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AN OUTBLEAK OF ACUTE ARSENIC POISONING CAUSED BY ARSENIC CONTAMINATED SOY-SAUCE (SHŌYU) : A CLINICAL REPORT OF 220 CACES

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At the beginning of January 1956, an outbreak of acute poisoning due to soy-sauce (shōyu) accidentally contaminated by arsenic (probably calcium arsenate) has occurred in the city of Ube, Yamaguchi Prefecture. Fortunately, the number of the patients was limited to 417 with no mortality owing to the early recognition of the true nature of the poisoning and immediate effective preventive procedures that were taken.

We wish to report the clinical picture of 220 cases, the majority of which showed symptoms that was somewhat different from those appearing in the literature. Another peculiarity of this series is that the arsenic was contained in soy-sauce.

The arsenic content of the soy-sauce which caused this accident was estimated to be about 0.1 mg per milliliter.

CLINICAL SYMPTOMS

I. Subjective Symptoms

The subjective symptoms presented by the 200 paitients were as follows; (i) edema of face, (ii) gastrointestinal symptoms (anorexia, nausia, epigastric fullness, epigastric and abdominal pain, vomiting, diarrhoea, opstipation and general fatigue), (iii) upper respiratory symptoms (headache, chillness, rhinorrhoea, sore-throat, cough, fever, eye-wax, sputum and joint-pain), (iv) skin symptoms (itching, desquamation and exanthema), and (v) symptoms of peripheral

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neuropathy (hypesthesia of legs). Edema of face, gastrointestinal and upper respiratory symptoms constituted the main symptoms of this series of arsenic poisoning. (Fig 1)

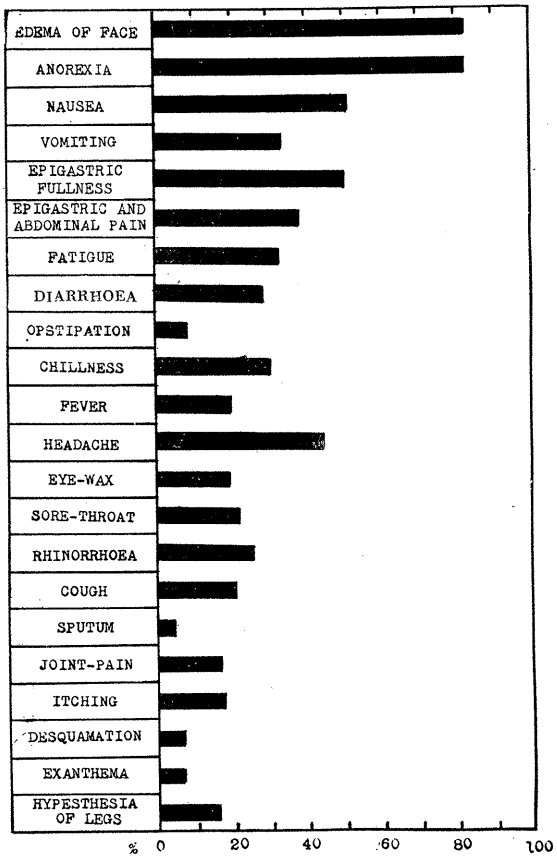

Fig. 1 Frequency of Subjective Symptoms

In most patients the onset was characterized by the appearance of edema, gastrointestinal or upper respiratory symptoms. Symptoms of skin and neuropathy appeared in the late stage, especially the latter appeared between the 11th and 20th day of illness.

Each symptoms tended to subside gradually from the 5th day of illness, despite continuous intake of the poison. Edema and gastrointestinal symptoms diminished rapidly from the end of the second week when the arsenic take was stopped, but the upper respiratory symptom persisted probably because of the season being winter. On the other hand, lesions of the skin was observed occasionally in the late stage. Symptoms of peripheral neuropathy appeared more frequently at later stage, coming on even after the cessation of arsenical intake.

(Fig. 2)

The onset of illness two days after the ingestion of arsenic soy-sauce was most frequent, the incidence becoming less frequent day by day thereafter. There

