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Author(s)	SONODA, Mitsuo; NAKAMURA, Ryoichi; TOO, Kimehiko; MATSUHASHI, Akira; ISHIMOTO, Hajime; SASAKI, Ryusuke; ISHIDA, Kenji; TAKAHASHI, Mamoru
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CLINICAL STUDIES ON MERCURY POISONING IN CATTLE

Mitsuo SONODA, Ryoichi NAKAMURA, Kimehiko TOO
and Akira MATSUHASHI

*Laboratory of Veterinary Internal Medicine,
Faculty of Veterinary Medicine,
Hokkaido University, Sapporo, Japan*

Hajime ISHIMOTO, Ryusuke SASAKI, Kenji ISHIDA
and Mamoru TAKAHASHI

*Livestock Industry Section,
Hokkaido Prefectural Government, Sapporo, Japan*

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INTRODUCTION

A sporadic outbreak of a curious disease occurred among dairy cattle, from early February to late May 1955, in Monbetsu District, Kitami Sub-prefecture of Hokkaido. The characteristic symptoms of this disease were dyspnea and depilation; out of 29 cases, 8 died while 2 were slaughtered.

The clinical studies made by the authors have disclosed that the symptoms were similar to those found in cases of "Mercury poisoning" as described by FRÖHNER,⁵⁾ LUGINGER,¹⁶⁾ ORTMANN,²⁰⁾ REICHE²³⁾ and UDALL.²⁷⁾ So the animals' feed was suspected of being the cause of the sickness. It was confirmed that the incident was due to poisoning resultant from ingestion of linseed meal treated with a mercurial fungicide, "Ceresan*".

From the results of the inquiry for anamnesis, it was found that 171 cattle were fed with the meal and 29 cases were affected. In view of the wide use of mercurial preparations for treating seed grains against fungi infection, a further experimental study was made by the authors on the effects of the feed and fungicide upon calves.

CLINICAL STUDIES

1. Outline of Incident

The outbreak covered all Monbetsu District inclusive of its neighboring Okoppe District. The supposed first case, a cross-bred Holstein cow, was detected February 2, 1955. She

* Remark: "Ceresan" is a fungicide containing 1.5% mercury; its components were 3.6% organo-mercury compounds (chlorophenyl-mercuric chloride, phenyl-di-mercuric chloride and methoxyethyl-mercuric chloride), 79% talc, 10% caorin, 2% mineral oil and 6% iron oxide.

developed the more severe cases of this disease. However, the onset was not always in parallel with the total amount of linseed meal fed but it seemed rather to depend upon the disposition of each animal. On the other hand, in the qualitative test for the mercury in the examined 15 feed samples, 2 were confirmed to be weakly positive.

2. Clinical Observations

The results of the clinical observations are indicated in table 2 and figs. 1~6. From the severity of the disease, they were classified into 3 groups, viz., severe, moderate and slight. The general symptoms were fever attack, depression and anorexia, lachrymation, decrease in milk production and cramp. In the examination of the integument, partial and diffusive depilation, eczema and swelling of the skin accompanied by itchiness on the entire body surface were found. In the digestive system, salivation, diarrhea and bloody feces were noticeable. On auscultation, bronchial catarrh was found in about half of the cases, especially, it was distinct in the severe or moderate ones. Anemia on all mucous membranes and petechial hemorrhage on the nasal and vaginal mucous membranes were apparent in the severe patients. Cardiac disturbance and swelling of lymphnodes were

TABLE 2. *Clinical Symptoms*

SYMPTOMS	SEVERITY AND NO. OF CASE					
	Severe 12	Moderate 7	Slight 10	Total 29	%	
General Condition	Fever Attack	10	7	2	19	65
	Depression & Anorexia	12	6	4	22	76
	Lachrymation	8	5	1	14	48
	Decline of Milk	10	7	6	23	79
	Cramp	2	0	0	2	7
Skin	Depilation	8	7	8	23	79
	Eczema	7	5	0	12	41
	Itchiness	4	3	1	8	27
Digestive Organ	Salivation	9	5	5	19	65
	Diarrhea	5	0	0	5	17
	Bronchial Catarrh	9	6	2	17	58
Mucosa	Anemia	7	3	0	10	34
	Petechiae	6	1	1	8	27
	Swelling of Lymphnode	8	6	2	16	55
	Cardiac Disturbance	7	1	1	9	31

