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Accounts

Multielement Profiling Analyses of Biological, Geochemical, and Environmental Samples as Studied by Analytical Atomic Spectrometry

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The progress of modern analytical atomic spectrometry is briefly reviewed with emphasis on ICP-AES and ICP-MS; these provide some excellent analytical features such as high sensitivity, wide linear dynamic range, and multielement detection capability. Thus, the multielement determination of the major-to-ultratrace elements from % to sub-ppt (1 ppt = 10^{-12} g ml^{-1}) level is possible for the biological, geochemical, and environmental samples. The standard or certified reference materials of plant, human blood serum, and the other biological samples were analyzed to establish the reliable analytical methods for the multielement determination by ICP-AES and ICP-MS. The modern analytical methods were applied to: (i) the correlation analysis of the elements in human blood serum, and (ii) the determination of rare earth elements in human blood serum on a personal basis. The speciation of trace elements in natural water was also carried out by the SEC (size exclusion chromatography)/UV absorption detection/ICP-MS combined system after ultrafiltration of the water samples. The SEC chromatograms indicated that most of trace elements in natural water existed as large organic molecule–metal complexes with the molecular weight of > 300000 and 10000—50000. In addition, trace elements in man and in the sea were discussed from the viewpoints of the geochemical classification of the elements on the earth, the Lewis's acid-base theory, and the principle of HSAB (hard and soft acids and bases). Such multielement information allows the multielement profiling analyses of various samples to elucidate the elemental distributions, physicochemical characteristics, and behaviors of the major-to-ultratrace elements in relation with the biological functions or with the geochemical and environmental phenomena.

In general, chemical analyses using the spectroscopic methods are termed "spectrochemical analyses". The main historical development of spectrochemical analysis is summarized in Table 1.[1,2] As is seen in Table 1, the first spectroscopic experiment was performed by Sir Isaac Newton in 1666.[3] Newton dispersed solar rays with a glass prism and observed an artificial rainbow on the wall in a dark room. He named the artificial rainbow "spectrum". It is usually said that Newton's discovery of this "spectrum" is the beginning of "spectroscopy". In 1800 and 1803, the infrared and the ultraviolet regions were found by Hershel[4] and Ritter,[5] respectively. Further important findings in spectroscopy were achieved by Fraunhofer in 1817.[6] Fraunhofer found many dark lines on the solar spectrum (artificial rainbow), which was produced by using a grating made of silver wires in a similar manner to the Newton's experiment. He assigned the main dark lines as A, B, C, ···, and H. These dark lines are referred to as the "Fraunhofer lines". Fraunhofer already knew that the dark line "D" had been coincident with the yellow line emitted from salt (NaCl) in the alcohol flame, but he could not interpret the physical meanings of the dark lines. In the 1850s, Kirchhoff and Bunsen did an interesting experiment for the observation of emission from sodium atoms in a flame sustained on the Bunsen burner as well as absorption of solar ray by sodium atoms. Then, they found that the absorption line of sodium was in coincidence with the emission line of sodium, which corresponded to the Fraunhofer dark line assigned to "D". The wavelength of the "D" line is now known to be 589 nm. In consequence, Kirchhoff interpreted that the Fraunhofer dark lines were observed as the atomic absorption phenomenon so that the cooler atoms in the corona region outside the sun absorb the continuous solar radiation from the hotter (excited) atoms inside the sun.[7] They also elucidated that *the individual atoms have their own intrinsic atomic lines*. As a result, Kirchhoff and Bunsen founded "flame emission spectrometry",[8] which was the beginning of "spectrochemical analysis". They discovered Rb and Cs by flame emission spectrometry. Later, Ga, In, and Tl were also found by flame emission spectrometry.

After the works by Kirchhoff and Bunsen, the studies on atomic spectra and atomic structures were greatly progressed in physics.[9] In consequence, the hydrogen atom model of

Table 1. Historical Development of Spectrochemical Analysis

1666	I. Newton:	Discovery of "spectrum" by observation of the solar ray with a prism.
1800	W. Hershel:	Discovery of infrared region by observation of temperature effect.
1803	J. W. Ritter:	Discovery of ultraviolet region by observation of light sensitivity of AgCl.
1817	J. Fraunhofer:	Discovery of Fraunhofer lines.
1860	G. R. Kirchhoff & R. Bunsen:	Foundation of flame emission spectrometry.
1885	J. J. Balmer:	Observation of spectrum of hydrogen atom.
1890	H. Kayser & J. R. Rydberg:	Formulation of atomic emission lines.
1896	P. Zeeman:	Observation of Zeeman splitting.
1913	N. Bohr:	Proposal of hydrogen atom model and discontinuous quantum conditions.
1925	W. Schrödinger:	Proposal of quantum mechanics.
1930	H. Lundegarch:	Development of a nebulization-type burner.
1955	A. Walsh & C. T. J. Alkemade:	Atomic absorption spectrometry.
1964	J. D. Winefordner:	Atomic fluorescence spectrometry.
1964-1965	V. A. Fassel, S. Greenfield:	ICP-AES (inductively coupled plasma atomic emission spectrometry).
1980	R. S. Houk, V. A. Fassel:	ICP-MS (inductively coupled plasma mass spectrometry).

Bohr and the quantum mechanics of Schrödinger were proposed to establish modern physics. During that period, a nebulization-type burner developed by Lundegarch gave a great push to the progress in spectrochemical analysis.

In 1955, almost 100 years after the experiment by Kirchhoff and Bunsen, Walsh published a paper about "atomic absorption spectrometry" as a new analytical method for trace analysis.[10] He used a chemical flame as an atomization source and a sodium vapor lamp as a light source in his preliminary experiment. In the same year, Alkemade and Milatz also suggested the possibility that atomic absorption spectrometry could be a method for trace analysis.[11] Their works opened the door of modern analytical atomic spectrometry for trace analysis. In 1964, Winefordner published the first paper concerning "atomic fluorescence spectrometry".[12]

In the early 1960s, Fassel in the USA[13] and Greenfield in the UK[14] had already started to explore a next-generation analytical method using an argon ICP (inductively coupled plasma) for atomic emission spectrometry. The argon ICP has many excellent spectroscopic characteristics as an excitation source for spectrochemical analysis, as will be described later. As a result, an analytical method using the argon ICP has been established as ICP-AES (inductively coupled plasma atomic emission spectrometry).[2,15,16] Fassel's group from the USA and the UK further noticed that the argon plasma could also be an effective ionization source because of its high plasma temperature, and they developed ICP-MS (inductively coupled plasma mass spectrometry) in 1980.[17] Since both ICP-AES and ICP-MS have simultaneous multielement detection capabilities with high sensitivity and wide linear dynamic range, these methods have been extensively used in a variety of scientific fields as well as in industrial fields.[2,18—23]

Over the last three decades, the present author has been engaged in some research projects on analytical atomic spectrometry; atomic absorption spectrometry and atomic fluorescence spectrometry in the 1970s, ICP-AES in the 1980s, and ICP-MS in the 1990s. These researches have been aimed at developing highly-sensitive analytical methods to allow simultaneous all-elements analysis. The present state-of-the-art technologies of ICP-AES and ICP-MS may make it possible to approach such a goal. In the present paper, the multielement determination of major-to-ultratrace elements in biological, geochemical and environmental samples by ICP-AES and ICP-MS is described from the viewpoint of the "multielement profiling analysis". The multielement profiling analysis was proposed as a new analytical concept by present author.[24,25] The term "multielement profiling analysis" is defined as a method for analysis of multielement data to elucidate the physicochemical and bio-geochemical properties and characteristics major-to-ultratrace elements from the elemental concentrations and distributions in the samples analysed. As a result, the biological functions and roles or the geochemical/environmental phenomena would be revealed, which could not be taken into insight from the analytical data for a signal element or a limited number of elements.

1. Instrumentation in Analytical Atomic Spectrometry

In principle, analytical atomic spectrometry consists of three different optical measurement methods: emission, absorption, and fluorescence spectrometry. These three meth-

ods are briefly described here, based on their fundamental principles.

Atomic Emission Spectrometry (AES):[2,26,27] Atoms and ions produced in the high-temperature media are thermally excited from the ground state to the excited states, and spontaneous emission from the upper state to the lower state is observed as the radiation energy. When the high-temperature media (> 5000 K) are available, atomic emission spectrometry provides various advantages over the other spectrochemical methods.

Atomic Absorption Spectrometry (AAS):[28—30] Atoms absorb the light at the wavelength of intrinsic atomic line (resonance line) so that atoms in the ground state are excited to the lowest excited state. At this time, absorption is observed as the intensity difference between the incident light and transmitted light, following the Lambert–Beer law, which is expressed as

$$A = \log (I_0/I) = kCl, \quad (1)$$

where A, I_0, I, C, and l are absorbance, intensity of incident light, intensity of transmitted light, the concentration of neutral atoms, and the length of the atomization cell, respectively. Atomic absorption spectrometry has an advantage because atoms in the relatively low-temperature media (< 3000 K) populate dominantly in the ground states, as estimated by the Boltzmann distribution law.

Atomic Fluorescence Spectrometry (AFS):[27,30] Atoms excited optically by the radiation from the light source emit radiation energy as fluorescence, when the excited atoms are de-excited to the ground state. Since the atomic fluorescence intensity is proportional to the light source intensity, laser-excited atomic fluorescence spectrometry provides the extremely high sensitivity with wide linear dynamic range.[31]

In atomic spectrometry, as is understood from the above description, atoms (and ions) should be produced first, and thus efficient atomization sources are necessary in analytical atomic spectrometry. Usually, flames, graphite furnace, metal boat or filament, glow discharge lamp, arc, and spark are used as the atomization sources.[20] In atomic emission spectrometry, these atomization sources have to be also the excitation sources.

In atomic absorption spectrometry, a hydride generation technique for As, Se, Sb, Ge, Te, Sn, Pb, and Bi, and a cold vapor generation technique for Hg, in which chemical reduction reactions using $NaBH_4$ are employed, have been developed to improve their analytical sensitivities, because the detection limits of these elements obtained by flame atomic absorption spectometry are very poor.[29] Furthermore, GFAAS (graphite furnace atomic absorption spectrometry) is still extensively used for trace analysis, especially in clinical and biochemical fields, because only 5—50 μl of the sample solution is required for one analysis. However, AAS is a method principally for single-element analysis, which creates a disadvantage in comparison to ICP-AES and ICP-MS.

Recently, several types of plasmas using rare gases are available as the atomization and excitation sources.[2,19] Among them, an argon ICP is the most popular and effective excitation source. The argon ICP is generated on the top of a plasma torch by applying sufficiently high radiofrequency (e.g., 27.12 MHz and 1—2 kW) with flowing argon gas. The plasma torch consists of three concentric quartz tubes making three different argon flows (*outer gas, intermediate* or *plasma gas*, and *inner gas*; See Table 2). The advantageous characteristics of the argon ICP are derived from high plasma excitation temperature (T_{exc} = 6000—9000 K) and high electron number density ($n_e = 10^{14}$—10^{15} cm^{-3}).[2] In the argon ICP, the plasma temperature and the electron number density in the central channel of the plasma are lower than those in the outer plasma region to form an annular-shaped plasma.[32—34] Such a plasma structure is referred to as the *so-called* "doughnut structure". This doughnut structure allows effective and reproducible introduction of the sample solution as aerosols into the central channel of the plasma. As a result, the argon ICP can be a very efficient atomization source as well as an excitation source.

A schematic diagram of the ICP-AES instrument is shown in Fig. 1. This is a multichannel-type ICP-AES instrument using a polychromator, which allows the simultaneous multielement determination of 30—50 elements. In addition, a sequential-type ICP-AES instrument with a computer-programmable monochromator is commercially available, by which 10—20 elements are determined sequentially within 1—5 min by fast scanning of the wavelength in the region of interest under the computer-control.

Hasegawa and Haraguchi investigated the excitation mechanisms in the argon ICP, together with extensive works of plasma diagnosis,[35—38] and proposed the "collisional-radiative model"[35,39—42] to interpret the comprehensive excita-

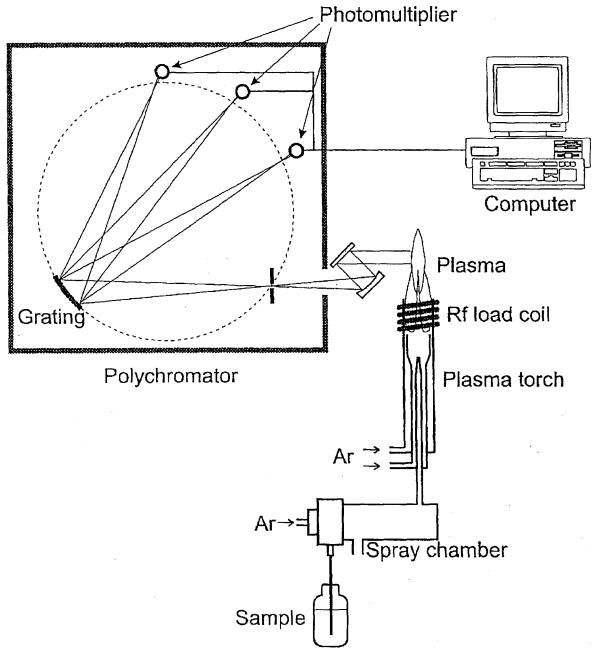

Fig. 1. Schematic diagram of the multichannel-type ICP-AES instrument.