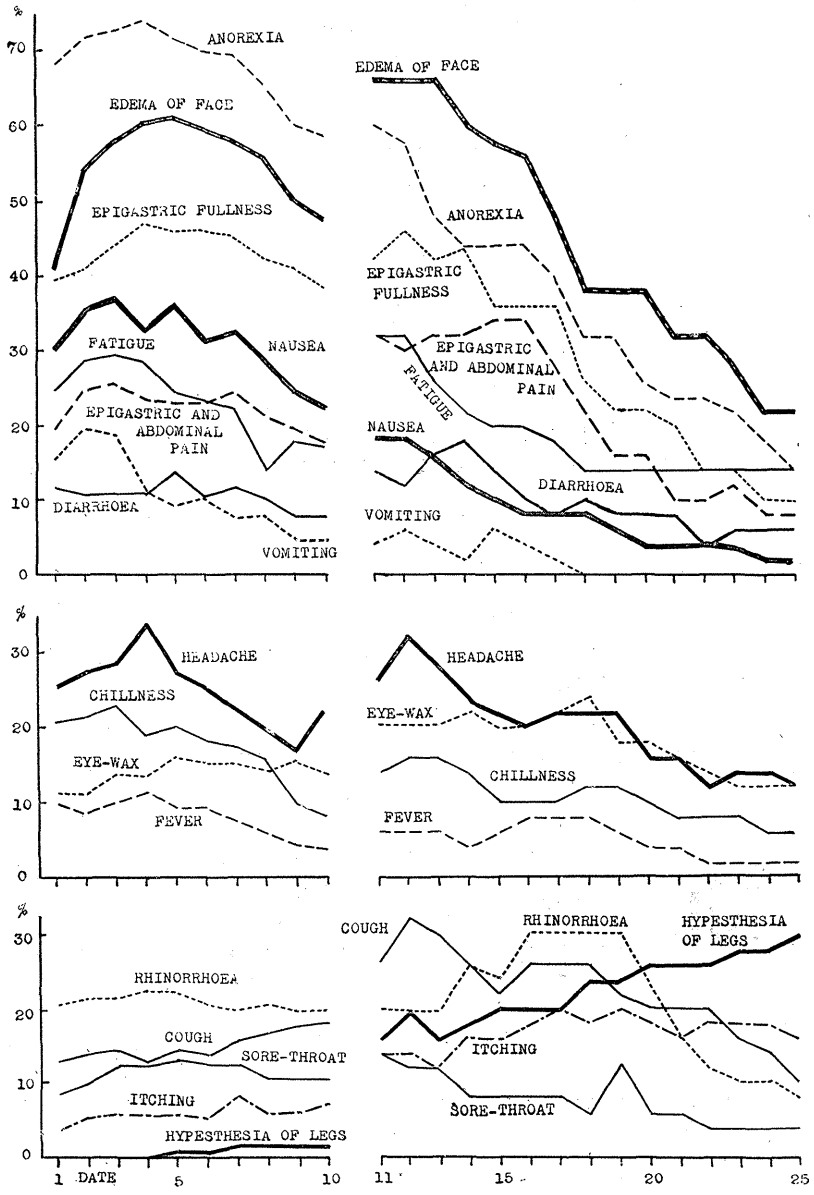

Fig. 2 Course of Subjective Symptoms

were also some cases in which the onset took place as late as 20 days after having taken arsenic containing soy-sauce, but these were all of peripheral neuropathic nature (Fig. 3)

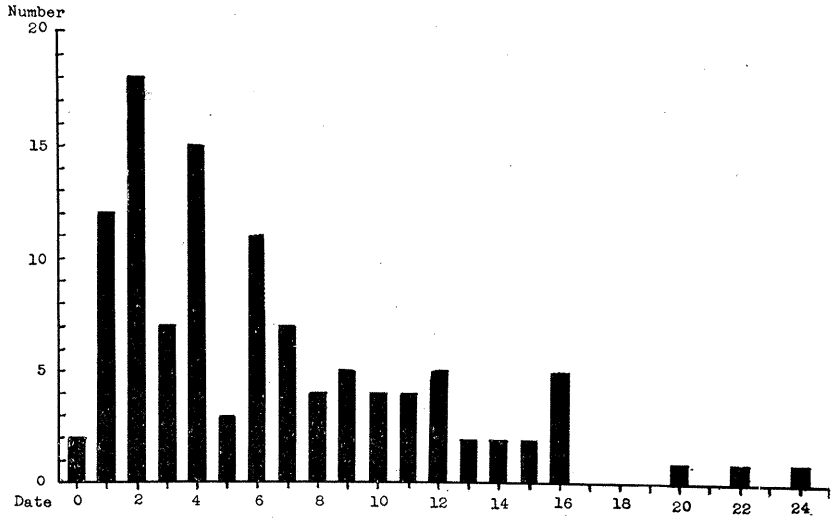

Fig. 3 Appearance of Symptoms after Taking Arsenical Soy-Sauce

II. Objective Symptoms

Edema of the face, especially of the eye-lids, was the most remarkable symptom and its frequency was mentioned above. General edema was not found except in three elderly patients with hypertension, in whom it was limited

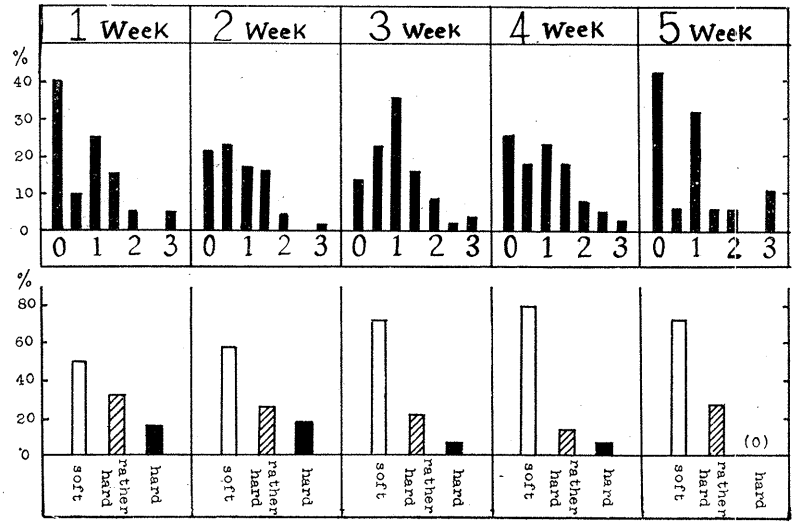

Fig. 4 Change of Liver in Size and Consistence

to the legs. The edema had continued for about 10 days and disappeared quickly soon after the suspension of the arsenic intake.

Heart and lungs were normal. Blood pressure was estimated in 62 patients, 55 of whom showing normal value, five hypertension and two hypotension.

In the majority of patients, the liver was enlarged to the extent of one or two finger breadths in the course of time and gradually decreased in size after excluding the poison from food. In the entire course of the disease the liver was soft or slightly firm in consistency. The patient showing an somewhat hard liver enlarged as much as three finger breadths was considered to be suffering from some other disease. (Fig. 4)

After the second week the abnormal patellar reflex was found in over 50 per cent, whereas it was abnormal in only 10 per cent of caces in the first week.

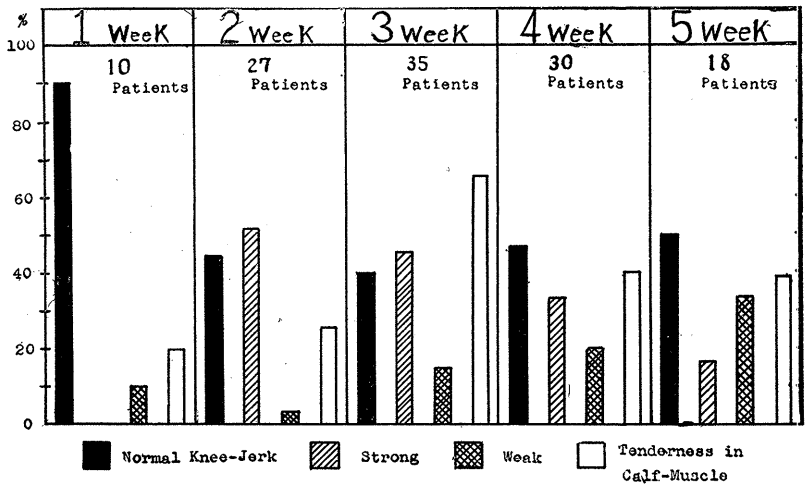

Fig. 5 Patellar Reflex and Tenderness in Calf Muscle

It did not readily return to the normal state even after the suspension of arsenic. The calf muscle was tender in 65 per cent of cases in the third week, whereas it so in 20 per cent in the first week. It also failed to return readily to the normal state after the exclusion of the poison. (Fig. 5)

