Chronic Cadmium Poisoning Induced by Environmental Cadmium Pollution. Renal Lesions (Multiple Proximal Tubular Dysfunctions) Identified in Residents of Cadmium-Polluted Hosogoe, Kosaka Town, Akita Prefecture, Japan

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Health examinations were performed in 137 people living in the cadmium-polluted community of Hosogoe, Kosaka town, Akita prefecture, Japan. Thirty-three of 137 residents had some indications of proximal tubular dysfunctions such as renal glycosuria, tubular proteinuria and generalized aminoaciduria, and 10 of them were diagnosed as having multiple proximal tubular dysfunctions. Detailed examinations revealed that none of these cases had any causal diseases other than chronic cadmium poisoning. The ages of the 33 cases ranged from 36 to 83 years, and all have lived in Hosogoe area for more than 28 years. The community of Hosogoe, with a leading Japanese copper refinery in operation since the 1870s, is surrounded with the farmland evidently polluted by cadmium primarily through the air. The mean concentration of cadmium in unpolished rice harvested in this area was found some ten times as high as that in the control area. The residents' mean cadmium intake and mean urinary cadmium concentration showed the values over 3 times as high as those in control. It is quite conceivable that the people of Hosogoe have had a high daily intake of cadmium for many years mainly via food. From these findings, renal lesions identified in the residents were diagnosed as chronic cadmium poisoning induced by the environmental cadmium pollution.

Key Words: Chronic cadmium poisoning, Environmental cadmium pollution, Proximal tubular dysfunctions, Fanconi syndrome, Tubular proteinuria, Urine proteins, Retinol-binding protein, Uric acid clearance, Generalized aminoaciduria, Renal tubular disorders

Since the so-called "Itai-Itai disease" found in residents of the Jinzu river basin

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in the 1950s was believed to have a close relation to the environmental cadmium pollution, and there were found many other places polluted by cadmium, the cadmium effect on health has become a serious and social problem in Japan¹⁻²⁾.

We have conducted health examinations

on the people of Hosogoe, Kosaka town, Akita prefecture, an area seriously polluted by cadmium, and found that many people were suffering from renal lesions induced by environmental cadmium pollution. This is the first report of detailed renal function tests on the people in a cadmium-polluted area.

MATERIALS AND METHODS

1) The Hosogoe area of Kosaka town is adjacent to a leading Japanese copper refinery that initiated operation in the 1870s. The soil of the area had been so significantly polluted by cadmium from industrial smokestacks that high concentrations of cadmium were detected at random survey in area's soil, rice and vegetables.

In 77 samples of unpolished rice produced in the area from 1970 to 1975, the mean concentration of cadmium (mean $\pm$ S.D.) was $0.66 \pm 0.72 \mu\text{g/g}$ wet weight, some ten times as high as the corresponding level for the counterparts in non-polluted areas.

2) Urine tests;

Qualitative analysis of morning urine was made by applying the 20% sulfosalicylic acid test and Testape test to determine proteinuria and glycosuria. Indications over +1 were accepted proteinuria and over weak positive for glycosuria. Cases with concurrent proteinuria and glycosuria were subjected to polyacrylamide gel zone electrophoresis for concentrated urine proteins³⁾, counter immunoelectrophoresis for urinary retinol-binding protein⁴⁾, and thin-layer chromatography for urinary aminoacids⁵⁾.

3) Renal function tests;

Renal plasma flow was determined by PAH-clearance, glomerular filtration rate by 24-hour endogenous creatinine clearance⁶⁾, phosphate clearance by Fiske-Subbarow's method⁷⁾, and uric acid clearance by the uricase method⁸⁾. For the determination of HCO_3^- -threshold and of acidifying ability of urine were used oral bicarbonate loading test and ammonium chloride loading test, respectively^{9,10)}

4) Diagnostic criteria for multiple proximal tubular dysfunctions:

In this study we applied the diagnostic term of "multiple proximal tubular dysfunctions" to cases fulfilling either of the following two:

1. Fanconi syndrome (Phospho-glucosaminaciduria)
2. Showing more than 4 of the following 6 indications, necessarily including renal glycosuria or generalized aminoaciduria,

Renal glycosuria, Generalized aminoaciduria, Decreased %TRP, High value of uric acid clearance, Decreased HCO_3^- -threshold, Tubular proteinuria.

RESULTS

1) Quantitative analyses for proteinuria and glycosuria (Table 1):

The results of urine tests performed in 137 residents (96% of the target population) are shown in Table 1.