Table 2. Instrumental Systems and Operating Conditions for ICP-AES and ICP-MS

ICP-AES (Multichannel-type)	Jarrell-Ash Plasma AtomComp Mk II
Plasma conditions	
Rf frequency	27.12 MHz
Rf power	1.0 kW
Outer gas	Ar 17 dm^3 min^{-1}
Intermediate gas	Ar 1.0 dm^3 min^{-1}
Carrier gas	Ar 0.5 dm^3 min^{-1}
Observation height	18 mm above work coil
Nebulizer	Cross-flow type
Polychromator	Paschen–Runge (75 cm focal length)
Grating	2400 grooves/mm
Entrance slit width	25 μm
Exit slit width	50 μm
Integration time	30 s
ICP-AES (Sequential-type)	Seiko SPS 1500V
Plasma conditions	
Rf frequency	27.12 MHz
Rf power	1.0 kW
Outer gas	Ar 16 dm^3 min^{-1}
Intermediate gas	Ar 1.0 dm^3 min^{-1}
Carrier gas	Ar 0.5 dm^3 min^{-1}
Purge gas	N_2 5 dm^3 min^{-1}
Observation height	10 mm above work coil
Nebulizer	Glass concentric type (Meinhard TR-30-A2)
Monochromator	Czerny-Turner (100 cm focal length)
Grating	3600 grooves/mm
Entrance slit width	20 μm
Exit slit width	30 μm
Integration time	10 s
ICP-MS (Quadrupole-type)	Seiko SPQ 8000A
Plasma conditions	
Rf frequency	27.12 MHz
Rf power	1.0 kW
Outer gas	Ar 16 dm^3 min^{-1}
Intermediate gas	Ar 0.5 dm^3 min^{-1}
Carrier gas	Ar 1.0 dm^3 min^{-1}
Sampling conditions	
Sampling depth	12 mm from load coil
Sampling cone	Copper, 1.1 mm orifice diameter
Skimmer cone	Copper, 0.35 mm orifice diameter
Nebulizer	Glass concentric type (Meinhard TR-30-A2)
Sample uptake rate	0.7 ml min^{-1}
Data acqisition	
Scanning mode	Peak hopping
Data points	3 points/peak
Dwell time	10 ms/point
Integration	20 × 5 times

tion and de-excitation mechanisms for argon gas and analyte elements. According to the model, ions of the analyte elements are overpopulated at the ground state or lower excited state in the argon ICP because of non-radiative de-excitation under the local temperature equilibrium (LTE).[39—41]

It has been elucidated from the studies on the excitation mechanisms that the argon ICP is an efficient ionization source, because most metallic elements are ionized more than 90% in the plasma.[43,44] Thus, ICP-MS, in which the argon plasma is combined with a mass spectrometer through the sampling interfaces (*sampling cone* and *skimmer cone*; See Fig. 2), is also useful for trace analysis. ICP-MS is also included in the category of analytical atomic spectrometry.[2,19] A schematic diagram of the ICP-MS instrument is shown in Fig. 2, which is composed of a quadrupole-type mass spectrometer. This type of the instrument allows one to determine about 30 elements in one measurement within ca. 2 min.

Owing to the excellent characteristics of the argon ICP, ICP-AES and ICP-MS are now available as the analytical methods with robustness. The analytical features of them

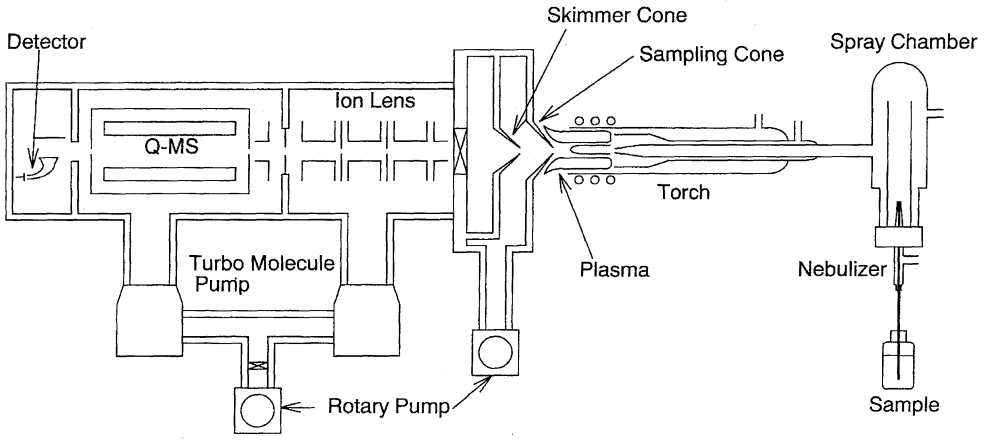

Fig. 2. Schematic diagram of the ICP-MS instrument with quadrupole-type mass spectrometer.

can be generally summarized as follows;

i) High sensitivities for almost all metallic elements including S and P.

ii) Wide linear dynamic range of the calibration curve (4—6 orders of magnitude).

iii) Simultaneous multielement detection capability.

iv) Good precision and reproducibility.

v) Less chemical and ionization interference.

However, the *spectral interference* (overlappings of emission lines) is a serious problem in ICP-AES.[2,19] Thus, a high-resolution monochromator is preferably employed in ICP-AES, in which a monochromator with longer focal length (100—150 cm) and a grating with a large number of grooves (3600—4800 grooves/mm) are used in special specification. In the case of ICP-MS, *matrix effects* due to major constituents in the samples and *polyatomic ion interference* due to ions of oxides, hydroxides, halides and carbides produced from major/minor constituents and plasma gases are the problems that must be overcome to obtain accurate analytical results.[19,44—46] Matrix effects are usually corrected by the internal standard method.[47] Polyatomic ion interferences are often corrected by the interference correction coefficient method.[48,49] In principle, the use of a high-resolution ICP-MS instrument consisting of a double-focusing mass spectrometer with mass resolution of 3000—10000 is desirable to minimize polyatomic ion interference.[20,50—52]

The instrumental systems and typical operating conditions of the ICP-AES and ICP-MS instruments are summarized in Table 2, where (i) a multichannel-type ICP-AES instrument of model Plasma AtomComp Mk II from Jarrell Ash (Franklin, MA, USA), (ii) a sequential-type ICP-AES instrument of model SPS 1500V from Seiko Instrument Inc. (Chiba), and (iii) a quadrupole-type ICP-MS instrument of model SPQ 8000A (Seiko Instruments Inc.) are listed for the examples. Such operating conditions for the instruments manufactured by other instrumental companies are quite similar to those shown in Table 2. In these instrumental systems, almost the same argon ICP can be used as the ionization source for ICP-MS as well as the excitation source for ICP-AES. Thus, it is seen in Table 2 that the argon ICP is operated under almost the same conditions, although the observation height ("sampling depth" in the case of ICP-MS) is slightly different. It should be noted here that the consumption of argon gas (total flow rate of outer, intermediate, and carrier argon gases) is about 15—20 dm^3min^{-1}. Such large consumption of argon gas often costs too much to the users.

In order to reduce argon gas consumption, a combined system of ICP-AES and ICP-MS was developed in the present author's laboratory.[48,53] Here only one argon ICP was used for ICP-MS and the emission signals from the argon ICP were led into a monochromator through an optical fiber. A schematic diagram of the ICP-MS/AES combined system is shown in Fig. 3; this system allows the simultaneous observation of ICP-MS and ICP-AES. The monochromator employed in Fig. 3 was the same as the one used in the ICP-AES instrument of model SPS 1500V, listed in Table 2. In the ICP-MS/AES combined system, the argon plasma equipped

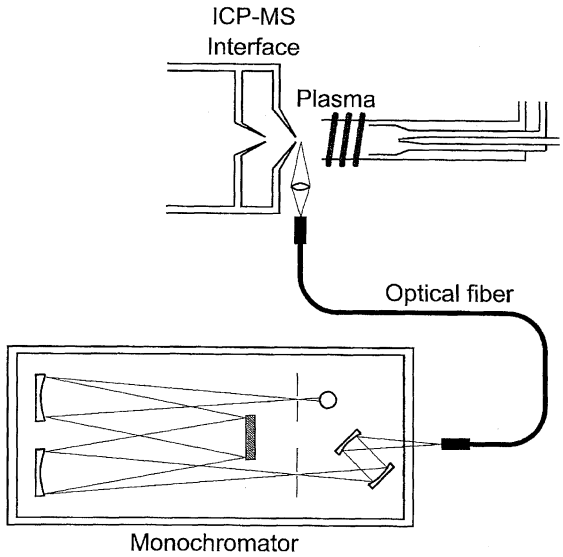

Fig. 3. Schematic diagram of the ICP-MS/AES combined system. In this system, only the argon plasma for ICP-MS is used under the optimized conditions for the ICP-MS measurement, and the emission signals are led to the monochromator for the ICP-AES measurement through an optical fiber.

for ICP-MS is operated under the optimum conditions for the ICP-MS measurement, and then the emission signals have to be observed under the same conditions. Consequently, the detection limits obtained by the emission measurement were deteriorated by ca. 5—30 times, but they were still sensitive enough to determine major and minor elements. This combined system provides the wider linear dynamic range of the calibration curve, for example, ca. 9 orders of magnitude for Y,[53] where the concentration ranges of 1 ng ml^{-1}—100 μg ml^{-1} and 1 pg ml^{-1}—1 μg ml^{-1} are covered by ICP-AES and ICP-MS, respectively. This wide linear dynamic range facilitates the intercalibration function for the analyte elements in the concentration range between 1 ng ml^{-1} and 1 μg ml^{-1}, because this concentration range can be determined at the same time by both ICP-AES and ICP-MS.

In addition, the development of atmospheric pressure microwave-induced plasma (MIPs) can be listed as one of the recent topics in analytical atomic spectrometry. In 1976, Beenakker developed a TM_{010}-mode resonance cavity (Beenakker cavity) for generation of a helium plasma at atmospheric pressure.[54] Since atmospheric pressure helium MIP allows the determination of non-metallic elements such as N, S, P, and halogens in the usual visible region,[55] the extensive works for use of the helium MIP were carried out in terms of fundamentals and applications in analytical atomic spectrometry.[56—63] Especially, the application of atmospheric pressure helium MIP-AES (microwave-induced plasma atomic emission spectrometry) to the element-selective detector for gas chromatography (GC) allows one to obtain the unique information in analyses of volatile halogenated organic compounds.[56—58] A GC/MIP-AES (helium) instrument is now commercially available from Hewlett–Packard Co. Also, the atmospheric pressure helium MIP provides the extremely low detection limits for Hg[59] as well as for $(CH_3)HgX$.[60] More recently, the atmospheric pressure MIPs using N_2, O_2, and air as plasma gas have been developed for the ionization sources in mass spectrometry.[64] The MIP-MS instrument manufactured by Hitachi Instrument Co. has been finding a market similar to that for the usual ICP-MS instruments.

2. Analytical Figures of Merit

In order to describe the analytical figures of merit, the definitions of some fundamental terms used in analytical atomic spectrometry are given below.[2]

Detection Limit: Detection limit is defined as the concentration of analyte element corresponding to 3-times the standard deviation (3σ) of background signal intensities, when the blank solution is measured under the same experimental conditions as the sample solution.

Absolute Detection Limit: Absolute detection limit is defined as the lowest amount of analyte element detected as the analytical signal. The absolute detection limit is estimated by the following equation:

Absolute detection limit = (detection limit)×(sample amount used for analysis),

where the units of absolute detection limit, detection limit and sample amount are g, g ml^{-1}, and ml, respectively.

Lower Determination Limit: Lower determination limit is defined as the concentration of analyte element corresponding to 10-times of standard deviation (10σ) of background signal intensities. This is an important measure to estimate the lowest concentration of analyte element, which can be determined with precision (or reproducibility) within 10%, when precision is expressed as the relative standard deviation (RSD) of the observed values ($n \geqq 3$).

2.1 Detection Limits. The detection limits obtained by GFAAS, ICP-AES, and ICP-MS, which are currently used most extensively in the various fields, are summarized in the periodic table of Table 3 for general comparison.[65] It is seen from Table 3 that ICP-AES and ICP-MS are applicable to the determination of 73 elements among 78 elements except for rare gas elements and radioactive elements. In general, ICP-MS provides a detection limit which is 2—4 orders of magnitude lower than that of ICP-AES.