TAEBL I

Skin Signs (225 Cases)

Herpes labialis	7	Cases	3.1 %
Perifoliculitis	5	〃	2.2 %
Exanthema	7	〃	3.1 %
Pigmentation	12	〃	5.3 %
White-spot	3	〃	1.3 %

As stated elsewhere, skin lesions appeared generally late in the disease, and very mild in character except in one patient who was considered to be hypersensitive to arsenic. (Table 1, Photo. 1, Photo. 2)

III. Ophthalmological Findings

Seventy patients were examined ophthalmologically and the findings were

TABLE II

Ophthalmic Troubles (70 Patients)

Symptom	Total	(%)
Discharge	32	(46 %)
Lacrimation	17	(24 %)
Itching	20	(28 %)
Conjunctival hyperaemia in lids crevice	20	(28 %)
Edema of eye-lids	61	(68 %)
Dimness of vision	18	(25 %)
Myodesopsia	7	(10 %)
Photophobia	3	(4 %)
Asthenopia	6	(8 %)

listed in Table 2. Relative central red scotoma, which was occasionally observed in the so-called toxic amblyopia, was demonstrated in 13 patients (18.6 %).

TABLE III

Ophthalmologic Findings of Typical Patients

Patient	Age	Sex	Central Scotoma	Findings of Fundus	Course of Visual Power
Y. M.	21	F.	+	Hyperemia of optic distk; Retinal muddiness around the papilla; Veins much distended and tortuous	18/I 1/II R. 0.8...1.0 L. 0.6...0.9
S. F.	27	M.	+	Marked retinal muddiness around the papilla; Veins much distended and tortuous	28/I 6/II R. 0.1...1.0 L. 0.1...1.0
H. T.	14	F.	+	Retinal muddiness around the papilla; Distended and hypertrophic veins	R. 1.0 L. 1.0

There was no apparent relation between the severity of the disease and the frequency of the scotoma. The "Kaninchenauge" was found in two patients. Three patients with retino-neuritis have eventually recovered the visual power as shown in Table 3. Only two patients had the concentric contraction of the field of vision, The iris, lens body, eye muscles and light reaction were normal.

IV. Laboratory Finding

(1) Hematological Findings

Abnormalities in the peripheral blood were frequently found among 32 patients examined. In some patients the lowered red-cell counts ranged from 3,000,000 to 4,5000,000 in the second week of illness. Leucocyte counts showed in the second week of the illness a tendency toward reduction, ranging from 3000 to 6000, with relative lymphocytosis of from 50 to 60 per cent. The basophilic stippling of red-cell was found in two patients. Bone-marrow cells examined in 5 patients were almost normal after the 4th week of illness.

(2) Urinalysis

Proteinuria was positive in 15 out of 170 patients. This proteinuria, however, cannot be due to the arsenical poisoning, since its incidence percentage was partially equal to that of hypertension.

Glycosuria was tested for 58 patients, and was found negative in all. Urinary urobilinogen was positive in 60 per cent and many of these were strongly positive in the first week. Percentage of urobilinogen positive cases increased to 80 per cent in the second and third weeks, followed by rapid decrease after the suspension of arsenic intake. Positive urobilinogen was only 10 per cent in the 5th week and no case with strongly posititive urobilinogen was found after the 4th week of illness (Fig. 6)

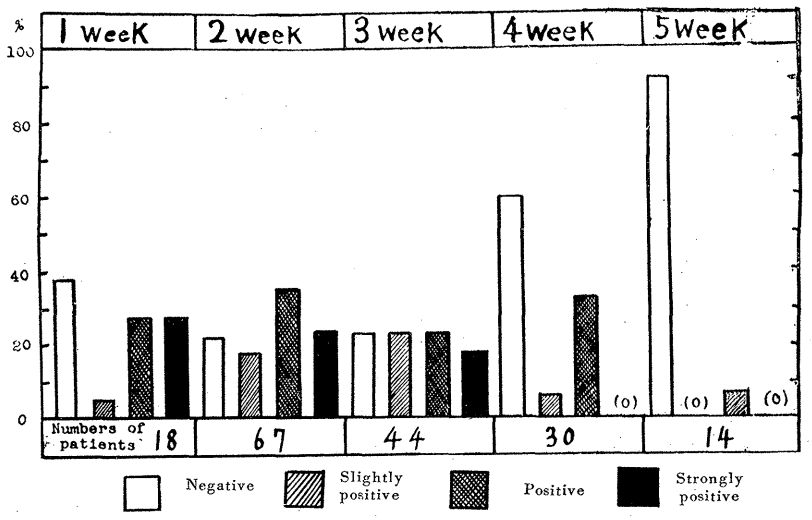

Fig. 6 Urobilinogen

(2) Fecal Examination

Some patients complained of the black colored feces in the early stage of illness and two patients had mucosanguinous stool resembling dysentery feces. The

mucous feces was noticed in many patients. The occult blood was tested for 34 patients during the 2nd and 3rd weeks and found positive in 85 per cent.

(4) Occult Blood in Gastric and Duodenal Juice

The occult blood of the gastric juice was examined in 6 cases and was found positive in all. That of duodenal juice was positive in 5 out of 7 patients. The acidity of the gastric juice was almost normal. (Table 4)

TABLE IV

Occult Blood in Gastric and Duodenal Juice

Patient	Date	Gastric Juice		Duodenal Juice
		Acidity	Occult Blood	Occult Blood
Tu. F.	19	30	++	++
F. M.	20	40	−	
N. M.	21	13	++	++
Y. M.	24	50	−	+
Te. F.	24	35	++	+
H. K.	24	20	++	+
T. Y.	27	10	++	+

(5) Biochemical Examination of Blood

The results of the biochemical exmination of blood are shown in Table 5. The following examinations were made; hematocrit, hemoglobin, blood sedimentation rate, serum albumin, serum grobulin, A/G ratio, serum ictric index, cephalin-cholesterol flocculation test, serum cholinesterase activity, serum total alkalin phosphatase, phenol turbidity test, serum total cholesterol, serum nonprotein nitrogen and serum urea.