Concurrent proteinuria and glycosuria was found on each occasion in 13-22% of them. In the four-time tests, concurrent proteinuria and glycosuria was identified in 33 (18 males and 15 females) of the 137 persons (59 males and 78 females). They included 14 people in 7 families, comprising 2 house-holds of husbands and wives, 2 of parents and children-in-law, and 3 of blood parents and children, in other words, 3 families of blood ties and 4 of no blood ties.

Control was used in 40 persons of over 35 years of age living in the non-polluted community of Iwasawa, Kosaka town. Urine test confirmed concurrent proteinuria and glycosuria in only one (2.5%) of the 40 subjects. This patient was one long suffering from diabetes mellitus.

2) Polyacrylamide gel zone electrophoresis (Table 2, 6):

Concentrated urine proteins were analysed in 19 of the 33 cases with concurrent proteinuria and glycosuria. Tubular proteinuria was found in 10 cases, including 9 (Case 1-6, 14, 16 and 17) diagnosed as having multiple proximal tubular dysfunctions. The remaining one case (Case 7) had also

Table 1. Precalence of proteinuria and glycosuria among the Hosogoe residents of over 35 years of age.

Number of persons examined		Proteinuria number (%)	Glycosuria number (%)	Concurrent proteinuria and glycosuria number (%)
January 1972				
Male	24	5 (21)	3 (13)	3 (13)
Female	51	9 (18)	7 (14)	7 (14)
Total	75	14 (19)	10 (13)	10 (13)
October 1972				
Male	40	13 (33)	9 (23)	5 (13)
Female	56	22 (38)	9 (16)	8 (14)
Total	96	35 (36)	18 (19)	13 (14)
October 1973				
Male	37	16 (43)	14 (38)	7 (19)
Female	48	16 (33)	6 (13)	4 (8)
Total	85	32 (38)	20 (24)	11 (13)
October 1974				
Male	41	16 (39)	12 (29)	12 (29)
Female	46	21 (46)	7 (15)	7 (15)
Total	87	37 (43)	19 (22)	19 (22)

Target population. 1972: Male 54, Female 63, Total 117 persons.

1973. Male 54, Female 62, Total 116 persons.

1974. Male 53, Female 61, Total 114 persons.

Total target population from 1972 to 1974 was 142 persons.

Total number of persons examined from 1972 to 1974 was 137 persons.

some indications of proximal tubular malfunctions such as renal glycosuria and a high value of uric acid clearance.

3) Analysis of urinary aminoacids (Table 2, 6):

Urinary aminoacids were analysed in 25 of the 33 cases with concurrent proteinuria and glycosuria. Generalized aminoaciduria was identified in 7 of them. Increased excretion of urinary aminoacids was found in 3, while the other 15 cases were normal.

All 7 cases with generalized aminoaciduria and 2 of the 3 cases with increased excretion of aminoacids were diagnosed as having multiple proximal tubular dysfunctions, while this diagnosis was established in only one case (Case 6) of the 15 normal persons.

4) Urinary retinol-binding protein (Table 2, 6);

Urinary retinol-binding protein was measured by the method of counter immunoelectrophoresis in all 37 cases showing proteinuria and in random 23 cases without proteinuria, totaling 60 cases, in October 1974 (Table 1). Those showing a retinol-binding protein concentration of over 0.4 mg/dl were determined as positive cases.

Of the 60 cases, 8 were positive. All these 8 were positive cases of proteinuria, including 6 with multiple proximal tubular dysfunctions. One of the other 2 was Case 7 mentioned above. The remaining one was not examined.

Only one (Case 3) of 52 cases with negative retinol-binding protein was a case of multiple proximal tubular dysfunctions.

As shown in Table 2 and 6, the above three methods were all proved to be highly reliable screening tests for multiple proximal

Table 2. Laboratory findings on 13 hospitalized cases with concurrent proteinuria and glycosuria (I).