TABLE 3. *Hematological Findings*

NO.	SEVERITY	CASE NAME	E. (mill.)	L.	Hb (%)	DIFFERENTIAL COUNTING OF LEUCOCYTES (%)					RESISTANCE OF ERYTHROCYTES		FINDINGS OF ERYTHROCYTES						
						N-St.	N-Seg.	Ly.	Mon.	Eos.	Bas.	Min.	~ Max.	Aniso.	Polychr.	Basoph. Stippling	Erythro- blasts*	Jolly Bodies	Reticulo- cytes**
1	Severe	B.K.	1.45	9,400	15	3.0	49.5	26.5	20.0	1.0	0	0.78	0.62	-	-	-	5	+	2
2	"	S.Y.	3.92	7,200	50	3.5	29.5	33.0	6.0	28.0	0	0.76	0.46	++	+	+	9	++	5
3	"	N.K.	4.09	9,000	45	10.0	36.5	37.0	16.5	0	0	0.76	0.68	-	-	-	1	-	0
4	"	O.Y.	5.34	9,600	75	0	50.0	38.0	6.5	5.0	0.5	0.74	0.42	-	-	-	0	-	0
5	"	H.K.	5.46	7,000	55	10.5	32.5	33.0	24.0	0	0	0.78	0.56	-	-	-	0	-	1
6	Moderate	K.N.	4.04	7,800	55	0	41.5	30.5	6.5	21.5	0	0.76	0.42	++	+	-	1	+	4
7	Slight	O.N.	6.33	12,000	80	0.5	28.0	59.0	3.5	9.0	0	0.70	0.46	+	-	-	0	-	0
8	"	A.N.	8.23	11,600	85	2.5	24.0	71.5	1.0	1.0	0	0.76	0.52	-	-	-	1	-	0
9	"	P.Y.	8.44	10,600	80	1.0	12.5	79.0	1.0	6.5	0	0.76	0.60	+	-	-	0	-	2

Note: *...per 200 leucocytes

***per 1,000 erythrocytes

also noted in the severe cases respectively. Of these symptoms, the characteristic findings in this malady were the decrease in milk production, pathological dermal changes, the disturbance in the digestive canal, bronchial catarrh and the hemorrhage on the mucous membranes. Further, in some instances, there were found epistaxis, bloody milk and nephritis.

The period from the time of discovery to that of termination in 10 cases, either died or killed, ranged from 1 to 43 days, being 20 days on the average. All cases that suffered from a continued high fever, severe dermal changes and hemorrhagic symptoms had to take a lethal course. The other recovered cases required as long as 3 to 6 months before complete recovery could be reached.

3. Hematological Findings

The hematological examination, as indicated in table 3, was conducted in affected 9 cases.

The mean value of erythrocyte numbers in 9 cases was 5.25 (1.45~8.44) million; of which 6 cases whose clinical symptoms were distinct showed an advanced anemia, while in 3 slight cases their average count was within a normal range of 7.67 (6.33~8.44) million. In the morphological examination of blood smears from the marked anemic cases, only a small percentage of pathologic erythrocytes such as macro- and microcytes, polychromic cells, reticulocytes, erythroblasts, and cells with HOWELL-JOLLY bodies were found. These findings indicate the force of regeneration of the erythrocytes to be very weak in the disease

The mean value of leucocyte count was 9,355 (7,000~12,000), but in the 6 severe or moderate cases a normal range of 8,300 (7,000~9,600) was observed on the average, although the average of 3 other slight cases was 11,400; that is there was a slight increase. In the differential counting, the 6 severe or moderate cases indicated neutrophilia. Two cases out of those 6 increased in rhabdocytes, while in the slight cases lymphocytes showed predominance, and in others monocytosis and eosinophilia were found in 6 and 2 cases respectively.