Abnormal values were occasionally met with as the symptoms became aggravated. However, these abnormal values were milder than those of hepatic disturbances as usually observed in our laboratory. Moreover, it seems that such results were obtained in the later stage because the examination was made on selected patients showing aggravated symptoms.

The frequency of abnormal value in each week is shown in Fig. 7. Reversed A/G ratio, positive CCF test, increased phenol turbidity test and accelerated blood sedimentation rate were observed more frequently with the progress of illness. Low hematocrit percentage, low hemogrobin value, high serum alkaline phosphatase and high serum icteric index were observed to be highest in the second week and tended to return to the normal level subsequently. High serum total cholesterol was noticed frequently in the third week. High serum cholinesterase activity, low serum protein, high urea and high serum nonprotein nitrogen were observed most frequently in the first week and were only rarely ob-

TABLE V

Biochemical Analysis of Blood

Name	Age	Sex	Date	Hematocrit (M)40–55 % (F)35–45 %	Hemoglobin (M)14–18mg/dl (F)12–16mg/dl	Blood segmentation rate(0–10mm)	Serum protein (6.5–8.0gr/dl)	A/G(1.1–1.8)
E.K.	61	F	4	38.2	12.5	4	6.6	1.24
M.Y.	19	M	4	50.6	17.1	0	**8.3**	1.14
T.N.	22	F	4	40.6	14.1	3	7.1	1.45
S.I.	29	M	4	—	—	—	—	—
S.T.	29	F	5	—	—	—	7.7	1.41
R.T.	50	F	7	49.6	16.4	0	7.7	1.33
M.T.	55	M	7	40.2	14.0	1	**6.4**	1.20
S.F.(1)	27	M	8	—	—	—	7.9	1.38
K.Y.	66	M	8	—	—	—	7.3	1.44
S.K.	38	F	8	**33.6**	**11.8**	**38**	7.5	**0.92**
S.Y.	69	F	8	—	—	—	7.1	**1.00**
M.O.	43	F	9	—	—	—	7.4	1.38
K.O.	49	F	9	—	—	—	8.1	1.32
K.A.	38	M	9	46.0	15.3	0	**6.4**	1.38
H.T.	20	F	9	37.6	12.6	7	7.8	**1.16**
K.S.	51	M	10	—	—	—	7.0	**1.04**
Y.K.	38	F	10	**28.8**	**9.0**	3	6.7	1.44
K.Y.	35	F	11	38.2	13.3	3	6.8	1.27
S.Y.	42	F	12	—	—	—	6.8	1.38
T.U.	41	F	12	—	—	—	7.0	1.27
K.N.	36	M	12	**39.4**	**12.9**	0	**5.6**	1.29
F.N.	36	F	12	**32.8**	**10.7**	4	7.4	**1.00**
M.N.	29	M	12	—	—	—	—	—
M.K.	48	M	12	45.1	14.4	1	7.0	1.38
F.M.	40	F	12	43.6	14.3	6	7.8	1.10
S.Y.	42	M	13	—	—	—	7.8	1.56
A.N.(1)	18	F	13	37.0	12.2	2	**6.0**	—
S.I.	47	F	13	**34.6**	**11.9**	0	6.7	1.92
M.F.(1)	39	F	13	**34.7**	**11.9**	10	7.7	**0.97**
T.U.	46	M	14	**38.2**	**12.9**	8	7.4	1.27
M.N.	33	M	15	41.8	14.0	1	6.9	1.24
T.F.(1)	30	M	15	—	—	—	—	—
M.Y.	41	F	18	**26.3**	**7.9**	**18**	7.1	**1.08**
T.A.(1)	32	F	18	**34.5**	12.5	5	7.2	1.44
A.N.(2)	18	F	18	—	—	—	7.3	**0.96**
M.N.	17	F	20	39.0	12.9	1	8.0	1.24
T.F.(2)	31	M	20	45.0	13.6	1	7.1	**1.00**
Y.M.	23	F	21	—	—	—	8.3	**0.85**
N.M.	61	F	22	**26.0**	**9.0**	**43**	6.9	**0.88**
K.N.	30	F	23	36.8	12.9	4	7.8	1.13
H.K.	32	M	23	41.1	14.1	0	7.6	**1.82**
S.F.(2)	27	M	25	47.3	16.7	0	7.4	**1.06**
T.A.(2)	32	F	27	39.1	13.3	3	7.5	1.58
T.Y.	15	M	29	44.9	14.6	2	8.4	1.15
H.N.	53	M	31	**21.2**	**6.2**	**48**	6.8	**0.75**
M.F.	39	F	32	46.2	16.3	4	7.5	**1.08**