2.2 Absolute Detection Limits. The absolute detection limits obtained by various analytical methods are compared in Fig. 4. Neutron activation analysis (NAA) has been most popularly used as a method for the multielement determination with the lowest absolute detection limits. However, NAA is inconvenient in practical analysis because it requires a nuclear reactor to yield the neutron flux to irradiate the samples analysed. It is seen from Fig. 4 that the whole range obtained by various methods can be covered only by the use of ICP-AES and ICP-MS. It should be also noted here that isotope ratio analysis is possible in ICP-MS. This characteristics of ICP-MS can be applied to isotope dilution (ID) analysis using an enriched stable isotope.[66] Now, ID-ICP-MS is considered to be one of the most reliable analytical methods,[67,68] in standardization of analytical procedures and analytical values for standard reference materials. Thus it is referred to as "the primary absolute analytical method".

Taking account of the detection limits and the linear dynamic ranges obtained by ICP-AES and ICP-MS, it is concluded that ICP-AES and ICP-MS are suitable for the determination of major (100—1%)/minor (1—0.01%) ele-

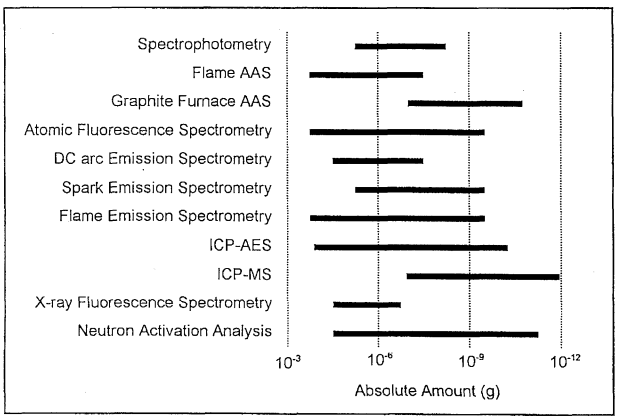

Fig. 4. Comparison of absolute detection limits obtained by various analytical methods.

Table 3. Detection Limits in GFAAS, ICP-AES, and ICP-MS

H – – –			Element GFAAS ICP-AES ICP-MS													He
Li 0.3 1 0.027	Be 0.003 0.1 0.05											B 20 2 0.1	C – 10 –	N	O	F	Ne
Na 0.02 10 0.03	Mg 0.1 0.1 0.018											Al 0.1 4 0.015	Si 10 5 5	P 0.3 30 5	S – 20 –	Cl	Ar
K 0.1 40 –	Ca 0.04 0.1 0.5	Sc 6 0.4 0.015	Ti 40 0.8 0.011	V 0.3 1 0.008	Cr 0.2 2 0.04	Mn 0.02 0.3 0.006	Fe 1 0.62 0.58	Co 0.2 0.85 0.005	Ni 0.9 3 0.013	Cu 0.1 1 0.04	Zn 0.003 1 0.035	Ga – 7 0.009	Ge 3 13 0.013	As 0.8 10 0.031	Se 0.9 15 0.37	Br – 1.6 –	Kr
Rb 1 – 0.005	Sr 0.1 0.1 0.003	Y – 0.8 0.004	Zr – 1.9 0.005	Nb – 10 0.002	Mo 0.2 2 0.006	Tc	Ru – 7 0.05	Rh 0.8 8 0.002	Pd 0.4 10 0.009	Ag 0.01 1 0.005	Cd 0.008 1 0.012	In 0.04 20 0.002	Sn 0.1 10 0.01	Sb 0.5 10 0.012	Te 0.1 10 0.032	I – 50 0.8	Xe
Cs 0.04 4000 0.002	Ba 0.6 0.2 0.006	La*	Hf – 5 0.005	Ta – 8 0.002	W – 10 0.007	Re – 2 0.005	Os – 0.5 0.003	Ir – 7 0.005	Pt 1 10 0.005	Au 0.1 3 0.005	Hg 0.2 5 0.018	Tl 1 10 0.003	Pb 2 20 0.01	Bi 0.4 5 0.004	Po	At	Rn
Fr	Ra	Ac**															

*	La – 2 0.002	Ce – 9 0.004	Pr – 9 0.004	Nd – 10 0.007	Pm	Sm – 8 0.013	Eu 0.5 0.45 0.007	Gd – 3 0.009	Tb – 5 0.002	Dy – 2 0.007	Ho – 1 0.002	Er – 2 0.005	Tm – 1.3 0.002	Yb 0.07 0.4 0.005	Lu – 0.3 0.002
**	Ac	Th – 14 0.0003	Pa	U – 50 0.0003	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr

[Remarks]

1) In each element box, the numbers at the upper, middle and lower positions indicate the detection limits obtained by GFAAS, ICP-AES and ICP-MS, respectively.
2) Unit : ppb (10^{-9} g ml^{-1}).
3) The sign – in the table indicates the impossible detection.
4) The elements without any numbers cannot be detected or are radioactive elements.

ments and trace (0.01—0.0001%)/ultratrace (< 0.0001%) elements, respectively. Thus, the multielement determination of major-to-ultratrace elements by ICP-AES and ICP-MS will be described in the following sections.

3. Multielement Determination of Major-to-Ultratrace Elements in Plant Reference Materials by ICP-AES and ICP-MS

As mentioned so far, the use of both ICP-AES and ICP-MS allows the simultaneous multielement determination of analyte elements in the concentration range from 1000 μg ml^{-1} to ca. 1 pg ml^{-1} i.e., ranging over 9 orders of magnitude. Consequently, the elements from major constituents to ultratrace constituents (hereafter referred to as "major-to-ultratrace elements") can be determined in any kinds of samples, if the samples can be decomposed to prepare their analysis solutions, although preconcentration is often required for trace and ultratrace elements. However, the analytical methods for such multielement determination of major-to-ultratrace elements should be carefully examined to obtain the accurate and precise data, which are able to be used for scientific discussion. Here, for example, the multielement analysis of the plant samples by ICP-AES and ICP-MS are described to introduce the present status of multielement determination of major-to-ultratrace elements.

The plant samples used for analysis are the plant reference materials such as Pine Needles (NIST SRM1575) and Tea Leaves (NIES No. 7) issued from National Institute of Standards and Technology (NIST; Gaithersburg, USA) and National Institute for Environmental Studies (NIES; Tsukuba, Japan), respectively. Since the samples for the ICP-AES and ICP-MS measurements should be in solution form, the above reference materials in powder were decomposed with acid digestion. The acid digestion procedures established for the

plant samples are as follows.[49,70]

Sample Pretreatment Procedure: Approximately 0.5 g of plant sample was taken in a PTFE Teflon® beaker with a Teflon cover. After 5 ml of concd HNO_3 was added into the beaker, the sample was kept standing overnight at room temperature. Five ml of concd HNO_3 was added again to the beaker, and the sample was heated on a hot plate at 75 °C for 0.5 h, 130 °C for 0.5 h, and 200 °C for 2 h. In order to decompose siliceous materials completely, 2 ml of concd HF was further added to the digest, and then heated again at 180 °C for 2 h and 230 °C for 3 h almost to dryness. The residue was dissolved with 7.5 ml of concd HNO_3 and diluted to 100 ml, in which the internal standard elements (Ge, In, and Re) were added to be 10 ng ml^{-1} each for correction of any matrix effect. Then, the solution was filtered with a membrane filter (pore size 0.45 μm). The final analysis solutions for plant samples were of 1 M HNO_3 (1 M = 1 mol dm^{-3}). The reagent blank solution without any plant sample was prepared by performing the same procedure to estimate the experimental blank values.

It should be stressed here that the HF treatment in acid digestion is inevitable for complete decomposition of siliceous materials in the plants. Without the HF treatment, the refractory elements such as Fe, Al, U, and Th, which are generally condensed in siliceous materials, provide the significantly lower values, compared to the certified values. Thus obtained analysis solutions were subjected to the ICP-AES and ICP-MS measurements. The matrix effects and the polyatomic interferences were corrected by the internal standard correction method and the interference correction coefficient method, respectively.[49]

The analytical results for pine needles and tea leaves reference materials are summarized in Table 4. The reference (or certified) values only for the pine needle samples are shown in Table 4, where *relative variance* values estimated by the following equation are also shown:

$$\text{Relative variance } (\%) = [(M_{obs} - M_{ref})/M_{ref}] \times 100 \quad (2)$$

Here M_{obs} and M_{ref} are the observed and reference (or certified) values, respectively. It is seen from Table 4 that the observed values for pine needles reference material obtained in the present experiment generally agreed well with the certified or reference values except for rare earth elements (REEs). These results indicate that the present experimental method including the sample digestion is reliable enough to apply it to the multielement determination of major-to-ultratrace elements in the plant samples. In the case of REEs, since there are only a few reported values, further interlaboratory comparison is required to establish their certified values.

Cherry blossom is the symbolic flower of Japan. Thus, the elemental concentrations and distributions in the cherry blossom and leaves as well as their seasonal variations are a matter of interest in plant analysis. The analytical results for the cherry leaves sample collected in the campus of Nagoya University are also shown in Table 4. After being air-dried, the cherry leaves samples were dried at 85 °C in an oven and then ground to powder with an agate mortar. Actually, the petals of the cherry blossoms were also analysed on the multielement basis. As is seen in Table 4, 40 elements in the concentration range from K 19800 μg g^{-1} to Tm 0.0023 μg g^{-1} could be determined in the cherry leaves, which were collected on May 15, 1996. It is noted here that the cherry petals contained K, P, and Zn more than the young cherry leaves (April 30) and the contents of these elements in cherry leaves decreased with growing until the end of May. On the other hand, the contents of Ca, U, Th, and REEs gradually increased until the beginning of September. The detailed discussion is not made here, but the multielement data for the plant samples provide some interesting information about plant growth and physiological activities of trace elements.

In consequence, it should be pointed out that various standard or reference materials as well as the certified values of the elements in them are very necessary for establishment of the multielement determination of major-to-ultratrace elements by ICP-AES and ICP-MS.

4. Elements in Human Blood Serum and Other Biological Reference Materials

The human body is composed of chemical components, although ca. 70% is water. Among them, the main constituents are O (65.0%), C (18.0%), H (10.0%), N (3.0%), Ca (1.5%), P (1.0%), S (0.25%), K (0.20%), Na (0.15%), Cl (0.15%), and Mg (0.15%).[71] These 11 elements are known as "*essential major and minor elements*", and the sum of them amounts to 99.4%. Here, "*essential*" means that these elements are inevitably necessary in man for the main components of amino acids, proteins, nucleic acids, bones, and other biological compounds to perform and maintain the biological and physiological functions.

The total of other elements except for the 11 elements listed above amounts to ca. 0.6%, and so they are at the trace and ultratrace levels. Hereafter, thus, these elements are simply referred to as "*trace elements*". Among these trace elements, the following elements are known to be essential in man:[71] Fe (85.7 μg g^{-1}; 6 g per 70 kg body weight), Zn (28.5 μg g^{-1}; 2 g), Mn (1.43 μg g^{-1}; 100 mg), Cu (1.14 μg g^{-1}; 80 mg), I (157 ng g^{-1}; 11 mg), Mo (143 ng g^{-1}; 10 mg), Cr (28.5 ng g^{-1}; 2 mg), and Co (21.4 ng g^{-1}; 1.5 mg). In addition, the following elements are also known to be essential in experimental animals;[71] F (42.8 μg g^{-1} in man), Si (28.5 μg g^{-1}), Sr (4.57 μg g^{-1}), Pb (1.71 μg g^{-1}), Sn (286 ng g^{-1}), Ni (143 ng g^{-1}), As (28.5 ng g^{-1}), and V (21.4 ng g^{-1}). It is stressed here that Pb, Sn, Ni, and As are usually considered to be toxic elements, but they are now known to be essential in animals at the trace level. Until recent years, most of trace elements were taken into account just as "mineral components", and their essentialities were rarely discussed on the elemental basis even in medicine, biology and nutrition. Furthermore, the toxicities of Hg, Cd, Pb, Cr(VI), As, and Sn have been emphasized because of environmental pollution problems. More recently, the Alzheimer's disease is supposed to be caused by Al (Al in human body 857

Table 4. Analytical Results for Diverse Elements in Plant Reference Materials of Pine Needles (NIST SRM 1575) and Tea Leaves (NIES No. 7), and Cherry Leaves (Nagoya University)