Case	Sex	Age	Years of residence	Urine						Plasma					
				RBP	Tubular proteinuria	GAA	Minimum pH	Maximum osmolality (mOsm/Kg.H ₂ O)	Culture (/ml)	Sediment	CR	UA	FBS	Ca	P
														(mg/dl)	
1	M	66	46	(+)	(+)	(+)	5.28	692	negative	n.p.	1.5	2.8	79	10.2	2.6
2	M	65	50		(+)	(±)	5.24	804	negative	n.p.	1.1	4.3	78	9.2	3.1
3	M	54	28	(-)	(+)	(+)	5.17	864	negative	n.p.	1.1	4.4	76	9.3	3.3
4	F	74	62		(+)	(+)	5.87	678	negative	n.p.	1.1	3.7	65	8.5	3.1
5	F	73	61	(+)	(+)	(+)	5.76	887	E.coli.1x10 ³	n.p.	1.2	2.9	74	9.3	2.5
6	F	67	61		(+)	(-)	5.74	585	negative	n.p.	1.2	4.1	74	9.0	3.4
7	M	69	69	(+)	(+)	(-)	5.23	530		n.p.	1.7	3.3	67	9.1	3.6
8	M	67	67		(-)	(-)	5.04	674		n.p.	1.2	5.3	66	8.9	3.4
9	M	64	46		(-)	(-)	5.17	768		n.p.	1.3	4.3	59	8.8	2.6
10	F	68	55		(-)	(-)	5.04	701	St. epid. 5x10 ⁴	massive pus cells	1.3	4.3	90	8.3	3.6
11	F	60	47	(-)	(-)	(-)	5.00	803	E.coli. 4x10 ⁴		n.p.	0.9	3.7	66	8.7
12	F	58	47	(-)	(-)	(-)	5.13	770	not identified 5x10 ⁴	n.p.	0.8	4.7	63	9.5	4.4
13	F	53	37	(-)	(-)	(-)	5.07	836	St.epid. 8x10 ³	n.p.	0.7	4.9	86	9.8	4.1

RBP: Retinol-binding protein. GAA: Generalized aminoaciduria. Minimum pH of urine: Values after 140 mEq of ammonium chloride per day administered for three days. Maximum osmolality of urine: Values after overnight fasting. St. epid.: Staphylococcus epidermidis. CR: Creatinine. UA: Uric acid. FBS: Fasting blood sugar.

Normal range: Same as in Table 6.

Table 3. Laboratory findings on 13 hospitalized cases with concurrent proteinuria and glycosuria (II).

Case	C _{PAH} [μl/min/1.48m ²]	Ccr	Cua	Cua/Ccr	PSP test (% 15 min)	HCO ₃ ⁻ threshold (mEq/l)	%TRP	GTT	Plasma						Cd in urine (μg/l)	Cd in rice (μg/g)
									Na	K	Cl	pH	Pco ₂ (mmHg)	CO ₂ - content (m mole/l)		
									[mEq/l]							
1	490	46	25	0.54	25	27	67	normal	145	3.9	106	7.406	38.0	24.5	45.0	0.57
2		66	17	0.26	29		73	normal	140	4.7	106	7.400	39.0	24.7	19.0	0.68
3		82	10	0.12	28		77	normal	142	4.4	101	7.418	43.4	28.0		0.22
4	257	53	15	0.28	28	26	84	normal	143	3.2	107	7.362	42.7	25.3	3.4	0.42
5	268	57	19	0.33	32	23	70	normal	144	3.4	109	7.367	41.8	26.2	16.0	0.16
6		48	9	0.19	20	23	78	normal	141	3.6	110	7.376	40.0	24.1	6.3	0.98
7		48	13	0.27	22	26	85	normal	144	4.1	108	7.421	38.1	24.7	9.8	0.46
8	325	67	7	0.10	11		78	normal	148	4.2	106	7.410	39.8	26.2	15.1	2.44
9		64	11	0.17	33		85	normal	142	3.8	107	7.427	38.9	25.5	6.4	0.64
10	338	54	10	0.19	25	26	78	normal	142	4.2	103	7.380	44.8	26.7	10.5	1.27
11	524	59	12	0.20	33	25	82	normal	141	4.2	103	7.398	42.5	26.2	14.2	2.44
12	460	102	10	0.10	33	24	90	normal	144	3.7	107	7.390	40.3	24.5	13.1	0.68
13	497	78	8	0.10	20	24	87	normal	140	4.2	103	7.403	40.5	25.3	12.1	1.26

C_{PAH}: Para-aminohippuric acid clearance. Ccr: Creatinine clearance. Cua: Uric acid clearance. 1.48m²: Body surface area of average Japanese adult. %TRP: Renal tubular reabsorption of phosphate. GTT: Oral 100g glucose tolerance test.

Cd in urine: Cadmium concentration in morning urine. Cd in rice: Cadmium concentration in unpolished rice of their own production.

Normal range: Same as in Table 6.

Table 4. Laboratory findings on 13 hospitalized cases with concurrent proteinuria and glycosuria (III).

