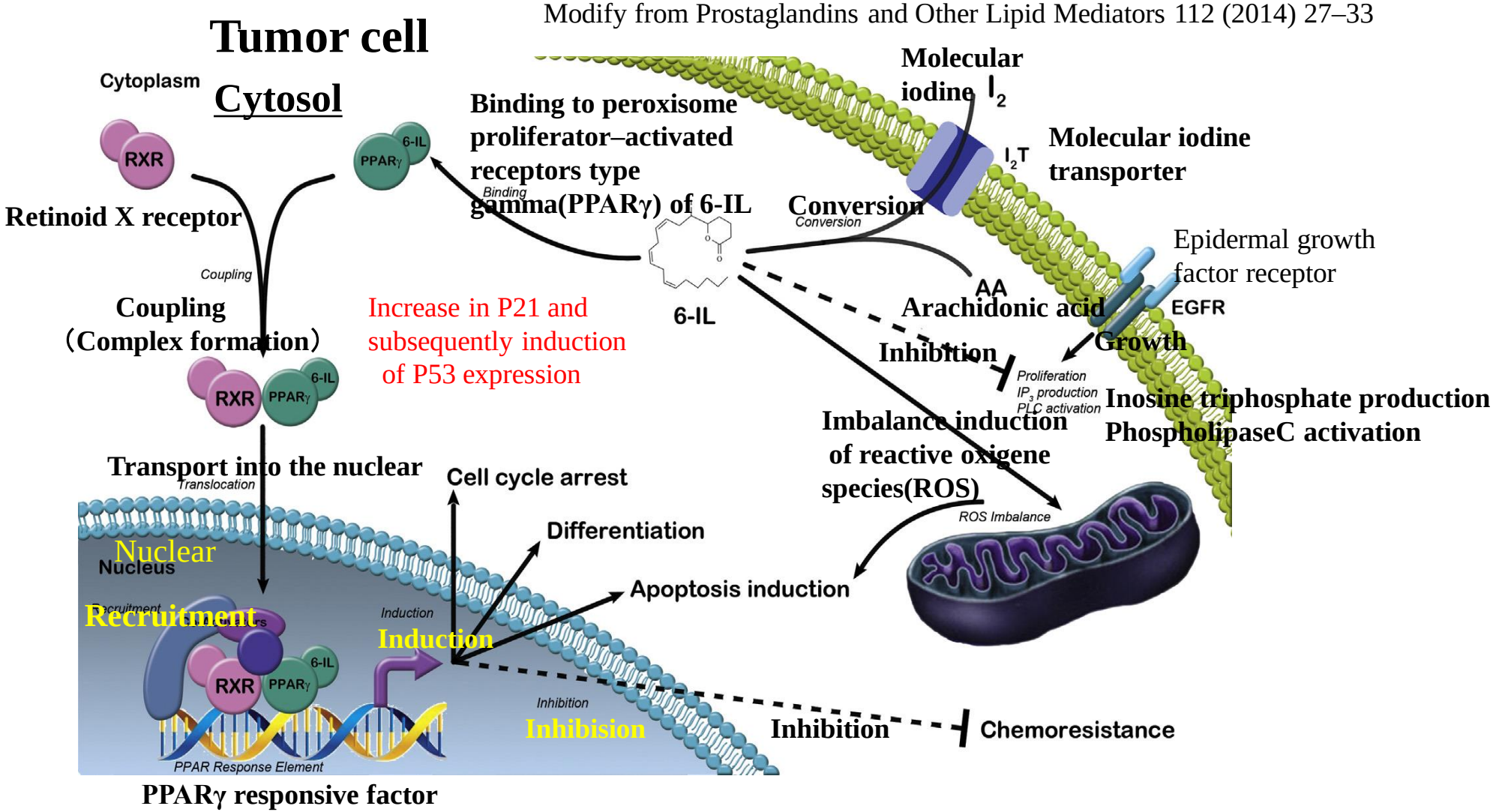
Ghent, W.R., et al.:Can.J.Surg.1993. 36:453-460

4. Possibility of Iodine as curative medicine

③ Powerful antitumor effect of iodine?