Element	Pine needles (NIST SRM 1575)			Tea leaves (NIES No. 7)	Cherry leaves
	Concentration		Relative	Concentration	Concetration
	$\mu g\,g^{-1}$		variance[c]	$\mu g\,g^{-1}$	$\mu g\,g^{-1}$
	Observed[a]	Reference[b]	%	Observed[a]	Observed[d]
B	14±2	17±2	−18	8.6±1.1	35.9±1.6
Na	47±9	36±16	31	15.6±1.3	13.5±1.9
Mg	1150±10	1180±120	−3	1400±10	2370±50
Al	590±6	545±30*	8	670±5	37±3
P	1160±20	1200±20*	−3	3000±14	1870±60
K	4010±70	3700±200*	8	18000±400	19800±200
Ca	4250±30	4100±200*	4	3090±8	11500±500
Mn	698±2	675±15*	3	611±2	49.4±2.9
Fe	210±5	200±10*	5	88±6	58.9±0.7
Co				0.11±0.002	0.044±0.004
Ni	2.46±0.01	2.7±0.6	−9	6.29±0.12	0.861±0.023
Cu	3.1±0.2	3.0±0.3*	3	7.6±1.8	7.01±0.61
Zn	66±5	65±8	2	31.7±1.7	15.2±0.5
Rb	11.8±0.1	11.7±0.1*	1	6.4±0.032	29.2±1.6
Sr	4.8±0.05	4.8±0.2*	0	3.77±0.13	18.6±1.3
Y	0.099±0.003	0.084	18	0.078±0.0014	0.341±0.035
Mo	0.13±0.01	0.14±0.05	−7	0.0118±0.001	0.544±0.035
Cd	0.2±0.02	0.21±0.05	−5	0.025±0.001	0.012±0.003
Sn				0.21±0.007	0.032±0.009
Cs	0.119±0.004	0.119±0.015	0	0.0213±0.0003	0.032±0.008
Ba	6.5±0.2	7.1±0.8	−8	5.76±0.07	25.6±1.0
La	0.139±0.005	0.16±0.03	−13	0.0677±0.0024	1.54±0.14
Ce	0.263±0.008	0.28±0.1	−6	0.0774±0.004	1.81±0.18
Pr	0.0308±0.0007	0.039±0.011	−21	0.0137±0.0005	0.229±0.022
Nd	0.115±0.003	0.15±0.03	−23	0.052±0.003	0.783±0.074
Sm	0.022±0.0005	0.018±0.004	22	0.0097±0.0008	0.111±0.012
Eu	0.00459±0.00006	0.006±0.001	−24	0.0023±0.0002	0.0244±0.0029
Gd	0.021±0.001	0.05±0.02	−58	0.0121±0.0017	0.0931±0.011
Tb	0.00316±0.00006	0.005±0.002	−37	0.0018±0.0001	0.0103±0.0007
Dy	0.0166±0.0007	0.051	−67	0.0084±0.0002	0.0477±0.0038
Ho	0.0034±0.0002	0.07	−95	0.00193±0.00008	0.00834±0.00086
Er	0.0101±0.0002	0.02±0.01	−50	0.0053±0.0006	0.0199±0.0012
Tm	0.00138±0.00001	0.005	−72	0.00062±0.00011	0.00229±0.00033
Yb	0.00968±0.00006	0.018±0.008	−46	0.0042±0.0006	0.0113±0.0007
Lu	0.00135±0.00001	0.0016±0.0004	−16	0.00062±0.00002	0.00165±0.00016
W	0.052±0.002	0.057	−9	0.006±0.0007	0.011±0.007
Tl	0.045±0.003	0.04±0.01	13	0.0059±0.0007	0.015±0.001
Pb	9.9±0.5	10.8±0.5*	−8	0.784±0.063	0.886±0.11
Th	0.031±0.003	0.037 ±0.003*	−16	0.0039±0.0009	0.008±0.001
U	0.016±0.002	0.020 ±0.004*	−20	0.0018±0.0001	0.0025±0.0001

a) Cited from Ref. 49. b) Reference values cited from Ref. 69. The values with asterisk mean the certified values given by NIST. c) See the text. d) Cited from Ref. 70.

$ng\,g^{-1}$, corresponding to 60 mg per 70 kg body weight). It can be pointed out that the toxiciticies of these heavy metals mostly occur due to excess intake of them in daily life. Here, however, it should be also stressed that many elements are essential to man and animals at the trace level, as described above. These situations show that rapid progress of the biomedical and bio-inorganic researches on trace elements have been greatly indebted to the progress of modern analytical atomic spectrometry for ultratrace analysis.[65,71—75]

In recent years, it is also known that the deficiencies of essential trace elements sometimes cause serious disorders of human body and functions.[71,73] Thus, clinical analysis of trace elements has been receiving great attention for monitoring our health, disease and nutrition.[73] The blood samples such as whole blood, plasma, and serum are often the subject of interest in clinical analyses because of easy sampling.[75] However, the accurate and precise determination of trace elements in the real blood samples on the multielement basis are not so easy even now because of the limited sample amounts available. The present author's group, hence, has been try-

ing to establish the analytical methods for the multielement determination of major-to-ultratrace elements in the human blood samples.[76,77]

The analytical results for human blood serum and other biological standard (or certified) reference materials are summarized in Tables 5 and 6. These were analysed by ICP-AES and ICP-MS after acid digestion using HNO_3 and/or $HClO_4$. In Table 5, the analytical data for human blood serum reference materials issued from NIES, Ghent University (Ghent, Belgium), and NIST are shown together with those for urine standard reference material from NIST.[65,76] Here, the analytical precision (SD; standard deviation) is given only for NIES No. 4.

Prior to the experiment for the determination of major-to-trace elements in the serum and urine samples listed in Table 5, contamination or blank values originated from water, chemicals, glasswares, and the other experimental tools used throughout the present experimental procedure were carefully checked in detail, by using second-generation serum certified reference material issued from Ghent University,[78,79] which is considered to be the most reliable serum reference material because of less contamination during preparation of the reference material. The analytical values obtained in the present experiment[77] were in rather good agreement with the reference values for the second-generation blood serum reference material from Ghent University.[78—80] As for NIES No. 4 and NIST SRM 909b, many elements have been newly determined in the present

Table 5. Elemental Concentrations of Biological Reference Materials of Human Blood Serum and Urine Determined by ICP-AES and ICP-MS

Element	Human blood serum[a] (NIES No. 4) ng ml^{-1}		Human blood serum[b] (NIST SRM 909b) ng ml^{-1}		Human blood serum[c] (Ghent Univ.) ng ml^{-1}		Human urine (elevated)[d] (NIST SRM 2670) ng ml^{-1}	
Na	2750000±30000	(3000000)	2940000	(2780000)	3130000		2610000	(2620000)
K	169000±1000	(173000)	130000	(134000)	148000		1380000	[1500000]
P	108000±1000	(107000)	90400		119000		614000	
Ca	77700±800	(78000)	81300	(88900)	103000		107000	[105000]
Mg	17000±100	(19500)	17400	(18600)	16800	[17100]	60100	(63000)
Si							10200	
Li			3030		1.6			
Fe	980±10	(1070)	1270		2300	(2350)		
Cu	970±0	(1040)	960		930	(1010)	387	(370)
Zn	930±20	(910)	1110		830	(870)	925	
Ba	848±103	[70—620]	153		0.48	[1.01]	1080	
Al	370±40	[300—1500]	150					
Mn							350	[330]
Ni							253	[300]
Rb	178±0	[200—320]	6.59		179	(168)	1020	
Co							113	
Cd							90.9	(88)
Cr							82.6	(85)
Sr	67.9±1.4	[50]	112		22.5		193	
Au	5.3±0.2	[6]					174	[240]
Sb	2.4±0.3	[0.8]	2.25					
Mo	2.21±0.10	[3.59]	13.6		0.95	(0.68)	40.2	
Zr	2.11±0.86		1.89					
Pb	2.0±0.9	[1.01]	1.09		1.20	[4.21]	118	(109)
W	1.70±0.00				0.344			
Ag	1.23±0.02	[1.32]	0.64					
Y			0.730					
Cs	0.59±0.00	[0.8—1.1]	0.94		0.95	(0.91)	21.5	
Ce	0.22±0.01				1.31			
Bi	0.137±0.007		0.250		0.060	[0.063]	56.3	
Pt	0.13±0.01							
La	0.10±0.01				1.05			
Nd	0.07±0.01				0.566			
Th	0.07±0.00				0.495			
U	0.06±0.00				0.308			
Pr	0.019±0.001				0.166			

a) The numbers in ( ) and [ ] are the acceptable and information values, respectively. b) The numbers in ( ) are the certified values given from NIST. c) The numbers in ( ) and [ ] are cited from Ref. 79 and Ref. 80, respectively. d) The numbers in ( ) and [ ] are the certified and information values, respectively.

Table 6. Elemental Concentrations of Biological Reference Materials of Human Hair, Bovine Liver, and Bovine Whole Blood Determined by ICP-AES and ICP-MS

Element	Human hair (NIES No. 13) ng g^{-1}		Bovine liver (NIST SRM 1577) ng g^{-1}		Bovine whole blood (IAEA A-13) ng g^{-1}	
Ca	812000±6000	[820000]	120000	(123000)	269000	(286000)
P	179000±2000		11600000		820000	[940000]
S					6230000	(6500000)
Zn	152000±1000	(172000)	133000	(130000)	10600	(13000)
Fe	143000±4000	[140000]	261000	(270000)	2360000	(2400000)
Mg	143000±1000	[160000]	571000	(605000)	87000	[99000]
Al	119000±3000	[120000]	2410			
Na	67400±800	[61000]	2500000	(2430000)	12600000	(12600000)
K	43000±2500		9420000	(970000)	2310000	(2500000)
Cu	14800±200	[15300]	183000	(193000)	3530	(4300)
Rb			16700	(18300)	2310	
Ti	11100±1600					
Pb	4400±80	(4600)	324	(340)	177	[180]
Mn	3940±590		9670	(10300)		
Sr	2490±20		128	(140)	245	
Ba	1830±70	[2000]	57			
Ni	1140±80		48.8			
Sn	451±15					
Cd	213±4	(230)				
Ce	139±9		23.0		1.88	
Zr	110±9					
La	81.6±4.1		16.4		1.15	
Co	65.4±4.7					
Ag			62.9	(60)		
Mo	57.3±0.3				15.1	
Nd	49.1±2.5		9.85		0.505	
Sb	47.4±1.3	(42)				
Pr	17.2±1.0		3.00		0.183	
Bi	14.4±0.4					
Th	10.6±2		0.50			
Gd	8.5±0.4				0.0258	
Cs	7.51±0.53		11.1		4.0	
W			6.7	(14)		
Sm	6.2±0.5				0.0111	
Dy	5.73±0.27				0.0106	
U	5.10±0.36		0.67	(0.8)		
Er	3.03±0.17				0.00511	
Yb	2.99±0.22				0.00721	
Y			1.75			
Eu	1.49±0.07				0.00255	
Ho	1.16±0.05				0.00199	
Tb	1.06±0.04				0.00274	
Tm	0.48±0.03				0.00090	
Lu	0.439±0.028				0.00142	

a) The numbers in ( ) and [ ] are the certified and information values, respectively. b) The numbers in ( ) are the certified values given from NIST. c) The numbers in ( ) and [ ] are the certified and information values, respectively.

experiment. According to the inter-laboratory experiment for the determination of trace elements in blood plasma, it was still difficult to obtain the consistent values even for Cu, Zn, and Fe within 10% (RSD).[81]

In Table 5, the elements whose certified, acceptable, reference or information values are known are marked with the signs such as †, ‡, ∗, and #, respectively. It is seen in Table 5 that the certified values are issued only for Na, K, Ca, and Mg in the case of NIST SRM 909b among blood serum reference materials listed in Table 5. As for the other reference materials, several acceptable, reference or information values are given to only a limited number of elements.

The blood serum standard or certified reference materials used in the present experiment were prepared from the composite of blood serum obtained from many patients in hospitals. Therefore, it is difficult or meaningless to discuss the significance of the concentration levels of the elements shown in Table 5 from the viewpoints of medical, clinical or

biological issues. However, such data may show to some extent the mean values for many peoples living in the local areas where the blood samples were collected, if no contamination occurred during the sampling and preparation processes.

The Cr content in the urine reference sample (NIST SRM 2670) listed in Table 5 is artificially elevated because this reference material is used for precision control in diagnosis of diabetes.[48] The concentrations of the other elements, however, appear to be at the natural level. It can be seen from Table 5 that the concentrations of many elements in urine are significantly higher than those in blood serum.

The elemental concentrations of human hair, bovine liver and bovine whole blood are summarized in Table 6.[65,76] These samples were also analysed by ICP-AES and ICP-MS after acid digestion without any preconcentration. Since all these samples are in freeze-dried powder, their concentrations are given in ng g^{-1} per dry weight. As is clearly seen in Table 6, many elements in human hair are found at significantly high concentrations. These results indicate that many elements are finally accumulated in hair. It is known that the elemental concentrations in human hair show some individual variation, depending on the health and nutritional conditions. Actually, diagnosis of human health using the individual hair samples is quite popularly performed in USA, where the concentration variations of about 20 elements in hair are measured on the multielement basis. The analytical results in Table 6 are the largest number of data so far obtained for the hair samples.[74] Thus, it may be expected that the present analytical method for hair will be applied to medical diagnosis in future.

