

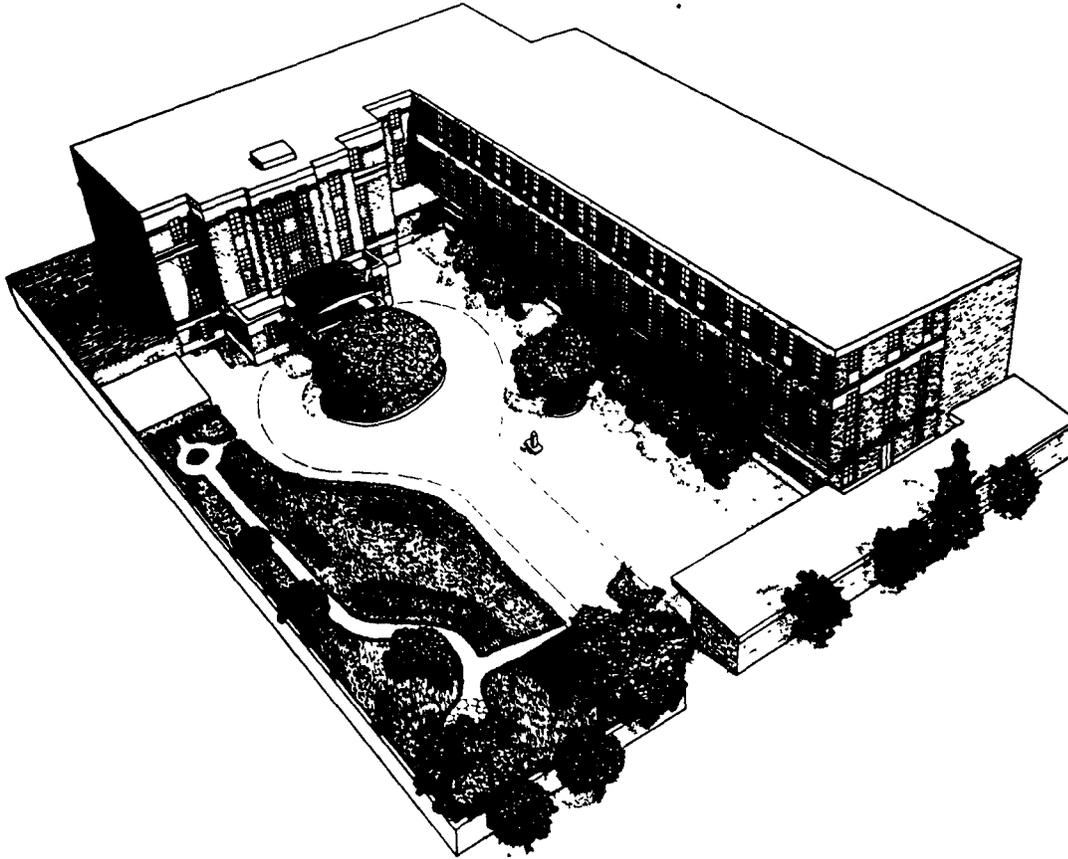
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Tissue copper, zinc, and manganese levels in  
Wilson's disease: Studies with the use of neutron  
activation analysis



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United States Naval  
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Taipei, Taiwan

CLINICAL INVESTIGATION DEPARTMENT

Jean-Jacques Gunning, A. B., M. D., Head

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ACTIVATION ANALYSIS

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## Tissue copper, zinc, and manganese levels in Wilson's disease: Studies with the use of neutron activation analysis\*

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(MC) USN,\*\* and S. J. YEH\*\*\* *Taipei, Taiwan, Republic of China*

