CAUSATION OF OUCH-OUCH DISEASE (Itai-Itai Byō)

—An Introductory Review—

PART I. NATURE OF THE DISEASE

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1. Entity of the Disease

"Ouch-Ouch disease" is this author's translation of "Itai-Itai Byō" in Japanese. The name of this disease first appeared in reference to medical science when Dr. Kono reported on it to the 17th Japanese Practical Surgeons Society in 1955.¹ Although it is not known when the disease first occurred among the people in that small area, Dr. Hagino² assumed that the disease had already existed around the Taisho-Era (1912-1926). Since then, this local endemic disease has drawn much interest which led to the establishment of a study group appointed by the Ministry of Health and Welfare. The study group was composed of members mainly from the University of Kanazawa, School of Medicine located near the area. The following review is based mainly on the reports^{3,4,5} of this study group and a recent publication⁶ issued by the Ministry of Health and Welfare. The reports are divided chronologically into three parts: 1964;⁴ 1967;³ and 1968.⁵ Immediately after the final report in April 1968,⁵ the Ministry of Health and Welfare announced a formal comment on the entity and causation of disease.

The occurrence of Ouch-Ouch disease has been restricted to a limited area near Toyama city, a small city, facing the Japan Inland Sea. As shown in Figure 1, Fuchu-machi, the focus of the disease, is located about 4 miles southwest of Toyama city. Around Toyama city there is a plain, which is good for rice farming, but it is very cold, with deep snow in the winter. Meteorologically, a district, from which Japanese people are reminded of gloomy, snowy and cold landscapes in winter. The Fuchu-machi of Ouch-Ouch disease is located at the

Fig. 1. The location of endemicity of Ouch-Ouch disease. (Ref. 3)

Table 1

Comparison of selected characteristics of the population involved in Ouch-Ouch disease and Japan (Ref. 3)

Community	Population	Population of farming	Male	Female
Kumano (in Fuchu)	1,723	1,495	738	755
Fuchu	23,924	15,628	7,730	7,891
Toyama prefecture	1,032,629	462,132	226,475	235,288
All Japan	93,406,830	34,545,710	16,868,188	17,677,522

fringe of the Toyama plain and has a population of about 24,000. Some vital statistics for 1961 are shown in Table 1.³ The data indicate average health standards throughout Japan. Figure 2⁴ shows the rates of the main cause of death, which do not deviate much from those of the rest of Japan and Toyama prefecture as a whole. Two-thirds of the population are farmers and the area is categorized as a "Farming community."

Doctor Noboru Hagino, who first announced that this disease was independent from any other known diseases, has been practicing there since his return to Japan from the old Army in 1946. He assumed that the disease must have existed back in the Taisho Era as mentioned. It is generally thought, however,

Fig. 2. Mortality rates from selected diseases. Japan and specific subdivisions, 1961. (per 100,000 pop.) (Ref. 3)

Table 2

Diagnostic criteria for suspected Ouch-Ouch disease (Ref. 4)

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- The first screening:
 - 1) Painfulness (Groins, Sacum, Back, Joint)
 - 2) Waddling gait
 - 3) X-ray finding (Healing zone of bone in upper arm and costal)
 - The second screening:
 - 4) X-ray finding (pelvis lateral side of scalp)
 - 5) Location of pain
 - 6) Urine test (positive sugar and protein)
 - 7) Blood test (Increased alkali-phosphatase, decreased inorganic phosphatase, decreased inorganic phosphorus)
 - 8) General clinical examination
 - The final examination: closer examinations
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the incidence has increased since World War II. Until several years after his report, some research workers had been performing their studies quite independently without criteria of the disease. But, in 1962, since the first study group including epidemiologists was composed at the prefectural level, the acceptance of the syndrome as a separate disease entity was confirmed. The criteria they used for the diagnosis and their epidemiological study are shown in Table 2.⁴

2. Clinical Picture and Definition of the Disease

The clinical course of this disease usually starts with lumbago. Some patients complain of so-called rheumatic pain in the groin, joint and other sites. The pain persists and gradually extends to various locations, finally resulting in a walking disability—producing a waddling gait, with the patient being confined eventually to bed. Fractures of the bone may occur and stature is decreased. Pain is so intolerable that the patients even cry “Itai-Itai.”