It is noticeable that the concentrations of P, Zn, Fe, Mg, Na, K, Cu, and Mn are extremely high in bovine liver reference material (NIST SRM 1577). As for whole blood (IAEA A-13) issued from the International Atomic Energy Agency (IAEA), Fe, Na and K are at the markedly high concentration level. On the other hand, REEs in bovine whole blood are extremely low, and then REEs in bovine whole blood were determined by ICP-MS after heme-iron coprecipitation, which was newly developed in the our laboratory.[82] The determination of REEs in human whole blood has been attempted, but it has been not successful until now, perhaps, because of their too low concentrations and incompleteness of the acid digestion.

5. Correlation Analysis of the Elements in Human Blood Serum

It is very important to obtain the reliable information of trace elements for medical diagnosis as well as for elucidation of their standard or normal levels in healthy persons. Therefore, the research program for the multielement determination of major-to-ultratrace elements in human blood serum has been carried out in cooperation with the University Hospital of Nagoya University (Prof. Hidehiko Saitoh).[77,83] So far, the individual blood serum samples have been collected from 92 healthy volunteers and analyzed individually by ICP-AES and ICP-MS after acid digestion with HNO_3. Prior to the analysis of the real samples, all the analytical procedures including the chemical reagents and experimental tools as well as the cleaning processes were examined, as mentioned earlier.

In the experiment, ca. 10 ml of whole blood was collected by a syringe with a Teflon®-coated needle and centrifuged at 3000 rpm. The blood serum sample which was obtained as the supernatant after centrifugation was subjected to the following analysis. About 0.5 g of blood serum sample was digested with 1 ml of concd HNO_3, and then the residue was dissolved in 5 ml of 0.1 M HNO_3. The dissolved solution was used as the analysis solution. The analysis solution was analysed directly by ICP-AES and ICP-MS without any preconcentraion. As a result, 14 elements could be determined with the analytical precision within 5% (RSD).

The analytical results for human blood serum are summarized in Table 7,[83] where the elemental concentrations are shown as the ranges of the maximum and minimum values. At the same time, the concentrations of albumin, transferrin, and total protein in the same individual blood serum samples were determined by the conventional analytical methods.

In order to examine the concentration distributions and their variations, the radar chart of the elements in human blood serum was prepared from the data in Table 7. In the preparation of the radar chart, all the analytical data for the elements were normalized to the average values. The normalized values were plotted on the axis of each constituent including albumin, transferrin and total protein and connected for each person. The thus obtained result is shown in Fig. 5.[83] It is seen from Fig. 5 that Na, Ca, Mg, albumin, and total protein all show small individual variations. Potassium, P, Cu, Zn, Se, Rb, and transferrin are also in the relatively small concentration ranges, while Fe, Mo, Cs, Sr, and Ag show large variations of their concentration distributions. Since the kinetic behaviors of the multielements in blood serum have not been well elucidated, it is difficult to discuss exact

Table 7. Analytical Results for Trace Elements in Blood Serum Samples Collected from Healthy Volunteers and Pregnant Woman

Element	Healthy volunteers[a]	Pregnant woman[b]
	Minimum—Maximum	
Na	2380—3550 μg g^{-1}	2980 μg g^{-1}
K	101—197	136
P	88—172	162
Ca	55.5—101.0	85
Mg	12.4—20.9	14
Fe	0.30—2.25	0.27
Cu	444—1150 ng g^{-1}	1440 ng g^{-1}
Zn	341—988	397
Se	51—224	154
Rb	95—231	127
Sr	14.1—63.4	30.7
Mo	0.26—3.67	1.63
Cs	0.32—1.15	0.33
Ag	0.07—0.54	0.20
Sb[c]	0.06—1.31	0.12

a) $n = 92$. b) 5 months in pregnance. c) $n = 39$.

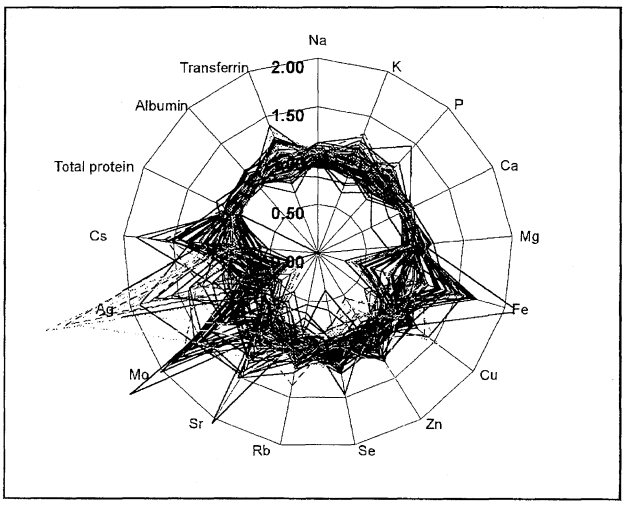

Fig. 5. Radar chart of the major-to-ultratrace elements in human blood serum. The blood serum samples were collected from 92 volunteers. In the chart, the data normalized to the averaged values are plotted on each axis.

biomedical meanings or significance of the multielement correlation data shown in Fig. 5. Even so, it may be concluded here that the elements showing small individual variations might be in homeostasis and might play the essential roles in serum outside the cells (red cells, white cells), while those with large variations might be playing more essential roles inside the cells; for example, Fe is working as the oxygen carrier with hemoglobin in red cell (erythrocyte).

The elemental concentrations of blood serum collected from a pregnant woman are also shown in the last column of Table 7.[83] It is apparent that the concentration of Zn is close to the minimum value and that of Cu is beyond the maximum value for healthy volunteers. In order to make further examination on the correlation between Zn and Cu, the correlation graphs for Zn vs. Cu and Zn vs. albumin were prepared using all the data for 92 persons. The correlation graphs are shown in Figs. 6A and 6B. It is seen from Fig. 6 that Zn and Cu show slightly negative correlation, while Zn and albumin exhibit clearly positive correlation. In particular, the reverse behavior of Zn and Cu appears characteristically in the blood serum of pregnant women. In another words, pregnant women are in zinc-deficiency because Zn in the mother bodies is transferred with albumin or their carrier proteins to the babies to help their growth. It is recently said that such reverse correlation between Zn and Cu may also appear as a stress symptom in the cases that Zn decreases and oppositely Cu increases in blood plasma.[84] The author thinks that the variation of the ratio of Zn to Cu could be an index for Zn-deficiency and for stress symptom, rather than the individual variation of Zn or Cu. In conclusion, further research on the multielement correlation of the elements in blood serum may reveal some potential roles of trace elements and their biological effects in man.

6. Rare Earth Elements in Human Blood Serum

As has been mentioned so far, a variety of elements are contained in blood serum. However, rare earth elements (REEs) have never been determined in human blood serum because of their extremely low concentrations, and so their existence in man is not well known. Since various REEs are used, in modern human life, for ceramics, superconductors, semiconductors, contrast reagents for MRI (magnetic resonance imaging), agricultural fertilizers and so forth, a large amount of REEs are emitted to the environment. Such emission of REEs to the environment may result in large exposure to man as well as to plants and animals. Thus,

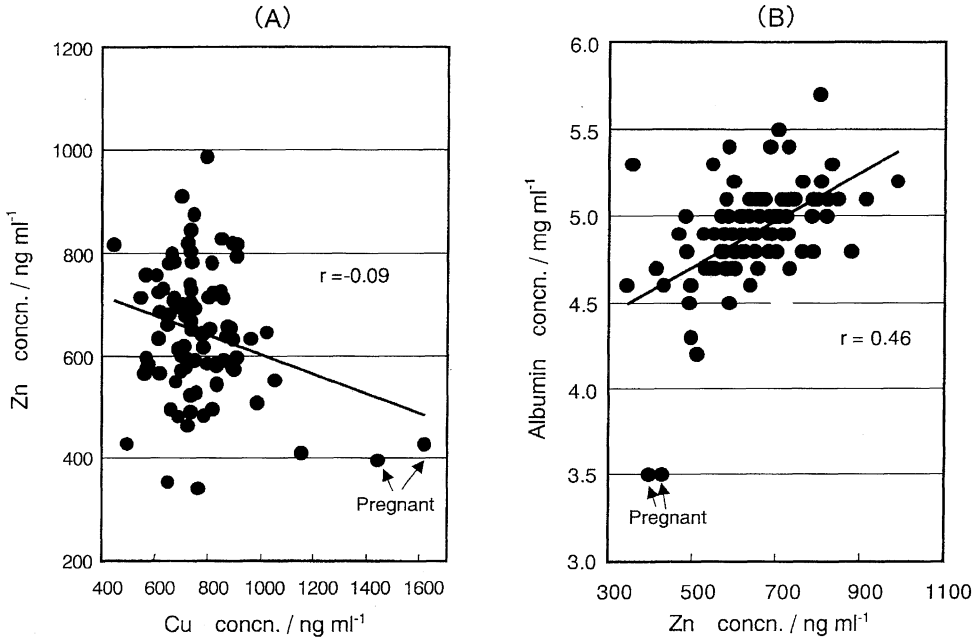

Fig. 6. Correlation graphs between the concentrations of (A) zinc vs. copper, and (B) zinc vs. albumin, where r in the graphs indicates the correlation coefficients. The data for two pregnant women are shown in each graph.

the determination of REEs in human blood samples (whole blood, blood serum etc.) is urgently required to know the background levels of REEs in man as well as to elucidate their biological or physiological functions.

In the preliminary experiment for the determination of REEs by ICP-MS,[85,86] the human blood serum reference material (NIES No. 4) in freeze-dried powder was digested with HNO_3 to prepare the analysis solution, and REEs were preconcentrated by using a chelating resin (Chelex 100). The chelating resin preconcentration was necessary to separate REEs from major constituents (Na, K, Mg, Ca), which often cause matrix effects to REEs in the ICP-MS measurement. The analytical method explored was applied to the determination of REEs in human blood serum by ICP-MS. However, the recovery values of REEs in the chelating resin preconcentration were 67—80%.[85]

In the next experiment to improve the recoveries of REEs, the acid digestion of serum was performed with HNO_3 and $HClO_4$ to achieve more complete decomposition.[87] Then, the recovery values of REEs were improved to be 80—90%.[87] It has been reported by some workers[89,90] that various amino acids, peptides and the other unknown organic compounds remained in the residues, when the biological samples were digested with HNO_3 or even with HNO_3 and $HClO_4$. Accordingly, incomplete decomposition of biological samples strongly influenced the recoveries of analytes in the chemical separation and preconcentration processes. This is because the residues including amino acids and peptides might cause the competitive reactions in complex formation of REEs with the chelating resin, which results in poor recoveries. It was found from further experiments that heating the solution at 80 °C during the chelating resin preconcentration was effective to improve the recoveries of REEs.[88,91]

Sample Pretreatment Procedure: First, human blood serum (ca. 8 ml) was taken in a Teflon® beaker (100 ml in volume). After adding 2 ml of concd HNO_3, the serum sample was heated almost to dryness on a hot-plate at 110 °C. Then, 2 ml of concd HNO_3 was again added into the residue and the solution was heated at 150 °C for 2 h. Furthermore, after adding 2 ml of concd HNO_3 and 1 ml of 60% $HClO_4$, the solution was again heated at 150 °C for 4 h until white fumes appeared. This procedure was repeated 2 times. Finally, 0.76 ml of concd HNO_3 and ca. 1 ml of pure water were added to dissolve the residue with heating at 110 °C for 1 h, and the solution was diluted to 100 ml with pure water, which was subjected to the stock solution for analysis in the following experiment. The final preconcentration procedure proposed is summarized in Fig. 7.[91] As is seen in Fig. 7, the final solution was reduced to 2 m of 0.1 M HNO_3 solution from 8 ml of the original blood serum. Thus, 4-fold preconcentration, in volume, was achieved by the pretreatment procedure described here. As a result, the recovery values of 91—102% were obtained for all REEs.

The concentrations of REEs in human blood serum collected from five healthy volunteers on an individual basis are summarized in Table 8.[91] As is seen in Table 8, REEs are in the concentration range from ca. 1 pg ml^{-1} for Eu to ca. 250 pg ml^{-1} for Ce. It is further seen in Table 8 that the concentrations of REEs for 5 persons are in good agreement with each other within a factor of 2.