Copper, zinc, and manganese were determined by neutron activation analysis on tissues obtained at autopsy from 3 patients with Wilson's disease and 2 patients who died from other causes. Tissues from the latter 2 served as controls. The mean copper concentration in the brain and liver of the 3 patients with Wilson's disease was 9-30 times greater than that of the 2 controls. The copper concentration in the other tissues studied from 2 patients who had received penicillamine therapy for 12-14 months was only slightly higher than the values from the controls. The patient who did not receive penicillamine therapy had marked elevations in copper concentration in all tissues studied. Zinc and manganese tissue concentrations did not differ appreciably between patients and controls. These data suggest that penicillamine therapy results in a reduction of the tissue copper as follows (1) most rapidly from the kidney, (2) more slowly from the liver and other selected tissues in this study, and (3) slowest from the central nervous system. The very high concentration of splenic and muscle copper in the untreated patient suggests that she was supersaturated with copper

Glazebrook<sup>1</sup> confirmed findings reported in the German literature of high copper concentration in liver and brain tissues of a patient dying of Wilson's disease. Since that time there have been several reports of copper concentration in tissues taken at postmortem examination from patients who have died

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Table I. Biochemical results in the 5 cases

Case†	Ceruloplasmin		Copper		Liver function tests			Uric acid (mg.%)
	Ratio units <sup>2</sup>	mg.-%	Serum (µg.%) <sup>2</sup>	Urine (µg./24 hr.) <sup>2</sup>	SGOT‡ (units)	SGPT‡ (units)	BSP‡ (%)	
1 WD	0.028	0	65	330	58	26	41	1.7
2 WD	0.075	6.5	19	660	11	12	15	2.5
3 WD	0.026	6.9	26	1340	20	27		4.2
4 C					37	26		
5 C					36	22	7	
Normal	0.230-0.580	16-50	75-150	<60	5-40	5-15	<5	3.5-5.5

\*Immunodiffusion with Hyland immunoplates

†WD = Wilson's disease, C = control.

‡SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; BSP = sulfobromophthalein

of Wilson's disease,<sup>2-5</sup> including a study of 2 Chinese patients from this laboratory.<sup>6</sup> These studies have shown that patients with Wilson's disease have increased copper levels in their tissues, most notably in the liver, brain, kidney, and cornea.

This study reports tissue copper, zinc, and manganese levels determined by neutron activation analysis in 14 selected tissues from 3 Chinese patients dying of Wilson's disease. These findings are compared with tissues from 2 control subjects dying from other causes. There are apparently no previous reports of tissue copper concentrations determined by neutron activation analysis from necropsy material, although Fell, Smith, and Howie<sup>7</sup> reported results from liver and spleen biopsies in one patient, Smallwood and associates<sup>8</sup> reported results from liver biopsy in 4 patients, and Hunt and his co-workers<sup>9</sup> reported results from liver biopsies performed in 3 patients. We are not aware of any necropsy reports of tissue copper concentrations from patients who have received a course of therapy with penicillamine of at least one year's duration.

Case reports

Case 1. S. T. L., a 17-year-old Chinese girl, had spontaneous ecchymosis and thrombocytopenia noted at the age of 12. Later she developed abdominal pain, splenomegaly, prothrombin time prolongation, and ascites. Tremor of the hands began at the age of 16 and the diagnosis of Wilson's disease was established. Two of her 8 siblings have Wilson's disease.

She had abdominal distension, Kayser-Fleischer (K-F) rings, and a right pleural effusion. The liver was not palpable and the span was decreased. The spleen was palpable 13 cm. below the left costal margin. Neurologic examination demonstrated tremor of the hands only. Areas of hyperpigmentation of the skin over both lower legs were noted.<sup>10</sup> She had pancytopenia; some biochemical findings are shown in Table I. She was started on penicillamine therapy (1.0 Gm. daily) for 12 months until her death. She became weaker with increasing neurologic disability and was bedridden the last 10 months of life. She died following the sudden onset of circulatory collapse 15½ months after her initial admission to Naval Medical Research Unit-2 (NAMRU-2).