Case	Plasma protein (g/dl)	Plasma protein fraction					Colour index	CCFT	ZTT	TTT	GOT	GPT	Al. P-ase (K.A)	T.Chol (mg/dl)	Neutral fat (mg/dl)	Phospholipid (mg/dl)
		Alb. (%)	α_1 (%)	α_2 (%)	β (%)	γ (%)										
1	7.8	57.7	3.6	9.8	9.3	19.6	6	(-)	12.9	6.4	41	29	9.2	159	154	158
2	7.0	65.6	3.1	9.3	8.9	12.2	4	(-)	4.0	1.2	23	14	5.4	205	86	223
3	7.6	59.7	3.5	7.2	12.6	16.0	4	(-)	6.2	5.1	19	7	5.8	215	78	200
4	6.4	61.7	2.6	9.1	9.7	16.9	5	(-)	7.9	2.5	13	2	15.4	130	62	149
5	7.6	59.1	2.4	9.0	9.6	19.9	6	(-)	12.6	6.2	25	20	10.8	208	80	195
6	6.8	52.6	3.4	8.5	10.3	25.2	9	(+++)	12.4	4.2	48	25	8.8	148	76	146
7	6.7	55.5	4.6	10.4	9.8	19.7	6	(-)	11.5	5.2	13	8	10.5	192	161	190
8	6.7	58.3	3.1	10.3	10.9	15.9	3	(++)	8.1	3.3	17	6	5.1	170	101	194
9	6.5	62.5	2.5	8.6	7.4	19.0	6	(++)	8.4	2.9	14	7	5.6	216	73	179
10	7.5	66.2	2.5	10.4	8.5	12.4	3	(+)	6.4	1.3	9	7	11.3	227	180	234
11	7.4	61.5	3.7	8.7	9.3	16.8	5	(-)	10.8	2.2	8	8	14.3	158	130	157
12	6.4	61.1	2.7	10.4	9.9	15.9	5	(-)	5.2	1.4	15	14	9.8	208	159	200
13	7.3	58.7	3.2	11.0	9.0	18.1	4		8.1	1.5	13	9	8.5	187	102	204

Plasma protein fraction: Analysed by cellulose acetate electrophoresis. Al.P-ase: Alkaline phosphatase. T.Chol: Total cholesterol.

Normal range of the liver function tests: CCFT (-), ZTT <12, TTT <4, GOT <40, GPT <35

Alkaline phosphatase <10.

tubular dysfunctions.

5) Laboratory findings in 13 hospitalized cases with concurrent proteinuria and glycosuria (Table 2-5):

Renal function tests were carried out so far in 25 of the 33 cases with concurrent proteinuria and glycosuria. Thirteen of the 25 cases were hospitalized for two months in Tohoku University Hospital to receive detailed examinations. The results were all obtained in these cases under conditions without any treatments.

All the 13 cases had lived in Hosogoe, Kosaka town for over 28 years, with no blood relations to each other, and no abuse of drugs. There were no bedridden cases. All cases showed slight proteinuria, with a range of 20-100 mg/dl in 24-hour urine protein concentration.

In Fishberg's concentration test, only 5 of the 13 cases had a maximum urine osmotic pressure of over 800 mOsm/kg. H₂O, the remaining 8 showing an evident reduction in the concentrating ability of urine.

In quantitative urine culture using mid-stream urine, no cases revealed bacteriuria.

In urine sediment, no abnormalities were found in all but one (Case 10).

In endogenous creatinine clearance, most cases showed a low value around 60 ml/min.

Eight of the 13 cases had a high value over 0.19 in uric acid clearance per unit nephron (uric acid clearance/creatinine clearance). In PSP excretion test 4 showed less than 25% in 15-minute value.

In HCO₃⁻-threshold, 4 cases had a low value of less than 24 mEq/l.

In tubular reabsorption of phosphate (%TRP), 7 cases had a low rate of 79% or less.

Fasting blood and sugar glucose tolerance test were normal in all 13 cases. From these findings glycosuria observed in these cases was diagnosed as renal glycosuria.

In arterial plasma pH and CO₂-content checked in all 13 cases none showed metabolic acidosis.

Intravenous pyelography performed in all 13 cases disclosed no abnormalities such as enlargement or deformities of the pelvico-calyceal systems, nor nephrocalcinosis. Case

Table 5. Laboratory findings on 13 hospitalized cases with concurrent proteinuria and glycosuria (IV).