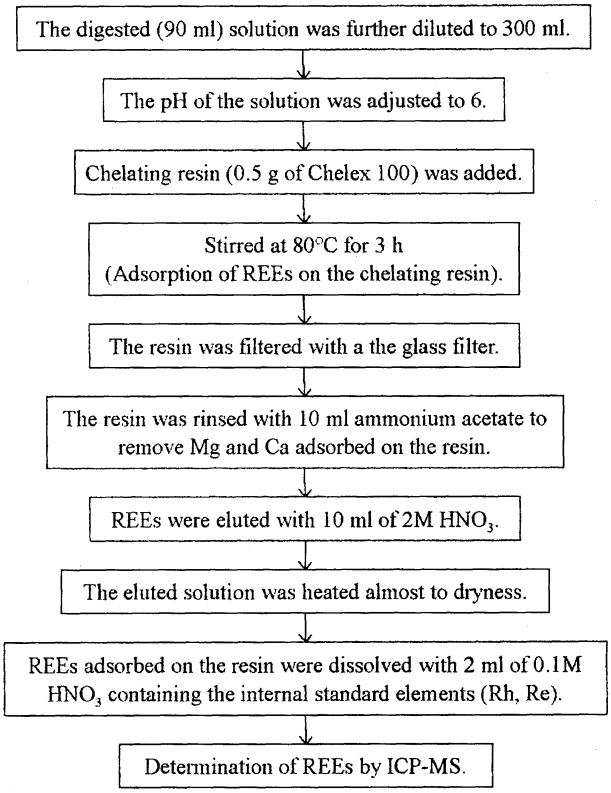

Fig. 7. Chelating resin preconcentration procedure of REEs in human blood serum. The digested solution used was prepared by digesting 8 ml of blood serum with HNO_3 and $HClO_4$ and diluting to 100 ml of 0.1 M HNO_3 solution. Chelating resin: Chelex 100 100—200 mesh, (Bio-Rad, Laboratories, Richmond, CA, USA).

Table 8. Concentration of REEs in Human Blood Serum Determined by ICP-MS after Chelating Resin Preconcentration

Element	Atomic number	Concentration/pg ml^{-1}				
		A	B	C	D	E
La	57	95.3	80.5	89.0	78.3	81.5
Ce	58	277	228	277	237	259
Pr	59	18.0	14.5	15.9	14.1	15.5
Nd	60	51.8	43.6	47.4	40.4	45.4
Sm	62	9.8	7.0	8.7	7.5	7.9
Eu	63	1.62	1.21	1.53	1.20	1.26
Gd	64	10.9	8.3	9.3	8.1	10.9
Tb	65	2.16	1.63	1.67	1.75	1.95
Dy	66	13.5	11.2	11.1	10.9	12.3
Ho	67	4.14	2.94	2.79	2.98	3.47
Er	68	14.5	10.3	9.7	10.4	12.1
Tm	69	2.73	1.64	1.74	1.96	2.15
Yb	70	20.5	13.9	12.8	13.5	17.5
Lu	71	3.68	2.66	2.40	2.53	3.49

In general, it is known that the distributions of the elements on the earth generally obey the rule of Oddo–Harkins,[92] which indicates that the concentrations of REEs with even

atomic numbers are higher than the neighboring REEs with odd atomic numbers. It is seen from Table 8 that the rule of Oddo-Harkins holds even in the case of human blood serum.

In geochemistry, the Leedey-chondrite normalized distributions of REEs (*so-called* "REE pattern") in rocks and minerals are examined for elucidation of their origins and chemical characterization.[93,94] In the REE patterns, the concentrations of REEs in the samples are normalized to those in chondrite. In Fig. 8, the REE pattern of human blood serum is shown together with those of human blood serum reference material (NIES No. 4),[85] coastal seawater,[95] and open seawater.[96] The concentrations of REEs are in the following order; human blood serum reference material (NIES No. 4) >human blood serum>coastal seawater>open seawater. It is seen in Fig. 8 that all the REE patterns show the similar V-shaped patterns. It is interesting that only the Eu-anomaly is observed for blood serum, while Ce- and Eu-anomalies are observed for seawater. The concentrations of REEs in human blood serum reference material (NIES No. 4) are higher by about 2—3 times than those in individual human blood serum.

It is often said that the origin of life was in the sea because the elemental concentrations of blood and seawater are very much similar to each other.[97] As will be mentioned later, such elemental compositions of human blood serum show quite good correlation with those of seawater. The similarity of the REE patterns in human blood serum and seawater, as is shown in Fig. 8, also suggests that the origin of life might be in the sea.[98]

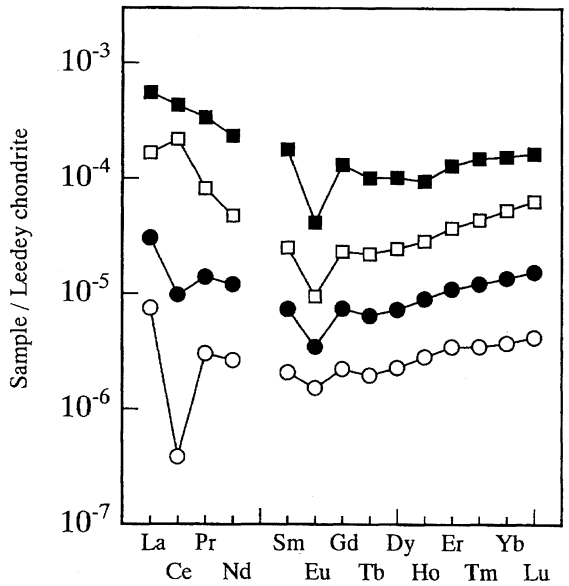

Fig. 8. The Leedey-chondrite normalized REE patterns for human blood serum and seawater.
□: human blood serum (Cited from Ref. 91),
■: human blood serum certified reference material (NIES No. 4) (Cited from Ref. 85),
●: coastal seawater (Cited from Ref. 95),
○: open seawater (Cited from Ref. 96).

7. Chemical Speciation of Trace Elements in Natural Water by Ultrafiltration Preconcentration and Size Exclusion Chromatography/ICP-MS

It is well known that some heavy metals such as Hg, Pb, Cr(VI), Cd, Se, and As are toxic to man. In fact, the Minamata disease and the "Auch-auch" disease were caused by mercury and cadmium, respectively. Thus, such *so-called* toxic heavy metals are now regulated by the environmental laws; such laws require water quality monitoring of these metals together with volatile organic compounds (VOCs) and agricultural chemicals. In such water quality analysis, the total concentrations of heavy metals are usually determined by AAS, GFAAS, and ICP-AES.

It is also known that the elements in different chemical forms provide the different physiological effects to biological functions in animals and plants.[99] Methylmercury (CH_3HgX ; X = halogens) is more toxic than inorganic mercury. In fact, the Minamata disease was caused by methylmercury. The environmental pollution of tetramethyllead [$(CH_3)_4Pb$] and tributyltin [$(C_4H_9)_3SnX$] compounds are also a serious problem. On the other hand, organic arsenic compounds such as $(CH_3)_4As$, $(CH_3)_3AsOH$, $(CH_3)_3AsCH_2COOH$ (arsenobetaine) etc. are non-toxic,[100] while inorganic arsenic compounds cause acute toxicity to man.[99] Furthermore, many metalloproteins and metalloenzymes have been known to play the essential physiological roles in the biological system and organs.[71,97] Thus, the identification and quantification of the chemical compounds including trace metals as well as non-metals are actually the subject of interest in the fields of not only chemistry, but also biology, medicine, and environmental science. Such analytical field is defined as "chemical speciation" or "elemental speciation".[101—103] The dissolved states of trace metals in natural water (river, lake, pond, and sea waters) have been discussed by many workers,[104—110] but such dissolved states have not been clearly appreciated so far. Thus, chemical speciation of trace metals in natural water is still the subject of interest in the speciation study. The present author's group has been engaged in the elucidation of the dissolved states of trace metals in natural water, particularly in terms of large organic molecule–metal complexes.[111—116]

The water samples collected from Lake Biwa and Kagamiga-ike pond in the campus of Nagoya University were used in the present experiment. The water samples were filtered with a glass filter (pore size 1 μm) and then a membrane filter (pore size 0.45 μm). The constituents which pass through the membrane filter with the pore size of 0.45 μm are usually considered to be the components dissolved in natural water. The concentrations of the major-to-ultratrace elements in the filtrate were first determined as the total concentrations by ICP-AES and ICP-MS. The analytical results for Lake Biwa and Kagamiga-ike pond are summarized in Table 9,[114] where the elements determined by ICP-MS were preconcentrated by the chelating resin prior to the determination. It is seen from Table 9 that the concentrations of most elements in Lake Biwa water are significantly lower

Table 9. Concentration of Dissolved Metal Ions in Natural Water Determined by ICP-MS and ICP-AES with Preconcentration Using Chelating Resin

Element	Wavelength[a] or m/z	Concentration/ng ml^{-1}	
		Kagamiga-ike pond	Lake Biwa
Si[b]	288.1 nm II	15500	620
Ca[b]	393.8 nm II	14100	10800
K[b]	766.4 nm I	4680	15000
Mg[b]	279.0 nm I	2570	2050
Na[b]	589.0 nm I	2490	6700
Al	308.2 nm I	151	3.0
Fe	259.9 nm II	84.8	1.6
Sr[b]	407.7 nm II	57.8	39.9
Ba[b]	493.4 nm II	45.7	7.87
Zn	64	35.5	1.2
Mn	55	30.9	0.15
Cu	63	7.16	0.64
Ni	62	4.74	0.37
Mo	98	1.84	0.42
Ce	140	0.22	3.0
La	139	0.061	1.8
Gd	158	0.13	0.69
Pb	208	0.99	0.020
Y	89	0.064	0.0092
U	238	0.020	0.026
Lu	175	0.0019	0.00080
Cd	110	0.28	0.0052
Co	59	0.18	0.0048
Ti	47	0.68	0.070

a) The numbers with the unit "nm" indicate the wavelengths in ICP-AES measurement, where I and II are atomic and ionic lines, respectively. Other numbers correspond to m/z in ICP-MS measurement. b) The elements determined by ICP-AES without preconcentration.

than those in Kagamiga-ike pond water.

Next, the filtrate obtained above was subjected to ultrafiltration preconcentration using an ultrafilter with the molecular permeation limit larger than MW (molecular weight) 10000. As a result, the elements contained in the molecules with MW > 10000 were preconcentrated by 500—1000 fold in this ultrafiltration process. The concentrations of the elements in the ultrafiltration-preconcentrated and ultrafiltrated water samples were also determined by ICP-AES and ICP-MS. Then, the distribution percentages (%) of the elements in the preconcentrated and ultrafiltrated waters were calculated as the ratios of the elemental amounts in the former and the latter to the total amounts obtained from the data in Table 9, respectively. The distributions (%) of the elements in large and small organic molecule (or simple inorganic ions) fractions for pond water are shown in Figs. 9(A) and 9(B).[116] The large and small organic molecules referred to here correspond to the elements existing in the preconcentrated water and the ultrafiltrated water, respectively. It is seen in Fig. 9(A) that most heavy metals except for Mo exist dominantly in the large organic molecule fraction, while alkali and alkaline earth elements exist mostly in the small organic molecule fraction. Since the large organic molecules are concentrated in the ultrafiltration-preconcentrated water, it is considered that the elements found in the preconcentrated water are bound with large organic molecules as metal complexes. On the other hand, the elements in the ultrafiltrated water are in simple ions or complexes with small organic compounds. Of course, alkali and alkaline elements mostly in ionic form.

The distributions of REEs in the large and small molecule fractions showed the characteristic dependence on their atomic number, as is seen in Fig. 9(B). The light REEs (La-Sm) distribute much more in the large molecule fraction than in the small molecular fraction, and the small molecule fractions increase with the increase in atomic number (i.e., heavier REEs). These results suggest that heavy REEs (Gd-Lu) form more stable complexes with small organic molecules in the ultrafiltrate water.