In regard to the resistance of erythrocytes to saline solution, there were no changes in the minimal resistance (0.75 on the average), but in the maximal a weakened resistance was found in 5 cases. There were, however, no significant variations in relation with the severity.

In the biochemical findings in serum, as shown in table 4, there was a slight decrease in the total protein and globulin down to 6.2 g/dl and to 28 g/dl on the average respectively. Albumin was as normal as 3.4 g/dl on the average, while A/G decreased antagonistic to globulin. A marked increase in blood sugar was found running as high as 94.7 mg/dl (60.0~144.0 mg/dl), but no alterations were observed in inorganic phosphorus, calcium, ferric and total ketone bodies.

4. Urine Findings

The urine examination was conducted in 6 cases. Results are showed in table 5. The material from 1 case was brown-yellow and all the others were normal in color, although

TABLE 4. *Biochemical Findings in Serum*

NO.	SEVERITY	CASE NAME	PROTEIN (g/dl)				GLUCOSE (mg/dl)	INORG. SUBS. (mg/dl)			TOTAL KETONE BODIES (mg/dl)
			Total	Alb.	Glob.	A/G		Ca	P	Fe	
1	Severe	B.K.	5.4	3.35	2.05	1.63	144	9.8	6.7	0.180	1.107
2	"	S.Y.	5.75	3.35	2.4	1.39	90	15.0	2.7	0.065	1.476
3	"	N.K.	6.6	3.6	3.0	1.20	88	7.0	3.3	0.120	1.533
4	"	O.Y.	6.8	3.2	3.6	0.89	94	10.0	4.8	0.060	1.968
5	"	H.K.	6.4	3.25	3.15	1.03	60	7.6	3.9	0.035	1.845
6	Moderate	K.N.	6.6	3.05	3.55	0.86	71	10.0	2.5	0.020	1.722
7	Slight	O.N.	6.6	3.5	3.1	1.13	97	12.6	4.4	0.060	0.369
8	"	A.N.	5.6	3.6	2.0	1.80	131	10.0	6.1	0.050	1.107
9	"	P.Y.	5.7	3.4	2.3	1.48	78	10.0	4.9	0.045	1.230

TABLE 5. *Urine Findings*

NO.	SEVERITY	CASE NAME	PHYSICAL FINDINGS				CHEMICAL FINDINGS							
			Color	Opacity	Specific Gravity	pH	Prot. Test		Sugar Test	Hb Test	Urobilinog. Test	Ketone Qual.	Bodies Quant. (mg/dl)	SEDI-MENT
							Qual.	Quant. (g/dl)						
1	Severe	B.K.	Citronic yellow	—	1.023	8.2	+	0.8	+	—	—	+	3.321	—
2	"	S.Y.	"	—	1.030	9.2	—	.	+	—	—	—	1.599	—
3	"	N.K.	Brown-yellow	—	1.040	9.2	++	4.5	++	++	—	—	3.075	+
4	"	H.K.	Citronic yellow	—	1.028	8.8	+	1.2	+	—	+	—	2.746	+
5	Moderate	K.N.	"	—	1.035	8.6	—	.	+	—	—	—	1.722	+
6	Slight	O.N.	"	—	1.022	8.6	—	.	—	—	—	—	2.583	—

they were all highly alkaline in reaction. Their qualitative test showed that 3 cases were positive in protein, 1 of which cases was positive also in benzidine reaction. On the other hand, all cases except 1 slight one were positive in glucose reaction. Only 1 case showed positive in urobilinogen test and no increases in total ketone bodies were observed in any of the cases. Only through macroscopic observation 1 case was recognized as hematuria and 3 cases were estimated to be hemoglobinuria.