On X-ray film healing zones are observed in various bones. Decalcification, deformity, thinning of cortex, thickening of bones and the formation of a so-called “fish spine” are not uncommon. Cause of death is variable. Although almost 100% of the cases are associated with positive urinary protein and sugar it is not usually due to advanced nephrosis or nephritis, with one case reported as having died with this diagnosis. Other common laboratory findings include increased amino acids such as alanine, glycine and lysine, as well as, slightly increased calcium in urine. Phosphorus in urine is somewhat reduced.

The investigators from University of Kanazawa, School of Medicine studied 5 cases closely.^{3,4} The clinical picture will be discussed as follows. These patients admitted to their hospital during the period of four years 1962–1965, are representative of their natural history of suspected and real Ouch-Ouch disease.

Case I.

Age 44, Female, Farmer.

Complaint: Lumbago and abnormal walk.

Family history: Not remarkable.

History: She was born and had lived in the endemic area throughout her life except for six months in Kobe where she had worked as a textile worker at the age of 16. Out of three pregnancies one was a twin-birth and both babies had died soon after birth. The other two were healthy. She had undergone a hemorrhoidectomy 2 years prior to admission. Menstruation was irregular and with occasional abnormal bleeding.

Present history: In 1958 she had felt severe pain in her lower back when she was shoveling clay and had received a massage treatment. The lumbago was little relieved and pain then appeared in the ileocecal joints. In 1959 she was treated by moxa cautery for 40 days but the lumbago became severe and a tense feeling in both groins appeared. She saw a doctor and was diagnosed as having

rheumatism. In September 1962, she became so disabled that she could not walk and visited the hospital carried on the back of her husband.

Present status: Height 145 cm. Weight 43 kg. Nutrition was not good, no anemia was recognized. Vertebrae were generally stiff. Tenderness was recognized on the 4th and 5th lumbar vertebrae and chest girdle, especially on the sternum and breast. Scapular joints showed limited range of motion. On the right side of the thyroid gland, a tumor, walnut sized and smooth, was found.

X-ray findings: There were many healing zones in various bones. Although she received treatment of Vitamin D administration and protein synthesis hormones, she died on [REDACTED].

Case II.

Age 58, Female, Farmer.

Chief Complaint: Back pain (lower and upper).

Family history: Unremarkable.

Previous history: 11 pregnancies, 11 deliveries. Menopause at age 48.

Present history: At age 46 she complained of lumbago which was diagnosed by a physician as neuritis. In December 1955, she was admitted to a hospital because of limited movement of her body. After 15 months symptoms were improved and she was discharged. In 1965 she was admitted to the [REDACTED] for an elaborate examination.

Status on examination: Height 128.5 cm. Weight 36.0 kg. Advanced kyphosis was noted. No tenderness was elicited. Limited range of movement was recognized in the right elbow. Extension of groins was limited to 129°.

X-ray findings: Healing zones were recognized in the sacrum, tibia and scapula.

Case No. I may not be "Ouch-Ouch disease," as they mentioned, because of a neck tumour which was diagnosed histologically as hyperparathyroidism. But it is important to mention that the clinical symptoms of case No. 1 were so similar to Ouch-Ouch disease that one can hardly differentiate them by clinical symptoms. Figure 3^{3,4} summarized the picture of amino acid excretion in the urine of those four cases. There is an obvious increase in excretion of glycine, alamine, lysine and glutamine with serine and proline moderately increased. Table 3⁴ shows daily excretion of phosphorus, calcium, amino acids, and heavy metals in urine and feces of five patients clinically diagnosed as Ouch-Ouch disease. They show generally, higher Ca, lower P and elevated Cd in urinary excretion and about normal in feces excretion. Table 4⁴ shows no significant abnormality in the hormones excreted in the urine. Figure 4⁴ is a summary of the trends of urinary phosphorus and blood calcium, phosphorus, alkali and acid phosphatase in the five cases. From the clinical picture of these cases they defined Ouch-Ouch disease as follows:

1. Pain of the back, and/or shoulder and/or other bones. Neuralgia-like pain of thigh and/or upper arm.
2. Waddling gait.
3. Fractures and shortening of height.