Next, the ultrafiltration-preconcentrated water samples from Lake Biwa and Kagamiga-ike pond were subjected to speciation analysis. The instrumental system used for the speciation of trace elements in natural water is shown in Fig. 10,[114,116] which is mainly composed of a separation column (size exclusion column; SEC), an UV absorption detector and ICP-MS as the element-selective detector. These instrumental components were connected through Teflon® tubings. The molecular permeation range of the SEC column used here was 10000—300000 in molecular weight (MW). Two hundred μl of the sample solution was injected into the SEC column, and eluted with tris-HNO_3 buffer solution (pH 7.3) as the mobile phase at a flow rate of 0.5 ml min^{-1}. The

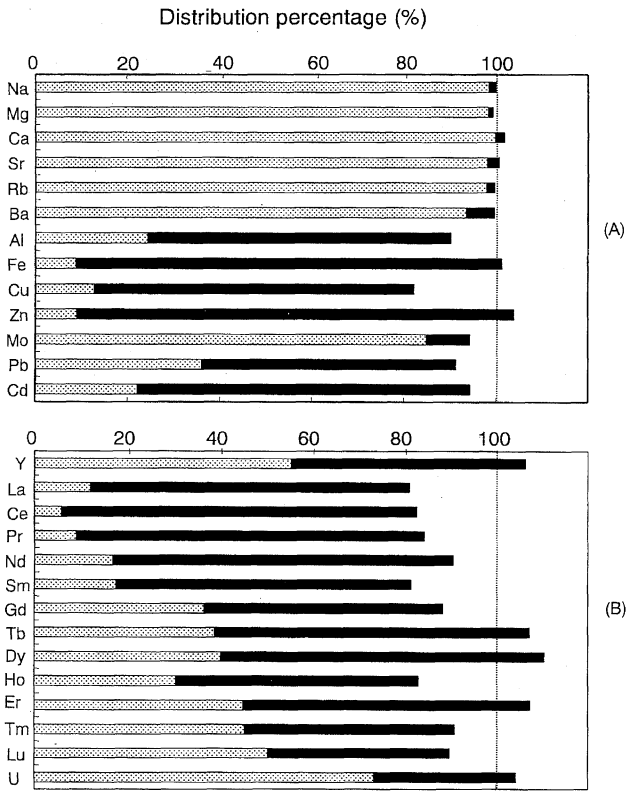

Fig. 9. Distribution percentages (%) of the elements in large and small organic molecules in pond water collected from Kagamiga-ike Pond. The large and small organic molecules indicate the molecules which are in the preconcentrated water and the filtrate water after ultrafiltration, where an ultrafiltration filter with a filtration limit of MW 10000 was used. (A) : Diverse elements, (B) : Lanthanide elements. Black bars : Large organic molecule fraction, dotted bars : small organic molecule fraction.

eluent was detected first by the UV absorption at 257 nm and then by ICP-MS. Other operating conditions for ICP-MS were similar to those shown in Table 2.

The SEC chromatograms for Fe, Cu, Zn, Y, Mo, La, As, Sb, I, Ce, W, and Pb obtained by the UV absorption and ICP-MS detections are shown in Figs. 11 and 12. Basically the corresponding chromatograms could be obtained for about 40 elements over a wide concentration range. As shown in Figs. 11 and 12, it is interesting to note that two chromatographic peaks (Peak 1 and Peak 2) are clearly observed in the UV-detected chromatograms, suggesting the existence of two main constituents in natural water. From the calibration curve for molecular weight, measured using standard protein molecules with the known molecular weights, Peak 1 and Peak 2 observed at the retention times of ca. 750 s and ca. 1500—1900 s corresponded to the molecular weights of

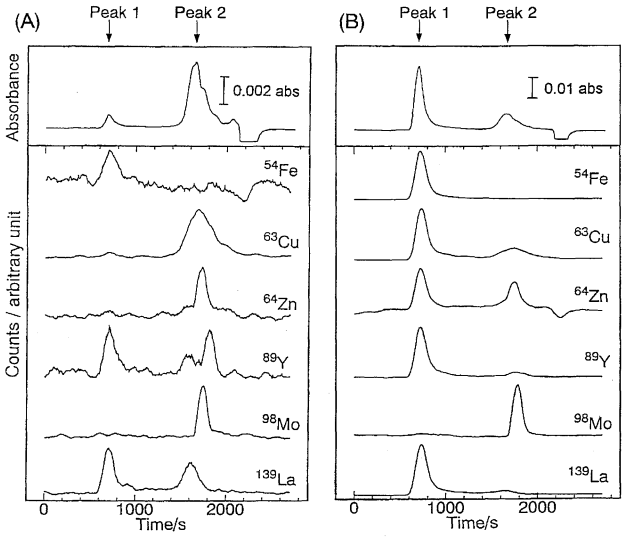

Fig. 11. SEC chromatograms for trace elements (Fe, Cu, Zn, Y, Mo, La) in natural water, obtained with the detection of UV absorption and ICP-MS. Sample: 100-fold ultrafiltration-preconcentrated waters from (A) Lake Biwa and (B) Kagamiga-ike pond.

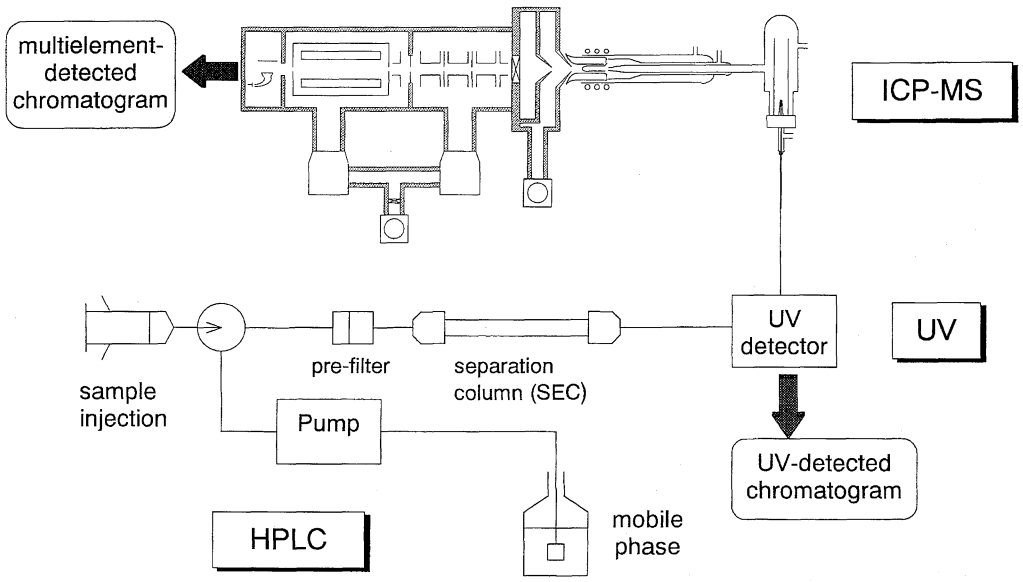

Fig. 10. Schematic diagram of SEC/UV absorption/ICP-MS combined system.

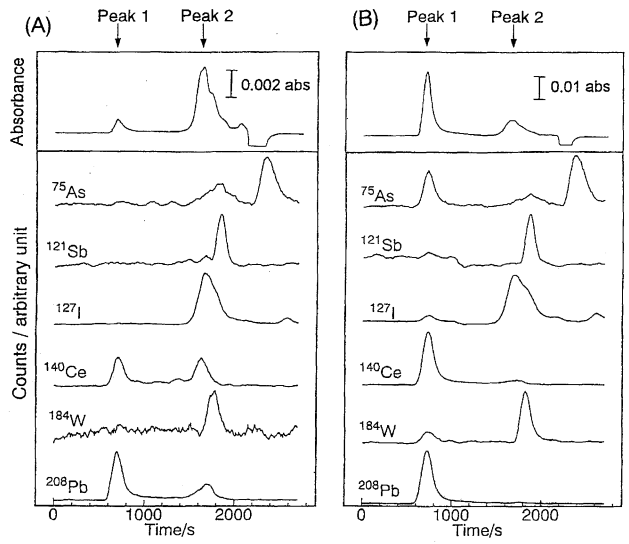

Fig. 12. SEC chromatograms for trace elements (As, Sb, I, Ce, W, Pb) in natural water, obtained with the detection of UV absorption and ICP-MS. Sample: 100-fold ultrafiltration-preconcentrated waters from (A) Lake Biwa and (B) Kagamiga-ike pond.

>300000 and 10000—50000, respectively.[111]

It is noted here that the intensities of Peak 1 and Peak 2 observed by the UV absorption detection are different from each other in the cases of Lake Biwa and Kagamiga-ike pond. As is seen in Figs. 11 and 12, Peak 1 is significantly smaller than Peak 2 in Lake Biwa, while the ratio is opposite in Kagamiga-ike pond. It should be noticed here that the absorbance unit for Kagamiga-ike pond is 5-fold larger than that for Lake Biwa. This indicates that Kagamiga-ike pond is much more polluted or eutrophicated with organic substances than Lake Biwa. Under such conditions, the concentrations of metal ions were also significantly higher in Kagamiga-ike pond than in Lake Biwa, as is seen in Table 9. From the comparison of the results in Figs. 11 and 12, in Kagamiga-ike pond, the Peak 1 intensities for most elements except for Mo, Sb, I, and W become remarkably larger than the Peak 2 intensities. The elements (Mo, Sb, I, and W) which form oxo-compounds in the aerobic condition are observed exclusively or dominantly at Peak 2 even in progress of eutrophication.

It is seen from Figs. 11 and 12 that all the elements detected by ICP-MS were found at the peak positions corresponding to Peak 1 and/or Peak 2. From these behaviors or characteristics observed in the figures, the elements in natural water are classified into the following 4 groups.

Group 1: The elements observed exclusively at Peak 1.-----Fe and Al.

Group 2: The elements observed predominantly at Peak 2, which exist as oxo-compounds.-----Mo, Sb, I, and W.

Group 3: The elements observed preferentially at Peak 2, while they are also observed at Peak 1, when water is polluted.-----Zn, Cu, and Mn.

Group 4: The elements observed always at both Peak 1 and Peak 2, but preferentially at Peak 1.-----Pb, Ti, Y, and all REEs.

The vertical changes of the SEC chromatograms for Fe, Cu, and La in Lake Biwa are shown in Figs. 13(B)—(D). The water samples examined here were collected at the sampling site with water depth of 75 m on November 15, 1994.

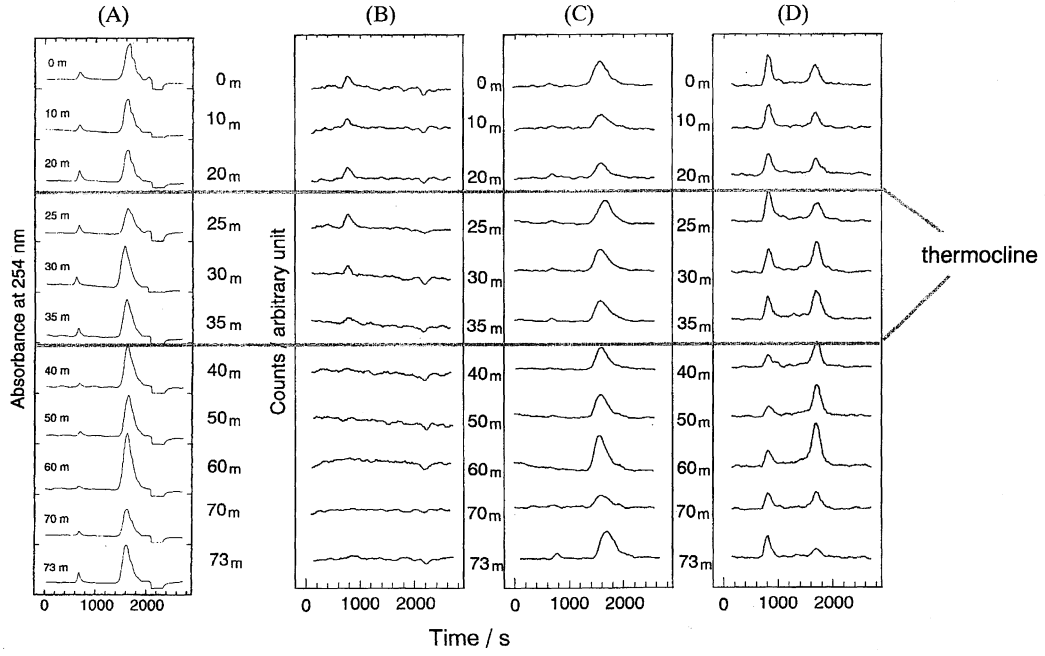

Fig. 13. Vertical changes of SEC chromatograms for trace elements in Lake Biwa water, obtained with the detection of (A) UV absorption and (B)—(D) ICP-MS.
Analytes: (B) Fe, (C) Cu, (D) La.
The lake water samples were collected at the site of 75-m water depth in the northern Lake Biwa on November 15, 1994. The two horizontal lines between 20 and 35 m in depth indicate the thermocline.

At this sampling season, the thermocline was formed between 20 m and 35 m in depth, as is indicated in Fig. 13. Since the upper-layer water above and the lower-layer water below the thermocline were not thoroughly mixed or circulated, the water temperature, pH, the Si concentration, and DO (dissolved oxygen) showed significant changes in the region of the thermocline. The SEC chromatograms for Fe, Cu, and La were selected as the representatives of Groups 1, 3, and 4, classified above.

The vertical changes of the chromatograms obtained by the UV absorption detection are also shown in Fig. 13(A). It is seen in Fig. 13(A) that Peak 1 (MW; > 300000) and Peak 2 (MW; 10000—50000) are observed in the UV-absorption detected chromatograms. The intensities of Peak 1 detected by the UV absorption become slightly smaller below the thermocline, although those of Peak 2 do not change from the surface to the bottom of the water column. It should be noted here that Peak 1 for Fe disappeared below the thermocline. These results suggest that the large molecules assigned to Peak 1 may be in the colloidal forms, and the particle formation including Fe and Al makes progress below the thermocline. Such particles may grow in size and eventually sink so as to form sediments on the bottom of the lake or pond. It is also observed that Peak 1 for La becomes smaller at the deeper water column. On the other hand, Peak 2 for Cu and Zn did not change so much through the water column.