5. Therapy

As soon as the linseed meal was suspected, a change was made in the feeding program and then a series of symptomatic treatment was carried out, especially with chemotherapeutic preparation such as penicillin, streptomycin etc., together with sinapsis cataplasm; also a large quantity of RINGER's solution was injected. In some chemotherapeutically treated cases there was a temporary fall in the body temperature at the initial period after injections, which did not last at all. Medication of potassium iodide and sodium thiosulfate had no effect upon the condition, while it may be considered that 200 to 400 mg of Kativ (vitamin K preparation) and 100 to 200 mg vitamin B were slightly effective.

EXPERIMENTAL STUDIES

Since the linseed meal produced by Y Oil Factory was suspected as the causal agent, experimental investigations were carried out, in order to confirm the point, by feeding 3 calves with the same meal and "Ceresan".

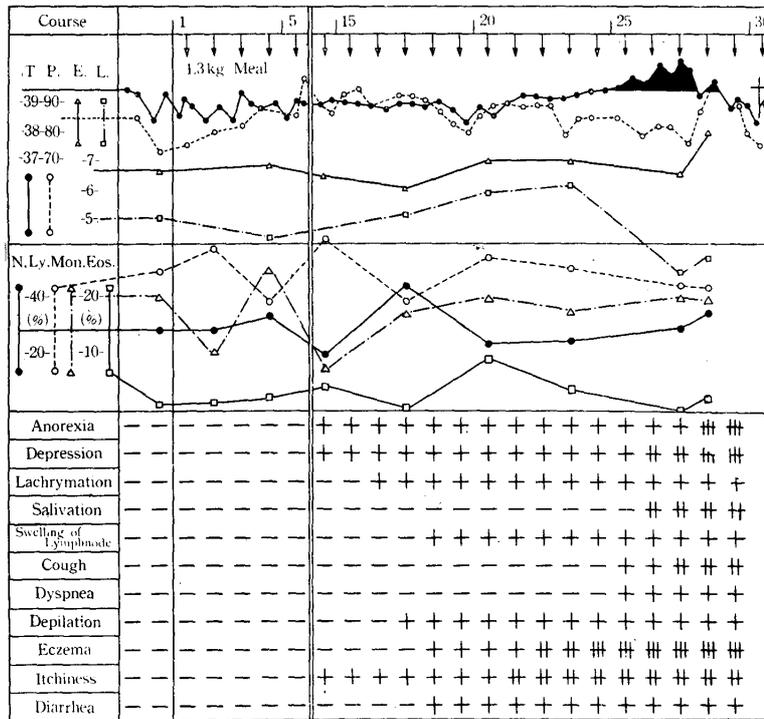
1. Result in Case No. 1

Male, Holstein cross-bred, 7-month-old, body weight 82.5 kg, fed a ration consisting of 1.3 kg meal, 0.3 kg rice-bran and 7 kg ensilage per day. On the 8th day, there appeared symptoms such as itchiness in skin, anorexia and depression in spirit; slight lachrymation and depilation around the tailhead were found from the 16th and 17th day respectively. From the 18th day, swelling in *Lnn. poplitei* and eczema on the forebreast and hypogastric region were observed together with accompanying dysphagia and diarrhea. Then, the eczema extended all over the body surface which thus partially became into ulcerous. Further, on the 25th day, the case was attacked with a fever of 39.8°C being accompanied by cough and dyspnea, followed by the appearance of salivation on the next day. On the 27th day, the cough became more frequent, and petechial hemorrhage more visible on the left conjunctiva, increased salivation, wide spread eczema and developed albuminuria were also noted. On the 30th day, the calf was killed on account of its uncontrollable general condition.

In the blood examination, no marked alterations were found in the erythrocyte number throughout the whole course, although there was a slight increase near the time of termination. The leucocyte count slightly increased from the 8th day, but suddenly decreased to 2,400~3,500 near the termination. In the differential counting of leucocytes, there was an increase in the neutrophilic leucocytes in the middle as well as ending period of the course. Lymphocytes showed a tendency to act antagonistic thereto. Monocytes increased

in general, and also eosinophilic leucocytes showed a temporary increase in the latter half of the experimental course.