Fig. 3. Amino acids of urine of Ouch-Ouch disease. (Ref. 4)

Table 3
Potassium, calcium and metals in urine and feces (Ref. 4)

Item	Normal	Case 1	Case 2	Case 3	Case 4	Case 5	
Urine	Amount (cc)	1,000~1,500		2,025	2,754	1,411	1,857
	Amount Ca (mg)	90~280		279	261	372	293
	Amount P (mg)	800~900	not tested	467	447	554	374
	Amount P/Ca	2~		1.70	1.73	1.52	1.38
	Amount N (mg)	120~240		357.5	372.5	350.0	360.0
	Amount Cd (γ)	2.7*		127.4	38.3	45.5	32.7
	Amount Pb (γ)	80		27.0	27.9	40.2	15.7
	Amount Zn (γ)	600~1,800**		284	1,350	584	414
Feces	Amount Cd (γ)	57.4*		66.7	37.0	48.0	25.5
	Amount Pd (γ)	?		95.9	67.5	9.5	10.0
	Amount Zn (mg)	3.2~7.9**		19.9	14.5	13.8	17.5

Figures are averages of 4-13 days

* Averages of 4 male adults

** Averages of American females

Fig. 4. Phosphorous in urine and serum-components of five patients. (Ref. 4)

Table 4
Hormones in the urine (Ref. 4)

Item	Normal value	Case 1	Case 2	Case 3	Case 4	Case 5
Estrogen	20~40 μ /day		35.8	20.9	28.7	18.6
17-KS	3~4 mg/day		5.61	4.36	3.16	1.75
17-OHCS	4~5 mg/day	not	1.83	2.38	2.60	3.32
Gonadotropin	32~64 M.U.N./day	tested	32	32	64	16
Pregnandiol	0~0.3 mg/day		0.21	0.15	0.83	1.14
Pregnantriol	0.5~1.0 mg/day		0.27	0.69	0.94	0.14

4. 1) Increased alkaline phosphatase with a decreased phosphorus and normal calcium concentration in the serum.
- 2) Positive proteinuria and glycosuria.
5. Bone changes by X-ray (healing zones, etc.).

3. Results of Mass Screening Examinations

During the period from 1962 to date, a number of mass medical examinations for the purpose of screening the disease as well as of epidemiological studies have been performed by the study group. Since the epidemiological features of the disease will be described in Part II, only the summary of clinical findings of the patients, suspects and healthy individuals in the endemic area will be compared with normal people in the control area.

In the mass screening tests examinees were divided into four groups based on X-ray findings. The first group was defined as patients with apparent abnormality on X-ray pictures and with some of the symptoms mentioned above. The second group, suspects who had suspected bone changes on X-ray. The third group, healthy people were defined as having no X-ray abnormalities, nor subjective symptoms in the endemic area. The fourth group was a pure control group supposedly normal in the control, non-endemic, area.

Figure 5⁴ shows the positive rates of urine protein and sugar among females older than 40 years of age in each group. It indicates nearly 100% of the patients show positive protein and sugar in urine, about 70%—80% among those suspected, less than 10% proteinuria among healthy people in the endemic area, and only a few percent among apparently normal persons in the control area. It is important to note that among the healthy people in the endemic area the rate of glycosuria is even higher than that of proteinuria.

Figure 6⁴ indicates the frequency distributions of calcium excretion in urine among the people of two areas. There is no obvious difference between two areas.

Fig. 5. Proteinuria and glycosuria. (Ref. 4)

Fig. 6. Distribution of Ca, P and P/Ca in urine. (Ref. 4)

But, phosphorus excretion in the endemic area is somewhat less than that in the control area. If you take the ratio P/Ca , [Figure 6 (bottom)] the difference of distribution between the two areas becomes very apparent, and the frequency distribution of Ca/P in the endemic area is shifted to the right side, to significantly higher values. The result of serum alkaline phosphatase determination is shown in Figure 7.⁴ We can see a higher level of the enzyme among patients and suspects, and even the "healthy" people in the endemic area, in comparison with "normal" people in the control area.

Fig. 7. Alkali-phosphatase in serum (older than 40 years of age, female). (Ref. 4)

Table 5
Main clinical and pathological findings of four cases in postmortem autopsy (Ref. 3)

Case No.	Age	Sex	No. of birth	Length of disease	Residence	X-ray	Ca	Blood P	Alk-P	Clinical diagnosis
1	62	♀	9	12	Endemic area	Bone atrophy (high-grade) Bone healing zone (evident) Deformation of pelvis Fish vertebra	normal	decreased	increased	Ouch-Ouch
2	62	♀	8	5	Endemic area	Bone atrophy (high) Bone healing zone (evident) Deformation of pelvis Fish vertebra	normal	decreased	increased	Ouch-Ouch
3	49	♀	10	0	Toyama city	Bone atrophy Deformation of vertebrae, pelvis and femur	increased	decreased	normal	Suspect for Ouch-Ouch
4	44	♀	3	5	Another town in Toyam prefecture	Bone atrophy Deformation of vertebrae Bone healing zone	normal	decreased	increased	Suspect for Ouch-Ouch