TABLE V

Biochemical Analysis of Blood

Serum albumin (3.7–4.8gr/dl)	Serum globulin (2.5–3.5gr/dl)	Icteric index (3–7)	C.C.F.T. (0)	Cholinesterase (ΔpH 0.7–1.1)	Alkaline phosphatase (1–5u.)	Cholesterol 150–300mg/dl	Phenol turbidity test (8–15u.)	NPN (20–30mg/dl)	Urea N 6–15mg/dl
3.6	3.0	3	0	0.7	4.8	150	13	26	**18**
4.4	3.9	4	0	0.9	5.8	180	10	**39**	**20**
4.2	2.9	5	0	0.8	2.1	200	14	25	11
—	—	—	0	**0.6**	3.7	—	13	—	—
4.5	3.2	4	0	0.9	2.4	225	**20**	23	11
4.4	3.3	5	0	0.7	3.1	255	**21**	23	11
3.5	2.9	4	0	0.8	4.4	200	15	28	**21**
4.6	3.3	**10**	0	0.9	**6.3**	198	**20**	26	15
4.3	3.0	3	0	0.8	6.0	220	**21**	20	8
3.6	**3.9**	3	0	0.7	2.6	187	15	20	9
3.6	3.5	4	0	1.1	3.5	140	10	28	14
4.3	3.1	4	0	1.0	4.9	175	14	19	11
4.6	3.5	**10**	0	0.9	7.0	190	**20**	28	15
3.7	2.7	3	0	0.8	3.4	100	6	**33**	**21**
4.2	3.6	4	**1**	0.7	2.6	—	11	22	11
3.6	3.4	4	0	0.9	**8.2**	175	15	26	10
4.0	2.7	4	0	0.8	1.8	155	15	23	13
3.8	3.0	4	0	1.1	2.4	127	8	27	**19**
3.9	2.9	4	0	**0.6**	3.8	170	**16**	16	10
3.9	3.1	7	0	1.1	6.0	175	15	23	13
3.5	**2.1**	5	0	0.8	4.3	—	14	19	10
3.7	3.7	5	**1**	1.1	5.3	—	13	22	11
—	—	—	**4**	1.1	2.5	—	**35**	—	—
4.1	2.9	**10**	0	0.7	3.8	—	—	**31**	**16**
4.1	**3.7**	5	0	0.8	1.8	—	**39**	25	11
4.7	3.1	**10**	0	1.0	4.2	190	15	22	13
—	—	3	0	**0.6**	3.8	160	11	23	12
4.4	**2.3**	4	**2**	0.8	3.6	205	15	19	6
3.8	**3.9**	5	0	**0.5**	2.0	165	11	19	7
4.2	3.2	5	0	0.9	5.5	150	9	29	**17**
4.2	2.7	4	0	0.9	4.4	175	10	25	13
—	—	—	0	0.8	4.3	—	13	—	—
3.7	3.4	3	0	0.9	3.2	150	10	16	8
4.3	2.9	3	0	1.2	3.1	150	10	23	11
3.6	**3.7**	3	0	**0.6**	3.8	160	**20**	22	11
4.7	3.3	3	0	0.9	**8.5**	205	14	**37**	**16**
3.6	3.5	3	0	0.9	5.3	175	10	**32**	10
3.8	**4.5**	3	**2**	1.0	3.7	290	**16**	28	10
3.2	**3.7**	4	**2**	0.9	3.9	172	9	31	11
4.1	**3.7**	2	**3**	0.9	2.6	215	**18**	23	15
4.9	2.7	5	0	1.0	7.6	175	10	22	10
3.8	**3.6**	5	0	0.9	3.4	230	**17**	**32**	**19**
4.6	2.9	3	**3**	1.0	3.0	168	13	15	8
4.5	**3.9**	3	0	1.1	**12.6**	250	**28**	25	11
2.9	**3.9**	6	**3**	**0.5**	3.3	145	10	18	8
3.9	**3.6**	3	0	1.0	2.7	228	13	23	10

served most frequently in the first week and were only rarely observed in the second week. The elevated nonprotein nitrogen, however, reappeared frequently in the third week.

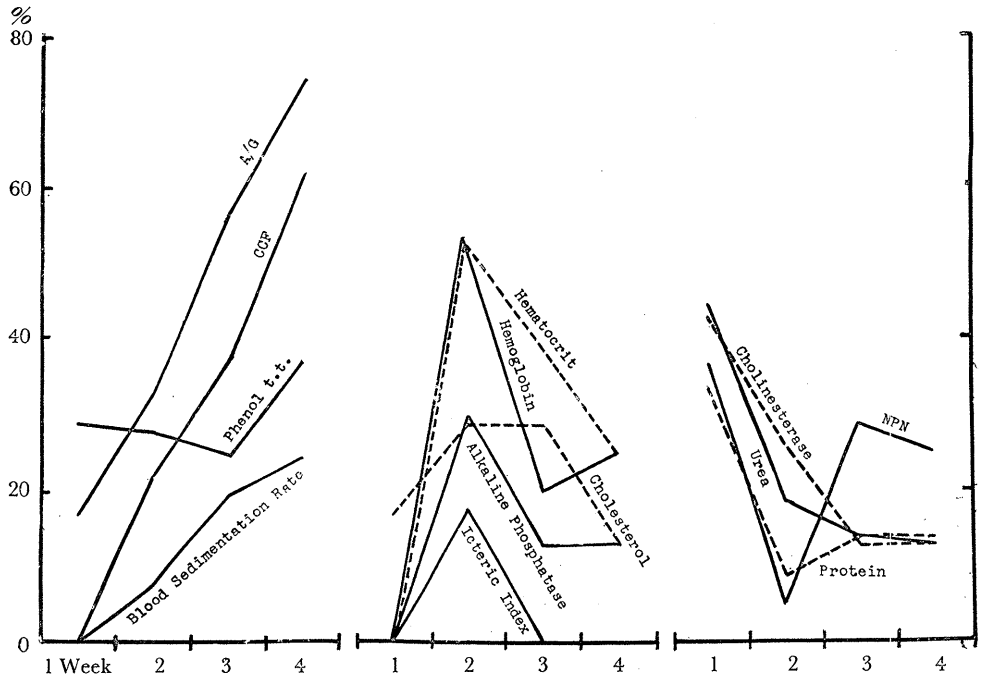

Fig. 7 Frequency of Abnormalities in Biochemical Analysis of Blood

TABLE VI

Serum Electrolytes and Renad Renal Urea Clearance

Week \ Normal Range	Na	K	Ca	Cl	Co_2	Urea Clearance
	134 | 146	3.6 | 5.2	4.3 | 5.8	100 | 110	27 | 34	Above 50%
	mEq/l					
1	149	3.7	4.4	107		
	138	4.2	5.1	102		
	138	4.6	5.0	103		
2	140	5.4	4.9	98		93 %
	134	4.1	5.0	103		
	134	4.5	4.9	102		73
3	134	4.8	5.0	105		53
	140	5.0	4.2	108		51
4	135	4.5	5.1	102	31	70
	135	5.3	6.0	103	27	41

The serum electrolytes (Na, K, Cl, CO_2) were nearly normal and the renal urea clearance was normal in 5 out of 6 patients. (Table 6)

(6) Liver Function Tests

Bromsulfalein retention test was made in 11 patients and was found normal in all, indicating absence of impaired dye-excretory function of the liver. (Fig. 8)

Protein-loading urobilinogen test which is employed in estimating urinary

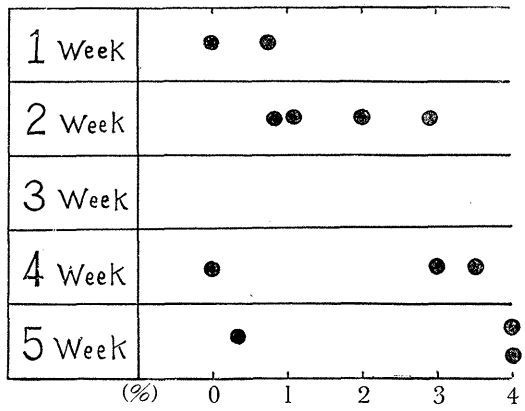

Fig. 8 Bromsulfalein Retention Test (30 Minits' Method)

urobilinogen after loading with milk and eggs can be applied in determination of the index of detoxicating capacity of the liver.[1] This test carried out in 19 patients showed the imparied function in all cases in the second week, which has gradually turned to normal afterwards. (Fig. 9)