Case	RBC ($\times 10^4/\text{mm}^3$)	Hb (%Sahli)	WBC (/mm ³)	ESR (mm/h)	STS	RA	CRP	ASLO (Todd)	LEtest	B.P.	Fundi	ECG	Remarks
1	563	107	4200	3	(-)	(-)	(-)	50	(-)	120/80	KW-IIa	normal	Silicosis
2	447	65	4400	2	(-)	(-)	(-)	12		142/76		atrial fibrillation	atrial fibrillation
3	370	85	5100	8	(-)	(-)	(-)	12	(-)	130/80	KW-IIb	LVH	
4	426	84	6600	18	(-)	(+)	(-)	50	(-)	130/80	normal	LVH	
5	443	80	4400	15	(-)	(-)	(-)	12	(-)	132/64	normal	normal	
6	443	82	3000	23	(-)	(±)	(-)	50	(-)	128/68	KW-IIa	LVH	cirrhosis of the liver
7	379	75	3700	17	(-)	(+)	+2	50	(-)	170/90	KW-III	LVH	Rheumatoid arthritis
8	376	73	4600	28	(-)	(-)	(-)	50		140/85	normal	LVH	Essential hypertension
9	456	88	6700	3	(-)	(-)	(-)	12	(-)	120/80	normal	normal	
10	415	85	3800	15	(+)	(+)	(-)	50	(-)	130/70	normal	normal	
11	389	83	3000	10	(-)	(-)	(-)	166	(-)	134/70	KW-IIa	normal	
12	418	85	7200	17	(-)	(-)	(-)	50	(-)	136/78	KW-I	normal	
13	394	80	9200	30	(-)	(+)	+1	50	(-)	128/80	normal	normal	Rheumatoid arthritis

RBC: Red cell count. Hb: Hemoglobin. WBC: White cell count. ESR: Erythrocyte sedimentation rate.

STS: Serological test of syphilis. RA: Hyland RA test. ASLO: Antistreptolysin-O titer.

LE test: Hyland LE test. B.P.: Blood pressure. KW: Keith-Wagener classification of Fundi.

ECG: Electrocardiogram. LVH: Left ventricular hypertrophy.

1 showed bilateral nephrolithiasis. Case 6 had undergone right nephrectomy for nephrolithiasis 20 years before.

On the basis of our diagnostic criteria, 6 (Case 1-6) of the 13 cases were diagnosed as having multiple proximal tubular dysfunctions.

Serum protein concentration was normal in all cases. In serum protein fractions no cases were abnormal except Case 6 with a high value of 25.2% in gamma-globulin fraction.

In liver function tests, dysfunction was evident in one (Case 6), slight in 6 other cases, but there were no abnormalities in the remaining 6 cases. Alkaline phosphatase was slightly high in 5, but normal in the other 8 cases.

In peripheral blood analysis, many of the cases were normal though some had slight anemia.

One case (Case 7) had a high blood pressure, which was diagnosed as essential

hypertension as the results of detailed examinations. The other 12 cases had no hypertension.

Many of the cases with multiple proximal tubular dysfunctions tended to show hepatic dysfunctions as well. But there were no particular correlations between the results of other laboratory data and the severity of tubular dysfunction.

The results of detailed examinations revealed silicosis in Case 1, atrial fibrillation in Case 2, cirrhosis of the liver in Case 6, essential hypertension and chronic rheumatoid arthritis in Case 7, and chronic rheumatoid arthritis in Case 13. There were no particular disorders in the other 8 cases.

6) Laboratory findings in 12 non-hospitalized cases with concurrent proteinuria and glycosuria (Table 6):

In these cases, the fasting 2-hour urine (6.00-8.00 a.m.) and blood (at 7.00 a.m.) were examined to determine endogenous crea-

Table 6. Laboratory findings on 12 non-hospitalized cases with concurrent proteinuria and glycosuria.

Case	Sex	Age	Years of residence	Ccr (ml/min/1.48m)	Cua	Cua/Ccr	%TRP	Urine			Plasma				Cd in urine (μ g/l)	Cd in rice (μ g/g)
								RBP	Tubular proteinuria	GAA	CR	UA	FBS	P		
14	M	83	63	32	6	0.19	55	(+)	(+)	(+)	1.5	4.9	80	2.1	17.3	
15	M	36	36	84	23	0.27	72	(+)		($\pm$)	1.0	2.6	75	2.8		0.57
16	F	80	80	28	10	0.36	47	(+)	(+)	(+)	2.1	2.9	76	2.0	15.3	0.50
17	F	73	57	22	8	0.36	78	(+)	(+)	(+)	1.7	3.0	94	2.7	12.6	3.86
18	M	56	56	42	4	0.11	89	(-)		(-)	1.1	5.0	55	2.7	11.3	
19	M	47	47	81	17	0.20	86	(-)		(-)	0.9	3.4	87	4.0		
20	M	43	43	103			89		(-)	(-)	1.0			3.0		0.67
21	M	42	42	80			86		(-)	(-)	1.0			3.1		0.64
22	M	35	35	73	9	0.12	86	(-)		(-)	1.0	3.4	68	4.0		
23	M	35	35	40	5	0.12	81	(-)		(-)	1.2	5.4	77	3.0		
24	F	61	61	146	47	0.32	82	(-)		(-)	0.8	2.1	75	2.8	11.7	
25	F	59	43	68	19	0.28	85	(-)	($\pm$)	($\pm$)	1.1	3.3	66	3.6		