4. Postmortem Findings

Since the community people in this village are reluctant to permit postmortem examinations because of their religion, only a few cases are available for report. However, one of the study groups performed postmortem examination on four cases including two suspicious cases whose main clinical symptoms are summarized in Table 5.³

Both clinical and postmortem findings of Cases 1 and 2 in Table 5 were different from those of Cases 3 and 4. Therefore, they suggested that Cases No. 3 and No. 4 belonged to a different disease category, viz, fibrotic osteoporosis due to a parathyroid tumor. The common postmortem findings in both Cases No. 1 and No. 2 were the loss of elasticity of all bones so that they were very easily cut by a knife. Histologically, in addition to the osteoporosis, the formation of osteoid in the osteon, at the inner wall of the Haversian canal was also observed in No. 1 and No. 2 cases. Also, with the healing zone recognized by X-ray, remarkable hyperformation of osteoid was found. These changes were recognized in all bones, except the cranial bones. The findings are very close to those accompanying osteoporosis: formation of fibrous bone marrow with many osteoclasts—a picture of fibrous panostitis. Furthermore, even the cranial bones were affected in latter cases.

In case No. 4, the healing zone corresponding to the X-ray findings was recognized, and this pathological finding resembled cases No. 1 and No. 2, but differed from them in that it lacked a picture of osteoid formation where there had been no X-ray findings.

According to the pathological conditions observed, they concluded that Ouch-Ouch disease was a type of osteomalacia and that the cause of death in Cases No. 1 and No. 2 was a result of highly disturbed nutrition, especially lack of Vitamin D. With regards to the metal content in the organs, they reported only on one case from the non-endemic area, which was pathologically diagnosed as hyperparathyroidism but not real Ouch-Ouch disease. In this case a much higher cadmium content was found in various organs in comparison with the control cases.

5. Comment

This review has not covered the whole report made by the study group in terms of the clinical manifestation or identification of Ouch-Ouch disease. However, I believe that I have been able to present enough data which suggests this is a separate disease entity. From the profile of clinical, as well as, the pathological picture of the disease, we understand that the disease is very similar to

Fanconi's syndrome.

When the disease was originally presented by Dr. Hagino, many competent orthopedists thought that the disease was only a senile osteomalacia in which the cause was thought to be unknown.

From the clinical picture, with a limited number of autopsies, they assumed that the proteinuria resulted from tubular changes in the kidney, which caused renal glycosuria. Some cases showed a markedly decreased renal clearance with GFR of less than 30, yet without any increase of NPN in the serum. Only one of these was uremic. They explained that the low renal clearance—assuming that the value of GFR indicated a lower level than it actually was—due to a reverse diffusion of substances filtered from glomeruli due to highly impaired tubules. Unfortunately, they did not perform any electrophoretic studies on the urinary protein, which I think, is essential to support this hypothesis. Here is the question. What is the cause and effect relationship between tubular failure and osteomalacia?

Namely: Two processes can be hypothesized:

- 1) ? → Osteomalacia → Large amount of excretion of calcium → Tubular impairment (as seen in presented Case #1).
- 2) ? → Tubular impairment (Fanconi's syndrome) → Loss of calcium with (lowered intake of calcium) → Osteomalacia.

The study group and some others made a second assumption and hypothesized that cadmium had caused the tubular impairment, since a patient's urine showed an increased excretion of cadmium and the environment (soil and rice) was contaminated by cadmium. In the next discussion, I will go into the testing of the hypothesis. But, at this time, the following questions can be raised.

1. Is the osteomalacia caused by a Fanconi-like syndrome as grave as seen in Ouch-Ouch disease?
2. There is a statement in medical textbooks that Fanconi syndrome may be caused by lead, uranium and cadmium. Are there reports in which the cases of Fanconi's syndrome occurred as a result of exposure to lead or cadmium?
3. Is it theoretically possible to establish a hypothesis that tubular impairment could cause a large calcium loss, large enough to result in osteomalacia?
 - a. Is it possible that in spite of serious tubular impairment, calcium concentration in urine is not very high and serum calcium stays normal?
 - b. If glycosuria is a secondary development following tubular impair-

ment, should not a higher rate of glycosuria than proteinuria be observed among the inhabitants?

- c. If the renal condition is due to lead or cadmium, would the patients have been expected to die from uremia or renal failure as observed in industrial workers?

Reference and acknowledgement will be seen at the end of "Part II."