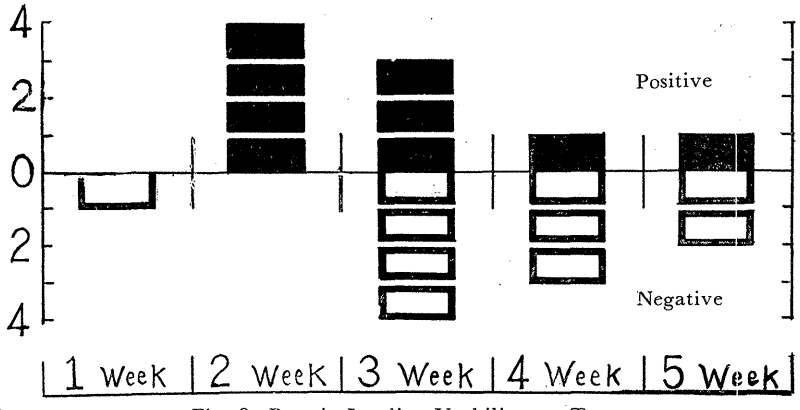

Fig. 9 Protein-Loading Urobilinogen Test

The hippuric acid test, protein-loading urobilinogen test and bromsulfalein test in the same patients also indicated the dissociation between the dye-excreting function and detoxicating function of the liver. (Table 7)

(7) Electrocardiographic Findings

Electrocardiograms of 20 cases were studied and were abnormal in 16, con-

sisting of altered Q–T interval and P- and T-waves. (Table 8) These abnorma-

TABLE VII

Liver Function Test in Individual Case

	Hippuric Acid Test		Protein-Loading Urobilinogen Test		BSP Test (30 Minuts)	
T.Y.	+	28*	+	32*	—	—
H.M.	−	15	+	11	3.5%	25*
S.H.	+	26	−	28	—	—
Y.M.	−	21	−	21	3.0%	21
N.M.	+	21	+	21	0%	22
H.K.	+	29	+	21	2%	27
T.H.	+	28	−	32	4%	28

* Date of Examination

lities were found absent on re-examination after the recovery of the clinical symptoms.

TABLE VIII

Electrocardiographic Findings

Examined Cases	20
Abnormal Cases	16
Tachycardia	5
Bradycardia	0
Arrhythmia	1
Pulmonary P	7
PQ-prolongation	0
QRS-change	0
QT-prolongation	4
QT-shortage	1
ST-depression	1
T-wave change	5
Low voltage	0

(8) Liver Biopsy

Biopsy materials of the liver were obtained from 5 patients and uniformly presented the following findings. The arrangement of the hepatic cells were very slightly disordered, individual cells markedly swollen and slightly hyalinated. The nuclei were generally slightly swollen; in some few areas they have undergone either dissolution or complete disappearance. Granules of bile pigment were richly found within the cells as well as extracellularly formed bile thrombi in some areas. The *Kupffer's* cells were swollen and the cell bodies were stained acidophilic. The wall of the vessels in the *Glisson's* sheath was hypertrophic with marked hyaline degeneration. The blood vessels of the lobules were slightly dilatated. In some cases small homorrhagic foci were scattered in the

lobules. The *Disse's* space was rather dilatated. In some cases a scattered small necrosis around the central area or a slight fibrosis of the lobules was observed. Fatty degeneration was absent on Sudan III stain. Glycogen was maintained normally on PAS stain (periodic acid Shiff's stain). On Unna-Pappenheim's stain, RNA was decreased and accumulated around the nucleus and also DNA was rather decreased. (Photo. 3, 4, 5, 6)

V. Excretion of Arsenic

The excretion of arsenic by way of urine, gastric juice and duodenal juice (C-bile) was shown in Fig. 10. With a wide range of individual differences, arsenic was demonstrated in the urine in appreciable concentration even 19 days after the suspension of arsenic intake. One of cases excreted it in urine in the concentration of 8.85 mg per liter on the 5th day after its suspension.

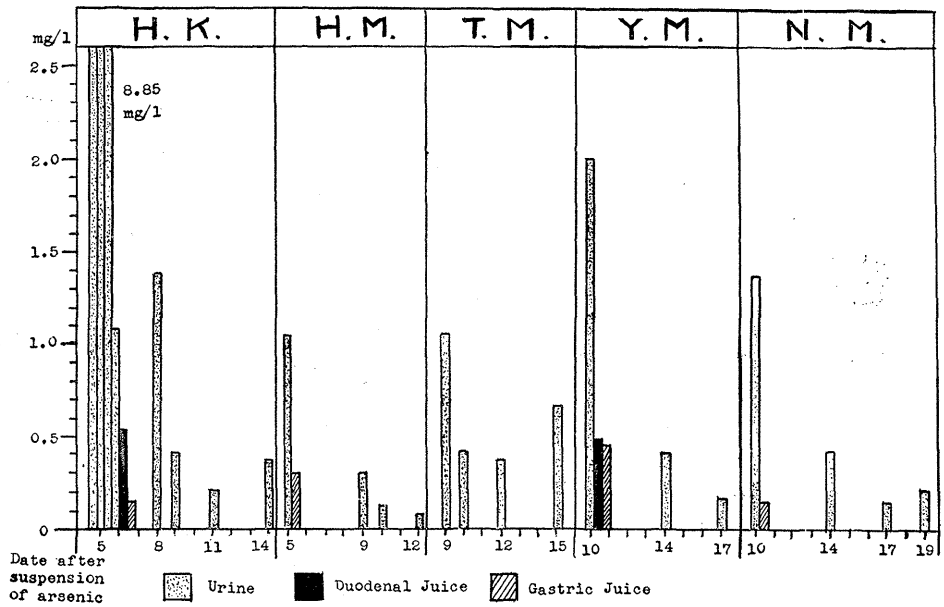

Fig. 10 Concentration of Arsenic in Urine, Gastric Juice and Duodenal Juice after Suspension of Arsenic Intake

Its excretion in the duodenal juice was higher in concentration than the gastric juice in which its concetration was far less than in the urine (6–25%).