Normal range: Cua/Ccr 0.05-0.15. %TRP 83-95. Plasma uric acid 3.8-7.5mg/dl (adult males), 3.0-5.5mg/dl (adult females), respectively. Plasma phosphate 2.8-4.3mg/dl.

Abbreviations: Same as in Table 2 and 3.

tinine clearance, phosphate clearance, uric acid clearance, blood sugar and plasma electrolytes.

Glycosuria observed in all cases was confirmed as renal glycosuria because their fasting blood sugar remained in a normal range.

A high value of plasma creatinine and a low value of endogeneous creatinine clearance were found in 2 cases.

In uric acid clearance per unit nephron (uric acid clearance/creatinine clearance), 7 cases had a marked high value of over 0.19.

Four cases had obvious hypophosphatemia of less than 2.7 md/dl, and a decreased %TRP of less than 79 was found in 4 cases.

Tubular proteinuria or urinary retinol-binding protein was positive in 4 cases. All these 4 also showed generalized aminoaciduria or increased excretion of urinary aminoacids.

These 12 individuals living in Hosogoe for over 36 years had no particular habitual drugs. Except for one case (Case 17) undergoing traction therapy for lumbago in the Kosaka hospital, there were no bedridden cases.

According to our diagnostic criteria, 4 (Case 14-17) of the 12 cases were diagnosed as having multiple proximal tubular dysfunctions.

No cases other than Case 15, the son of Case 1, had blood ties with each other among the total 25 cases.

7) Bone X-ray findings:

Bone X-ray examinations were performed in all 13 hospitalized and 5 of the 12 non-hospitalized cases (Case 14, 16, 17, 20 and 24), totaling 18.

All but Case 20 showed diffuse decreased bone density, the observed changes were severer in females than in males. Spine formation of vertebral bodies was found in some males and fish vertebrae or vertebral flattening in some female cases. In the left pubic bone of Case 1, there was an indication suspected as Looser's line. No such sign was recognized in the other 17 cases. Bone biopsies were not carried out in these cases.

8) Urinary cadmium levels in cases with concurrent proteinuria and glycosuria, and cadmium concentrations in unpolished rice of their own production (Table 3, 6):

The result of urinary cadmium levels

were provided by courtesy of the Akita Prefectural Government in 1973. Cadmium concentration levels in household unpolished rice were used of those cross-checked by Dr. Shin Homma (Tokyo University of Agriculture and Technology) and the Akita Prefectural Government in the rice produced in 1970-1975.

Urinary cadmium levels checked in 8 cases of multiple proximal tubular dysfunctions were abnormally high in 6 of them ranging 12.6-45.0 $\mu\text{g}/\text{l}$. Seven of 9 cases with the same dysfunctions had high levels of cadmium concentration ranging 0.42-3.86 $\mu\text{g}/\text{g}$ wet weight in their household unpolished rice. In other words, as many as 9 of 10 cases diagnosed as having multiple proximal tubular dysfunctions had an abnormally high value in urinary cadmium level or in cadmium concentration in the rice of their own production, or both.

Abnormally high values of cadmium concentration in urine and the household unpolished rice were observed as well in most of the cases with concurrent proteinuria and glycosuria showing no multiple proximal tubular dysfunctions.

DISCUSSION

Regarding the cause of so-called "Itai-Itai disease" in the Jinzu river basin, Toyama prefecture, the Ministry of Health and Welfare issued an official statement in 1968 as: "So-called Itai-Itai disease is first insinuated by chronic cadmium poisoning which leads to renal dysfunction followed by osteomalacia. And pregnancy, breast lactation, hormonal disturbances, aging, or calcium deficiency may further participate in developing this Itai-Itai disease".

The Ministry of Health and Welfare and the Environmental Agency, establishing "Method of health examinations for people in areas of environmental cadmium pollution (1969)", have been carrying out health examinations for people in cadmium-polluted areas in Prefectures of Miyagi, Nagasaki, Fukushima, etc. But so far so-called "Itai-Itai disease" has not been identified in any people of the cadmium-polluted areas except

for the Jinzu river basin.