Intracellular production mechanism and possible antitumor mechanism of 6-iodolactone**(6-IL)**

Modify from Prostaglandins and Other Lipid Mediators 112 (2014) 27–33



5. What is adverse effect by iodine dosing? Is it problem?

Conclusion: Unclear at the present stage

As possibility of adverse effect by dosing of excessive iodine

1) The possibility that transporter for iodine on thyroid shuts and as a result hypothyroidism occurs by dosing of excessive iodine
2) The possibility that thyroiditis as an autoimmune disease causes by dosing of excessive iodine over a long period
3) The possibility that hyperthyroidism causes by dosing of excessive iodine for goiter patient under the condition of iodine deficiency state

Recommended Dietary Allowance (RDA) for adult men and women in USA is 0.15mg a day. The upper intake limit of iodine for general population is 1.1mg a day. ⬇

But daily intake level of iodine in Japanese people is extremely high.

However, there were a few reports that specific side effects were not found even by dosing of 3-6mg a day for 5 years

Kessler JH. The effect of supraphysiologic levels of iodine on patients with cyclic mastalgia. *Breast J* 2004;10:328-336

Ghent WR, Eskin BA, Low DA, Hill LP. Iodine replacement in fibrocystic disease of the breast. *Can J Surg 1993;36:453-460.*

Power of IODINE

Iodine is very important for cancer treatment

Characteristics of iodine

1. Main current use application

- Stabilizing agent
- Liquid crystal display
- X-ray contrast agent
- Disinfectant
- Prophylaxis for radiological contamination

2. Chemical forms of iodine (I) in natural environment

Molecular iodine	I_2
Iodide	KI, NaI
Iodate	$NaIO_3$
Periodate	H_5IO

3. Function of iodine in human body

1) Iodine is taken from thyroid（gland）follicular cells and binds to tyrosine amino acid and forms thyroid hormone which is involved in energy metabolism and growth.

2) Iodine has a high affinity for oxygen and therefore works as anti-oxidant that it protects polyunsaturated fatty acid from oxygen radical inside the cell.

3) Iodine is included in mucosal fluid and inhibits overgrowth of bacteria containing normal flora in mucosa .

* Iodine level in salivary juice with bacterial flora is 20 to 100 times as many as that in plasma usually in antiseptic condition.

4. Relation between iodine and cancer ①

It is said that the fact that incidence of cancer is extremely low in patients with graves disease attracted an attention to iodine. Iodine has been utilized for cancer therapy since early times, which uses liver oil and seawead extract. It is said that Geruson therapy using Lugol's solution and animal thyroid gland powder, which is the base of cancer nutritional treatment, enhances by iodine a reduced systemic metabolism.

Hunabashi et al. found that an apoptosis which means programmed cell death is induced in cancer cells by mixing seaweed into feed in experimental rat cancer model. Continuously they confirmed that the number of cancer cells with apoptosis has been increasing as time passes when seaweed was added into culture plate of cancer cells at a concentration of 0.007g per broth 1mL and after 96 hours, 56.5% of cells died by apoptosis and further 63.3% of cells died when a double dose of seaweed was given. This was a high rate compared with common anticancer drugs.

4. Relation between iodine and cancer ②

It is well known that the people of Japan is associated with a lower incidence of breast cancer and prostate cancer than western people. It is pointed out that this is related to that Japanease consumes seaweed almost daily. It means to take more iodine to take more seaweed. As one of the proofs, there is a report that mean daily iodine consumption in Japanease is 5280 μ g, which is 25 times higher as many as 209 μ g in western people.

4. Relation between iodine and cancer ③

Some studies demonstrated that iodine has prophylactic and anticancer effects for breast cancer and prostate cancer. For example, Ghent et al. found that the fibrocystic breast as precancerous stage reacts differently to sodium iodide, protein-bound iodide and molecular iodine. Molecular iodine is nonthyrotropic and was the most beneficial (Iodine replacement in fibrocystic disease of the breast Ghent WR, Eskin BA, Low DA, Hill LP. Can J Surg. 1993, 36:453-60).

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5. Why do iodine have an anticancer effectiveness?

Molecular iodine (I_2) shows antioxidant action inside the cell for oxygen derived free radicals which promotes the development of cancer. It is suggested that this antioxidant effect cccurs by the following two mechanisms.

- Molecular iodine (I_2) competes with peroxidizing action for intracellular components by reactive oxygen or neutralizes most harmful hydoroxy radical (HO・）by forming hypoiodous acid（HOI）.
- Molecular iodine (I_2) enhances indirectly expression or activity of antioxidant system.
- Molecular iodine (I_2) has any affects for normal tissue cells but induces an appoptosis (programmed cell death) and antiproliferative activities for cancer cells (Dugrillon et al., 1990, Endocrinology. 127:337-343, Langer et al., 2003, Exp. Endocrino. Diabetes)