CHART 1. *Experimental Feeding Test in Calf No. 1*



2. Result in Case No. 2

Male, Holstein cross-bred, 7-month-old, body weight 85 kg, fed a ration consisting of 1.5 kg meal, 0.7 kg rice-bran and 5.0 kg hay per day. For a period of from 1 to 2 weeks after the commencement of the experiment, gastro-intestinal catarrh accompanied by a slight loss of appetite developed; from the 23rd day the calf suddenly developed a fever of 41.5°C and at the same time anorexia, depression, laboured breathing, rustle in vesicular breathing, reduction in gastro-intestinal peristalsis and a tendency for depilation were observed. However, 2 days after, the fever abated to normal and the symptoms rapidly disappeared, after which no symptoms reappeared until the termination of the observations.

The blood examination indicated a rise and fall between 6.82 and 9.7 millions in the erythrocyte numbers, and a large variation was shown in the leucocyte numbers from 6,000 to 18,400, the lowest count, or 6,000~6,200, being especially in the period of fever attack. In the differential counting of leucocytes, lymphocytes always were more predominant than neutrophilic leucocytes through the course, although they showed a considerable decrease in the period of fever attack. Neutrophilic leucocytes were inverse to the former. In other white cells the changes were not worth special mention. The biochemical examination on the serum did not reveal any distinct changes in protein, glucose, inorganic phosphorus, calcium and total ketone bodies. Similar results were

obtained from the urine examination throughout the whole course.

Feeding test with "Ceresan". This test was conducted with the same calf after the 40 days' previous feeding test with meal. "Ceresan" was given at the rate of 0.1~1.0 g/kg of body weight per day, on the increase daily. Clinically, the general condition took a turn for the worse from the 8th day with appearance of congested conjunctivae, depressed rumination and diarrhea; slight depilation as well as cardiac disturbances developed from the 9th and 11th days respectively. These symptoms advanced gradually, further the calf showing laboured breathing from the 17th day and finally died on the 20th day.

The erythrocyte numbers markedly increased up to the middle part of the application but suddenly decreased to 5.22 million in the terminal period, whereas the leucocytes varied within a normal range of 6,600 to 8,800. Lymphocytes always showed predominance in the percentage except on the 6th day, however neutrophilic leucocytes were the opposite to the former. Monocytes showed a slight increase until the middle part of the application but decreased later, and eosinophilic leucocytes showed practically in parallel to the variation in neutrophilic leucocytes.

No noticeable changes were found by chemical analysis with respect to protein, glucose, calcium, inorganic phosphorus and ketone bodies. In the urine findings, albuminuria appeared from the 12th day, but no other abnormality was found.

3. Result in Case No. 3

Male, Holstein cross-bred, 15-month-old, body weight 150 kg, fed a ration consisting of 2.5 kg sound linseed meal, 1.0 kg rice-bran, 10 kg ensilage and 7 kg hay per day.

Clinical and hematological observations showed no abnormalities; the nutritional conditions turned to the better.

CONSIDERATIONS

Mercury poisoning in domestic animals has been described in horse,²²⁾ cattle, dog,^{7,26)} cat,⁶⁾ swine,^{3,18)} sheep²¹⁾ and canary,⁵⁾ but in cattle, especially, many cases have been reported because they are particularly sensitive to mercury. ORTMANN²⁰⁾ and others^{1,4,5,8,16,21,28,29)} reported about the poisoning due mostly to faulty use of mercurial ointments or antiseptics for cattle.

The clinical symptoms of mercury poisoning in cattle from these reports, are summarized as follows: Stomatitis (salivation, loosening of teeth, foul odors from oral cavity), gastroenteritis, respiratory symptoms (cough, nasal discharge, dyspnea, broncho-pneumonia, foul odors expiration), dermal changes (eczema, pustule and ulcer, depilation, thickening of skin like elephantiasis), general exhaustion and psychic symptoms (anorexia, depression, emaciation and tremor), nephritis (dysuria and anuria, albuminuria, hematuria), hemorrhage (in all organs, especially in mucous membranes and skin, epistaxis, bloody milk, hematuria, bloody feces).