If health hazards induced by environmental cadmium pollution are to be decided by the identification of so-called "Itai-Itai disease", it may be affirmed that there are no cadmium-induced health hazards in any cadmium-polluted areas where so-called "Itai-Itai disease" has not been recognized.

The existing method of health examinations has mostly followed the method for detection of so-called "Itai-Itai disease" used in Jinzu river basin. This method, emphasizing the detection of bone involvements, seems to have paid little attention to the detection of renal lesions, especially tubular dysfunctions.

This is quite evident from the fact that examinations of the kidney in this method only covered qualitative urine test, measurement of urine proteins, electrophoretic analysis of urine proteins, and PSP excretion test.

We believe that health examinations laying emphasis on bone involvements without full attention to renal lesions, are difficult to identify early and exact changes of health hazards induced by the environmental cadmium pollution.

Rationale are as follows:

1. Renal lesions in chronic occupational cadmium poisoning are multiple proximal tubular malfunctions, developing low molecular weight proteinuria or tubular proteinuria, renal glycosuria, generalized aminoaciduria, decreased %TRP, a high value of uric acid clearance, and renal tubular acidosis¹¹⁻¹⁵.

Osteomalacia frequently associated with Fanconi syndrome is well known to be mainly caused by phosphate leak and renal tubular acidosis¹⁶.

In view of renal lesions from chronic cadmium poisoning being essentially multiple proximal tubular malfunctions, there is a possibility that cases with this cadmium poisoning develop osteomalacia through renal lesions. Reports of Lafitte, Gervais and Adams citing osteomalacia in cadmium-workers well suggest the above possibility^{16,17,18}.

It may be justifiable to relate osteomalacia in the residents of cadmium-polluted areas to health hazards induced by the environmental cadmium pollution. Even in this case, however, osteomalacia patients being considered to represent cases of highly advanced proximal tubular malfunctions, it is reasonable to believe that there would be many more cases with less-advanced proximal tubular malfunctions short of developing osteomalacia.

2. In discussing osteomalacia in so-called "Itai-Itai disease", there is an argument suspecting cadmium-induced enteropathy as its primary cause, and renal tubular malfunctions rather as a secondary factor^{2,19}. Even on this standpoint, coexistence of cadmium-induced bone involvements and renal lesions is not fully denied.

3. Among main lesions associated with chronic occupational cadmium poisoning, although lung emphysema and anosmia have been cited aside from renal lesions, it is generally believed that proximal tubular malfunctions originating from low molecular weight proteinuria or renal glycosuria is the highest in incidence^{11,14,15,20}.

Both lung emphysema and anosmia secondary to the inhalation of cadmium dust^{11,14,15,20} are considered to occur less frequently in cases with chronic cadmium poisoning caused by mass intakes of cadmium via food.

4. In experimental animals given cadmium, the resultant development of osteomalacia has been indefinite, but there is no doubt about the development of proteinuria, glycosuria and aminoaciduria representing proximal tubular malfunctions^{11,20,21}.

On these grounds, we prefer the development of proximal tubular malfunctions as the most appropriate indication of health hazards induced by environmental cadmium pollution. In other words, when "the incidence of concurrent proteinuria and glycosuria is significantly higher in both sexes in a cadmium-polluted area than in control areas, and there are residents with multiple proximal tubular dysfunctions difficult to be traced to any other causes than chronic

cadmium poisoning", it seems conceivable to believe that health hazards exist with environmental cadmium pollution.

In our urine tests we found concurrent proteinuria and glycosuria in 13-22% of the Hosogoe residents against 2.5% in controls.

In contrast with the incidence of concurrent proteinuria and glycosuria known as around 2-5% for people in non-polluted areas²², the figures for the Hosogoe residents were strikingly high in both sexes.

Concurrent proteinuria and glycosuria was detected in 33 of 137 residents who had undergone urine tests. The 33 residents were from middle to old age living in Hosogoe for long years. Renal function tests performed in 25 of the 33 cases revealed multiple proximal tubular dysfunctions in 10 of them.

There are many diseases known as causing multiple proximal tubular dysfunctions. In Table 7 we show Morris' classification with some modification²³.

Causal diseases were traced for multiple proximal tubular dysfunctions identified in 10 cases out of the 137 residents.

In 6 (Case 1-6) of these 10 cases, detailed examinations carried out for two months in Tohoku University Hospital denied any idiopathic, hereditary or acquired diseases other than chronic heavy metals poisoning.