VI. Amounts of Arsenic in the Hair

The arsenical content in hair about 2 weeks after suspending arsenic take was found to be quite high as is shown in Table 9. The root portion contained more arsenic than the rest of the hair.

Discussion

One of the most tragic accidents of the arsenical poisoning due to arsenic contaminated food was that of poisoning by arsenical beer of Manchester, England (1900),[2] and that of arsenical dry-milk poisoning in Japan.[3)4)]

Table IX

Amounts of Arsenic in Hair

Patients \ From the Root	0~1cm	1~4cm	4~7cm	7cm~End
Y.Y.	13.0	1.6	1.5	1.5γ/gr
N.M. / Y.M. / N.F. Average	6.6	2.4	2.2	1.8
F.M.	3.8		0.6	0
Control	0.4 , 2.8			

The symptoms of arsenical poisoning are those of catarrh, neuritis and skin lesion. The essential symptom of acute arsenical poisoning, such as arsenical gas poisoning,[5] is limited to that of catarrh. The main symptoms of chronic beer poisoning[2] are peripheral neuropathy and skin lesion, and those of chronic arsenical dry-milk poisoning[3)4)] are skin lesion and liver damage.

In our arsenical soy-sauce poisoning, the duration of arsenic ingestion was only 2 or 3 weeks in most of the cases and the main symptoms were catarrh and edema of the face, while the skin lesion and neuropathy were mild and but rarely observed. Edema was mentioned only in a few reports; one of them being that of arsenical beer poisoning,[2] in which a slight degree of edema was found limited to the vicinity of eye-lids. Another instance is that of arsenical dry-milk poisoning,[3] in which edema was observed in 38% of cases, not limited to the face. It is difficult to explain the genesis of this edema of the face from the results of the serum electrolytes, blood pressure and heart and renal functions. It might possibly be explainable by assuming an increase of the capillary permeability.

The arsenic content of the beer in the arsenical poisoning was 2–4 mg per liter. In the arsenical dry-milk poisoning it was 1.5–3.6 mg per 100 gm, and it was presumed that infants became ill after taking 3.5 mg of arsenic daily for 33 days.[3] In our arsenical soy-sauce poisoning the arsenic content was 10 mg per 100 ml; and 3 mg of arsenic was estimated to be ingested daily. While its daily intake was thus equal to that of dry-milk, the symptoms of poisoning

appeared in a few days after the beginning of arsenic intake. The difference in sensitiveness to arsenic between soy-sauce and dry-milk might be caused by presence or absence of protein.

It has been generally recognized that anemia, leukopenia with relative lymphocytosis, and basophilic stippling of erythrocyte are observed in the arsenical poisoning. Similar finidings were observed also in our cases, though they were rather mild. We failed to find marked changes in the bone marrow cells; it seems that the examination was made too late in the stage or the poison may have been too small in amount to produced the change.

As a rule, diarrhoea is one of the catarrhal symptoms of the arsenical poisoning, but hematemesis and bloody feces have scarcely been reported.[5] We have occasionally observed diarrhoea and gastric, duodenal and colonic hemorrhage.

The fact that liver is frequently enlarged and hard has been reported recently in arsenical dry-milk poisoning,[3)4)] as well as in other instances of arsenical poisoning.[6)7)8)]

Nagai and his associates[4)] have reported that the the serum cobalt reaction is slightly abnormal in 68 per cent of the arsenic poisoned patients, but *Hamamoto*[3)] and *Heyman et al*[9)] have not observed any definite abnormality of the serum flocculation tests. We have observed that the abnormalities of clinical laboratory tests of serum were insignificant, despite an enlarged liver.

It has been generally recognized that the urobilinogen is markedly increased in the urine in arsenical poisoning.[3)4)] We have observed that the urinary urobilinogen, the protein-loading urobilinogen test and the hippuric acid test became positive in the early stage of the illness, suggesting that the detoxicating function of the liver was disturbed.

While *O'Leary et al*[7)] and *Hamamoto*[3)] have noticed that the bromsulfalein retention test is normal, *Nagai et al*[4)] and *Silver*[6)] have found it to be delayed. We could not find any disturbance of the dye-excreting function of the liver in the early stage of arsenical poisoning. Furthermore, *Watanabe*,[10)] in our clinic, has demonstrated that the bile-output and dye-excretion in the bile are greatly accelerated by feeding rabbit arsenic containing soy-sauce at the dose of 0.1 mg of arsenic per kg of body weight for 7 days.

The histologic changes of the liver, such as hemorrhagic necrosis and fatty degeneration, have been observed in arsenical poisoning.[4)6)11)12)] In our biopsy specimens of the liver, we have observed slight but definite changes such as cell degeneration, jaundice, small patches of necrosis scattered around the central area,mild fibrosis of the lobules and decrease of nucleic acid in liver cells. However, we could not find any change in either fatty degeneration or glycogen reduction of the liver. It must be pointed out that the clinical laboratory tests of the blood guggested only a slight involvement of the liver, whereas the biopsy

revealed very definite degenerative changes.

Of ophthalmological complications we observed conjunctivitis and edema of the eye-lids which are well recognized in the literature. We wish to place on record the occurrence of so-called "Kaninchenauge" in the some instaces of arsenical poisoning. We were also able to confirm the neuro-retinitis, described by *Uhthoff* (1904), and relative central red scotoma, described by *Liebrecht* (1891), as occurring in arsenical poisoning.

In the electrocardiographic examination, abnormalities of S-T level, Q-T interval, and P- and T- waves have been observed.[3)4)5)9)12)] We have confirmed both these findings and their reversibility.

There are many reports in the literature concerning the high arsenic content of the hair in arsenical poisoning.[4)9)14)15)] We have confirmed the high content of the arsenic in it and it was contained more abundantly in the root portion of the hair.

Among the numerous reports on the excretion of arsenic, *Pavy*[16)] states that in acute poisoning arsenic disappears from urine 8 to 10 days after the suspension of the arsenic intake, while in chronic poisoning it is demonstrable in urine 26 to 31 days afterwards and this prolonged excretion may represent a release of arsenic from various tissue stores, such as liver, spleen and kidneys. *Frekel-Heiden* and his associates[17)] report that the amount of arsenic excreted in the feces is 8 times that of urine, but *Nagai et al*[4)] maintain that the urinary arsenic excretion is rather higher than the fecal.