The author's group is proposing the "string ball model",[114] which can explain the particle formation mechanism for Peak 1 and the preservation mechanisms for Peak 2 (Zn and Cu are required as the essential elements for living organisms). According to the string ball model, hydroxides of Fe and Al are adsorbed along with organic substances on the surface of fine particles of silicates suspended in water. At this time, trace elements, which are detected at Peak 1 in Figs. 11 and 12, are also adsorbed on the growing particles and/or form the complexes with organic substances adsorbed on the particle surface. As a result, the particles thus formed grow in size.

On the other hand, some protein-like organic molecules provide Peak 2, and such molecules form stable complexes with Zn and Cu which are soluble in natural water. Since Zn, Cu, and Mn are essential elements for living organisms, the minimum requirements of these elements should be preserved for survival of living organisms and plants in natural water. In fact, the existence of dissolved alkaline phosphatase (Zn-enzyme)[107,117] and nitrate reductase (Mo-enzyme)[118] in natural water, which are originated from microorganisms, are found by the enzymatic activity measurement.

8. Trace Elements in Man and the Sea

In the present paper, the elemental concentrations and distributions of human blood serum and the other biological samples have been discussed from the viewpoint of multi-element profiling analysis. Therein, the possibility of the origin of life in the sea was suggested from the similarity of the REE patterns for human blood serum to that for seawater. Although the details of seawater analysis are not described here, trace element analysis of seawater has been extensively carried out,[95,119—125] and at present the concentration levels of almost all stable-isotope elements and their vertical distributions in open sea have already been elucidated.[96,126] However, such researches have been mostly concentrated on or related to the elemental distributions and cycles, biological activities, and water dynamics in the sea. Recently, the present author and co-workers have been trying to solve a puzzle of chemical evolution[98] from the distributions of major-to-ultratrace elements in human blood serum and seawater.

The correlation between the concentrations of the elements in human blood serum and seawater is illustrated in Fig. 14. In the illustration of the figure, the most reliable analytical data for blood serum[65,76,80,91] and seawater[96,126,127] were carefully selected, including the results obtained in the present author's laboratory, and they were plotted at the corresponding positions on the graph. The straight line on the graph indicates the equivalent correlation. Therefore, the elements located above the correlation line are at the higher concentration in human blood serum than in seawater, while those below the correlation line are at the higher concentration in seawater than in blood serum.

According to "the geochemical classification of the elements" proposed by Goldschmidt,[128] based on the affinity of various elements for oxygen and sulfur, the elements on the earth are classified as follows:

(a) **Siderophile Elements:** The elements (Fe, Co, Ni) which are main constituents of the central core of the earth, and trace elements enriched therein.

(b) **Lithophile Elements:** The elements (O, alkali elements, alkaline earth elements, Si, Al, Ti) which are main constituents of silicate rocks and clay minerals in the earth

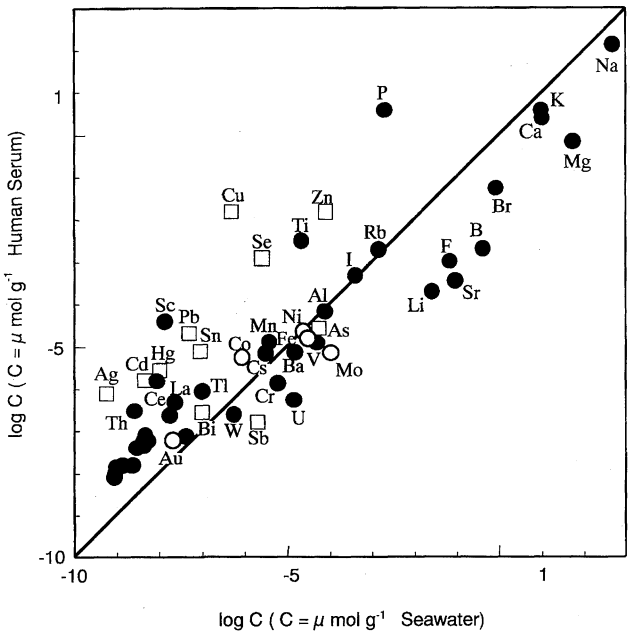

Fig. 14. Correlation between the concentrations of the elements in seawater and human blood serum.
○: lithophile elements, ●: siderophile elements, □: chalcophile elements.

crust, and trace elements enriched therein. These elements have large affinity for oxygen.

(c) **Chalcophile Elements:** The elements (S, Cu, Zn, Se, Cd, Hg, Pb) which exist as sulfide minerals in the earth crust, and trace elements enriched therein. These elements have large affinity for sulfur.

(d) **Atmophile Elements:** The volatile elements (H, C, N, (O), and rare gases) which mainly exist as atoms and molecules in the atmosphere. These elements are not shown in Fig. 14.

Besides the above classification, the elements, which are the main constituents of animals and plants, and trace elements playing the essential roles in the biological systems are often referred to as "biophile elements". These biophile elements mostly correspond to the essential major and trace elements, mentioned earlier.

Taking into consideration the correlation of the elemental distributions between human blood serum and seawater in relation with the geochemical classification of the elements described above, we can deduce the following interesting facts. Among major and minor constituents in both serum and seawater, Na, K, and Ca are almost in good correlation with each other, while Mg is significantly higher in seawater. As for the other alkali and alkaline earth elements, Rb, Cs, and Ba are almost at the same concentration levels in blood serum and seawater, but Li and Sr are significantly higher in sea water. As for other elements, it is noticeable that P is markedly higher in blood serum, while Br, B, and F are much higher in seawater.

In general, it can be pointed out that the elements belonging to siderophile elements (○) and lithophile elements (●) which have larger affinity for oxygen are in quite good correlation between serum and seawater. This indicates that these elements exist almost at the same concentration level in human blood serum and in seawater. On the other hand, it should be noticed here that Cu, Zn, Se, Cd, Pb, Hg, and Ag which belong to chalcophile elements (□) are at the markedly higher concentration levels in human blood serum. Among chalcophile elements, As and Sb are exceptionally at almost the same concentration level in both serum and seawater. As mentioned earlier, chalcophile elements have larger affinity with sulfur. Among them, Zn, Cu, and Se are known as biologically essential elements, and they are deeply concerned with physiological functions in the biological systems. On the other hand, Cd, Hg, and Pb are known as the toxic elements to the living organisms, and, as a matter of fact, they caused the Auch-auch disease, the Minamata disease and a lead-poisoning symptom as the result of the environmental pollution. The facts that these essential and/or toxic elements are higher in human blood serum indicate larger bio-accumulation of the chalcophile elements in human blood serum. One should recall the fact that the chalcophile elements showing larger bio-accumulation also have larger affinity for sulfur. These characteristic properties may be appreciated by their bindings with sulfur in cystein (amino acid) consisting of proteins in the blood and cells.

In addition, the following two points should be stressed here as the characteristic trends found in Fig. 14:

(i) The elements (Mo, V, U, Cr, As, Sb, W), which easily form oxo-compounds under the aerobic condition, are higher in seawater. This can be interpreted as the fact that those oxo-compounds are highly stable and soluble in water.

(ii) Rare earth elements (REEs) are higher in blood serum. This result suggests that REEs have relatively larger formation constants with bio-organic compounds like proteins. These chemical properties of REEs may be understood from the facts described in the previous sections concerning with blood serum and natural water.

According to the Lewis acid-base theory,[129] metal ions and ligands are defined as *acid* and *base*, respectively, when metal ions form complexes with inorganic ions or organic molecules. In this Lewis theory, thus, metal ions and ligands are the acceptors and the donors of the unshared electron pairs, respectively, localized on the coordination atoms in the ligands. Lewis's theory is the most extended or general acid-base theory in chemistry.

Furthermore, as for the chemical properties of metal ions in formation of some compounds and complexes, the principle of "Hard and Soft Acids and Bases (HSAB)" was proposed by Pearson.[130] The soft acids are metal ions which likely form complexes with polar bases such as S^{2-}, RSH, Br^-, I^-, CO, CN^-, and so forth. The chalcophile elements such as Zn, Cu, Cd, Pb, Ag, and Hg belong to the soft acids. On the other hand, the elements which form stable complexes with non-polar bases such as OH^-, CO_3^{2-}, NO_3^-, F^-, Cl^-, NH_3, SO_4^{2-}, and so forth belong to the hard acids. The lithophile elements such as Mg, Al, Cr, and Si, as well as the siderophile elements such as Fe, Co, and Ni, belong to the hard acids. In addition, it can be said that the hard acids and bases generally form stable compounds under the oxygen-existing (oxidative) or aerobic conditions. On the other hand, the soft acids and bases have the chemical properties to form stable compounds under the reductive or anaerobic conditions.

Taking into account the chemical properties of metal ions and ligands based on the principle of HSAB, some interesting conclusions can be drawn from the elemental distributions in human blood serum and seawater. The facts that chalcophile elements belonging to soft acids are enriched in human blood serum, as is seen in Fig. 14, suggest that the anaerobic conditions are maintained in human blood serum. Under such conditions, metal ions such as Zn, Cu, and Cd which belong to soft acids have stronger bonding abilities with the SH group in cystein, which is a soft base. As mentioned in the section concerning REEs in human blood serum, there is a possibility that since the origin of life the biological systems have been maintaining the mechanism of homeostasis in which the concentrations of the elements are kept almost constant. Furthermore, the facts that soft metal ions are at the higher concentration levels in blood serum suggest that selection of metal ions playing the important roles in synthesis of biological compounds as well as in actions of the biological functions might have occured in the ocean 3—3.5 billion years ago, when there was much less oxygen on the

earth. Later on, after photosynthesis began in the ocean ca. 2.5 billion years ago, the aerobic conditions were produced in the ocean as well as in the atmosphere. Then, it can be assumed that chemical evolution of life might progress as competitive reactions of oxygen or sulfur with metal ions under the aerobic or anaerobic conditions.

It can not be said that the discussion or conclusion described above has been well proved by the experimental data. However, it may be stated here that the correlation between the multielement distributions in human blood serum and seawater provides some interesting and important suggestions to elucidate the origin of life and the following chemical and biological evolution in the sea, where trace elements might be deeply involved. Of course, further research is strongly required to take deeper insight of the essential roles of trace elements in our lives.

Finally, it may be also pointed out from Fig. 14 that the heavier elements with larger atomic numbers appear to distribute much more in human blood serum than in seawater. This fact suggests that the heavier atoms might be used in the biological reactions for the original life system, probably under the anaerobic condition. In fact, in some anaerobic fungus, a metalloenzyme using W at the active center shows nitrate reductase activity,[131] which is now known as a Mo-cofactor enzyme.

Conclusion

The progress of modern atomic spectrometry, especially in ICP-AES and ICP-MS, has made it possible to determine the major-to-ultratrace elements on the multielement basis. As a result, various samples from biology, medicine, geochemistry, environment science, and so forth can be analysed from the viewpoints of multielement distribution patterns. Such an analysis for multielement data of the major-to-ultratrace elements is proposed here as multielement profiling analysis.[24,25] Furthermore, the highly-sensitive multielement detection capabilities of ICP-AES and ICP-MS allow the detection of almost all elements with stable isotopes, which means that we are now approaching to "all-elements analysis" of all materials on the earth, including us human beings. Such all-elements analysis would open "all elements chemistry" in the near future.

In 1936, I. Noddack proposed a hypothesis called "the all present theory of the elements" (or "omnipresence theory of the elements").[92,132] In the theory, Noddack stated that *all the elements in the periodic table would be found in all rock or mineral samples on the earth, if the highly-sensitive analytical methods might be explored in the future.* Actually, the present author's group has succeeded in the determination of 69 elements among 70 stable elements except for non-metallic, rare gas, and radioactive elements in the river and sediment samples,[133] although all the results were not shown in this paper. Furthermore, as described in the present paper, various major-to-ultratrace elements can be determined in blood serum and plants as well as the other biological samples. Taking into account the present state-of-the-art of scientific technologies, the Noddack's all present theory of the elements would be extended to not only geochemical samples, but also the biological systems. Recently, the present author published a paper entitled "*the extended all present theory of the elements and biological trace elements*".[134] In the paper, it is stated that *all the elements in the periodic table are supposed to be contained not only in the geochemical samples (rocks, minerals, soils etc.), but also in animals and plants.* This is not exceptional even for man. Thus, the final goal of analytical atomic spectrometry should be the determination of all elements in man's organs and then in only one biological cell for comprehensive and systematic appreciation of their biological functions.

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