Although in non-hospitalized 4 cases (Case 14-17), examinations were not as thorough as those in hospitalized 6 cases, findings in personal inquiries, physical examinations, analyses of serum and urine proteins, and others, also denied other causes than chronic heavy metals poisoning.

The Hosogoe area of Kosaka town, adjacent to a leading copper refinery in Japan, has been polluted by cadmium for industrial smokestacks since the 1870s, with frequent hard hits on agricultural products, livestock and trees. Examinations performed by Dr. Shin Homma and the Akita Prefectural Government repeatedly disclosed high concentrations of cadmium in the area's soil, rice and vegetables.

It is therefore conceivable that Hosogoe residents have long been forced to take in

Table 7. Causal diseases of multiple tubular dysfunctions.

I.	Idiopathic
	sporadic
	familial
II.	A part of hereditary diseases
	Cystinosis
	Galactosemia
	Tyrosinemia
	Wilson's disease
	Glycogen storage disease
	Lowe's syndrome
III.	Secondary to aquired diseases
	Multiple myeloma
	Light chain disease
	Nephrotic syndrome
	Recovery stage of acute tubular necrosis
	Sjögren's syndrome
	Vitamin-D deficiency
	Vitamin-D intoxication
	Malabsorption syndrome
	Primary hyperparathyroidism
	Kidney transplantation
	Heavy metals poisoning
	Drugs
IV.	Experimental
	Maleic acid
	Malonic acid

abnormally large amounts of cadmium mainly through food.

Kojima in 1974 conducted extensive studies for 156 people in cadmium-polluted communities of Kosaka town including Hosogoe, ages ranging 50-69 years and for 93 people of the same age group in non-cadmium-polluted Ikawa town, Akita prefecture²⁴⁾. The results revealed that 58 of the 156 Kosaka residents had a high concentration of urinary cadmium over 10 $\mu\text{g/l}$, while none of the 93 Ikawa residents showed such a high level. The average urinary cadmium concentration was 8.0 $\mu\text{g/l}$ for the Kosaka residents, but only 2.4 $\mu\text{g/l}$ for the Ikawa residents, showing a statistically significant difference between the two. In cadmium levels in feces, a mean of 50.5 $\mu\text{g/day}$ was shown in 64 Ikawa people, includ-

ing none with over 150 $\mu\text{g/day}$, in contrast with a mean of 176.8 $\mu\text{g/day}$ for 118 Kosaka people, with over 150 $\mu\text{g/day}$ in 50% of them and over 300 $\mu\text{g/day}$ in 16%.

The mean cadmium intake by people of non-cadmium polluted areas in Japan is assessed as 60 $\mu\text{g/day}$ ²⁾.

Intestinal absorption of cadmium is less than 10% of its intake, so the daily excretion of cadmium in feces is considered almost equivalent to the daily intake of cadmium²⁵⁾.

The daily intake of cadmium in Ikawa people estimated from their daily excretion of cadmium in feces agrees very well with the figure shown by the Ministry of Health and Welfare.

The fact that the residents of cadmium-polluted Kosaka town had a mean daily cadmium excretion in feces over three times that for the residents of control area clearly shows that Kosaka people are still under serious exposure to cadmium.

As shown in Table 3 and 6, abnormally high concentrations of cadmium were detected in urine and household rice in 9 of 10 cases with multiple proximal tubular dysfunctions, and in 20 of 21 cases with concurrent proteinuria and glycosuria. These cases were all people living in Hosogoe from 28 to 80 years. It is quite sure that they have had a high daily intake of cadmium for long years via food.

Renal lesions and abnormal exposure to cadmium identified in many of the Hosogoe residents agree completely with those in chronic occupational cadmium poisoning and experimental cadmium poisoning^{11,14,15,20,21)}.

From these findings we concluded that proximal tubular malfunctions identified in the Hosogoe residents were due to chronic cadmium poisoning induced by the environmental cadmium pollution.

According to our belief in the importance of renal function tests in health examinations for people in cadmium-polluted areas, we diagnosed cadmium-induced proximal tubular malfunctions for the first time in the world.

In 1974, the Environmental Agency set about health examinations for residents in

cadmium-polluted areas in three prefectures of Akita²⁴⁾, Yamagata²⁶⁾, and Hyogo²⁷⁾ using a new method which has taken in renal function tests paying regard to our method and results mentioned above.

The results are quite similar to ours on the Hosogoe area. The incidence of proximal tubular malfunctions was significantly higher in people of cadmium-polluted area than in controls.

It is believed necessary that in other cadmium-polluted areas as well health examinations should similarly be conducted to identify health hazards with environmental cadmium pollution.

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