These exactly coincide with the clinical symptoms described by the present authors. The psychic symptoms said to be characteristic in human mercury

poisoning were rarely observed in our cases. But that seems ascribable to the different route in taking mercury. HOFF¹¹⁾ and IHARA¹²⁾ have clarified that psychic symptoms were more frequently observed when the mercury was taken as its vapor than when the contact or intake was direct. In domestic animals, the distinct psychic symptoms found in cats poisoned by mercurial vapor were reported by GORTON.⁶⁾ Considering from the results of the clinical examinations and of the 3 experiments described above, there seems to exist some difference between the individuality and sensitivity for mercury in cattle. PETRELIUS²¹⁾ expressed the same opinion concerning the relationship between the onset of disease and the difference in disposition from his experimental results on mercury poisoning with the use of cattle and sheep. In the hematological observations, the decrease in erythrocyte numbers was remarkable; this finding coincides with the results from the works of HASHIBA⁹⁾ and MURAKAMI¹⁹⁾ in human and rabbit. Especially in severe cases, in spite of marked anemia, the appearances of young cells were very minor. ZANGGER³⁰⁾ and FRÖHNER⁵⁾ stated that mercury was a hemolytic poison for blood, but, from the results obtained by the present authors, it may also be supposed that the regenerative force of erythrocytes in marrow is possibly disturbed in this disease. The finding in respect to neutrophilia accompanied by an increase in rhabdocytes observed in severe cases and lymphocytosis found in slight cases, was in agreement with the results of many workers in human^{2,9,13-15,17,19)} and rabbits.¹⁹⁾ Namely, it is considered that a small amount of mercury stimulates the lymphatic tissues acting as the catalase, while a large quantity of mercury exerts a harmful action on the situation of the lymphatic cell production as reported by LÜDDICKE.¹⁵⁾

In the authors' cases, a marked increase in glucose was observed in serum analysis. Mercury seems to disturb glycogenesis in the liver. The albuminuria found in 50% of clinical cases revealed the disturbance of the kidneys with certainty. It has been said, in acute human cases of mercury poisoning, that the pathological changes of the kidneys together with albuminuria or hematuria have been found in most cases. GREEN et al.⁷⁾ described similar findings in dogs. The tests for the presence of mercury were weakly positive only in some of the collected feed samples. Therefore, it follows that victims were poisoned by an extremely small quantity of mercury in meal because of their supersensibility.

As clear from the above descriptions, it was proved by the authors that this disease was due to poisoning with ingested linseed meal treated with a mercurial fungicide, "Ceresan".

SUMMARY

The authors investigated clinically and experimentally a series of cases of

mercury poisoning in cattle all over Monbetsu District in Hokkaido, from early February to May 1955. The results thus obtained are summarized as follows:

1. This disease was due to poisoning by ingested linseed meal treated with mercurial fungicide, "Ceresan".
2. Out of a total of 171 cases fed with the linseed meal, 29 cases fell into sickness, 10 cases of which died or were slaughtered.
3. The outstanding symptoms were fever attack, depression and anorexia, decline in milk secretion, bronchial catarrh, pathological changes in skin, lachrymation, salivation and diarrhea, swelling of lymphnodes, anemia and petechiae on the visible mucous membranes, and cardiac disturbance.
4. Marked anemia and neutrophilia with nuclear shift to the left were observed in the severe cases, but in the slight cases, lymphocytosis was found.
5. Biochemically, an increase of glucose in serum was distinct.
6. In mercurialism of cattle, it seems that the onset differs with the individual sensitivity to mercury.

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EXPLANATION OF PLATE

- Fig. 1. Depilation and thickening of the skin (severe case).
- Fig. 2. Depilation on the body surface (moderate case).
- Fig. 3. Dermatitis on the udder (severe case).
- Fig. 4. Eczema on the inside of the knee (slight case).
- Fig. 5. Petechial hemorrhage on the vaginal mucous membrane (severe case).
- Fig. 6. Salivation (severe case).