There have been but a few reports concerning the excretion of arsenic in the bile. *Kuroda*[18)] has demonstrated by experiments on dogs that salvarsan injected subcutaneously is excreted in feces and bile in equal amounts, which amounts to 25 to 30 per cent of that excreted in the urine. In our cases we have observed that the urinary arsenic excretion continued even 19 days after the suspension of arsenic intake, and that its excretion in both gastric and duodenal juices took place but the concentration was only 6 to 25 per cent of that in the urine.

Summary and Conclussion

In the preceding pages we have tried to draw a clinical picture of acute arsenic poisoning from soy-sauce accidentally contaminated which occurred in the City of Ube, Yamaguchi Prefecture, in January 1956. The main symtoms observed in 220 cases out of the total 417 patients were edema of the face, gastrointestinal and upper respiratory symptoms followed by skin lesions and neuriritic signs which occurred in a limited number of patients in the late stage. In the majority of patients, the symptoms appeared 2 days after the intake of arsenic and subsided gradually after the 5 th or 6 th day of illness, despite continuous intake of the poison. These symtoms disappeared rapidly two weeks

after eliminating the arsenic contaminated sauce from the diet. Neuritic symptoms, on the other hand, began to get aggravated later in the second week after suspension of arsenic intake.

The liver was palpable as enlarged for one or two finger breadths in most of the cases, and returned to the nomal size in convalescence. Electrocadiogram revealed abnormalities in Q-T interval and P- and T- waves. Ophthalmologically, conjunctivitis, central scotoma and neuro-retinitis were detected.

Laboratory data indicated slight anemia, leukopenia, relative lymphocytosis, positive urinary urobilinogen in 60 to 80% of the cases, normal electrolytes and urea clearance. Fecal occult blood was positive in many of the patients, and in some, occult blood was demonstrable in gastric and duodenal juice. Chemical analysis of serum was suggestive of slight but definite degenerative changes such as decrease of nucleic acid in liver cells. Hepatic detoxicating function was impaired in about half of the case, but BSP test remained normal.

Arsenic was demonstrated in urine in an appreciable concentration even two weeks after the suspension of arsenic ingestion. A low arsenic concentration was also detected in both gastric and duodenal juice. The root portion of the hair contained more arsenic than the rest of the hair.

The duration of arsenic ingestion was two or three weeks in most of the cases, and arsenic content of the soy-sauce which caused this accident was estimated to be about 0.1 mg per milliliter.

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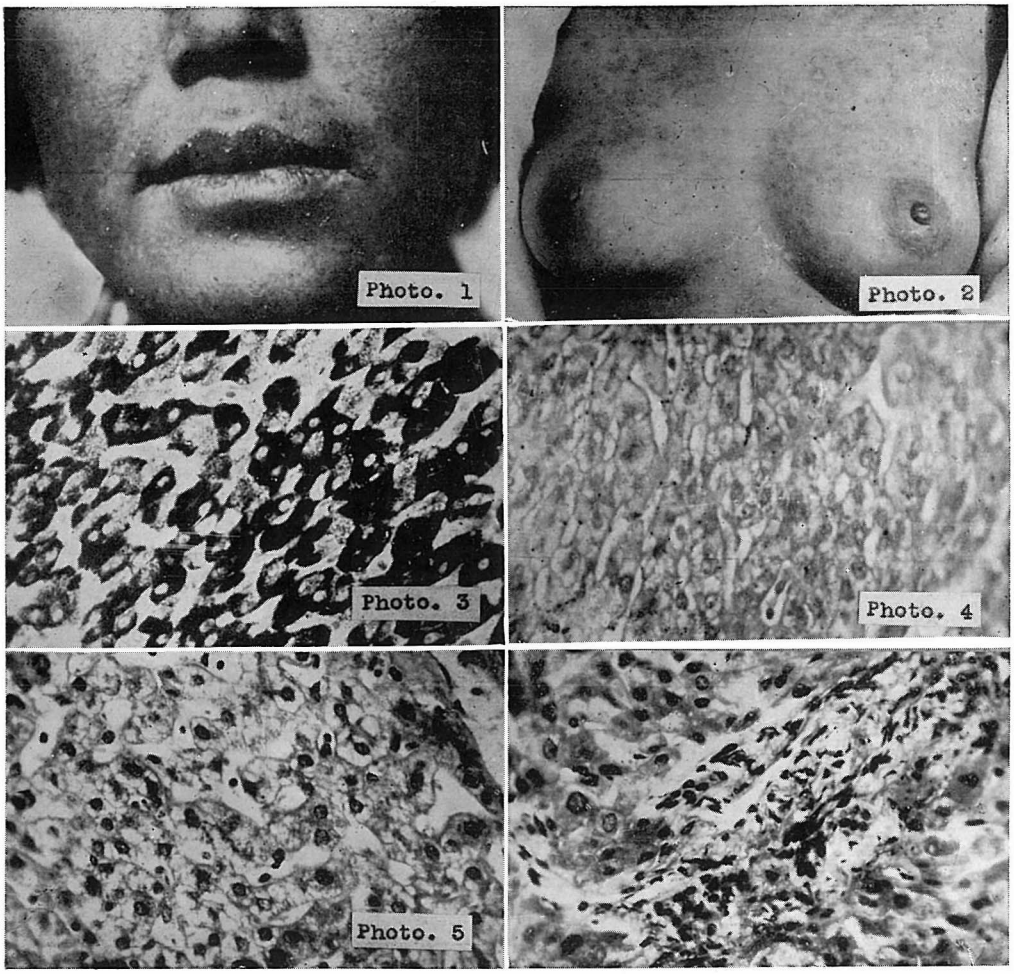

Photo. 1., Photo. 2. : Y. M. 23 years old. A case of remarkable exanthema.
Photo. 3. : I. K. PAS stian : Normal liver glycogen.
Photo. 4. : I. K. Unnna-Pappenheim's stain ; Decreased RNA and DNA in liver cells.
Photo. 5. : I. K. Hematoxylin-Eosin stain ; Degeneration in liver parenchyma.
Photo. 6. : S. Y Hematoxylin-Eosin stain ; Fibrosis and cellular infiltration in Glisson's sheath.