At postmortem examination, severe postnecrotic cirrhosis of the liver, congestive splenomegaly, organized thrombosis of the portal vein, and encephalomalacia of the putamen and globus pallidum with atrophy of the basal ganglia were seen. The immediate cause of death was hemorrhage into the splenic hilum from the rupture of splenic vein varices.

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Table II. Copper, zinc, and manganese concentration in micrograms per gram

Tissue	Copper				
	1	2	3	4	5
Cerebral cortex	301	183	277	11.0	21.6
Basal ganglion	201	177	207		
Thalamus		225	259		
Cerebellum	250	235	264	21.4	32.1
Spinal cord	73	60	126	3.7	5.8
Liver	179	164	792	6.7	25.5
Kidney	10	17		28.2	11.5
Spleen	8	12	323	4.7	5.3
Lung	8	11	26	3.5	
Stomach	6	35	63	5.2	7.4
Skeletal muscle	16	6	102	2.8	3.4
Pancreas		12		5.1	7.3
Diaphragm		10	61		
Adrenal gland			64	6.2	

\*Case 1 was on penicillamine treatment for 12 months; Case 2, for 14 months; Case 3 did not

*Case 2.* During a family survey, S. C. 1, an asymptomatic 19-year-old Chinese boy, was found to have Wilson's disease. Two of his 9 siblings have Wilson's disease, while 2 others died, probably from the same condition.

Physical examination demonstrated a healthy-appearing Chinese boy with K-F rings. Liver span was reduced and the spleen was palpable 3 cm. below the left costal border. Neurologic examination was normal. Some of his biochemical data are shown in Table I. Penicillamine therapy (1.0 Gm. daily) was started and he remained asymptomatic. He developed pneumococcal pneumonia and died 14 months after the institution of penicillamine treatment.

Postmortem examination demonstrated postnecrotic cirrhosis of the liver, congestive splenomegaly, normal brain and spinal cord, and marked congested hepatization of both lungs.

*Case 3.* C. C. F., a 14-year-old Chinese girl, was admitted to NAMRU-2 in a terminal condition 5 days prior to her death. She had "hepatitis" at the age of 5, consisting of jaundice, epigastric pain, and anorexia which lasted for 2 to 3 weeks. At the age of 7, she was noted to have low plasma ceruloplasmin and high urinary copper excretion. One year later, K-F rings, splenomegaly, and labile emotions were noted. She dropped out of school at age 11 following the onset of unstable gait, slurred speech, and rigidity of the left arm. Three weeks prior to admission she became bedridden, mentally confused, had nasal bleeding, intermittent vomiting, and fever. There was no history of recent falls or head trauma. Three older siblings had died of Wilson's disease.

On admission to NAMRU-2, she was noted to be chronically ill, febrile, malnourished, dehydrated, and comatose. K-F rings were present. Liver span was 6 cm. and the splenic tip was palpable. Hyperpigmentation of the skin over the shins was present. She reacted to painful stimuli, moved aimlessly, had a sucking reflex, and brisk deep tendon reflexes. Some of her biochemical values are shown in Table I. Hyperpyrexia to 107° F. persisted until death. Hematemesis and melena occurred and, despite supportive therapy, her coma deepened and she died 5 days after admission.

Postmortem examination demonstrated severe postnecrotic cirrhosis of the liver, mild congestive splenomegaly, and a perforated duodenal ulcer. The cause of death was a right subdural hematoma with massive encephalomalacia and collapse of the right frontal lobe, hemorrhage and softening in the midbrain, and edema of the left cerebral hemisphere with dilation of the lateral ventricle.

*Case 4 (control)* C. C. F., a 33 year old Chinese man with a 2 year history of ulcerative

of dry tissue in t

1	2
64	79
56	97
	123
110	134
28	83
156	168
111	86
100	94
74	73
81	131
210	119
	82
	172

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Zinc					Manganese			
1	2	3	4	5	2	3	4	5
64	79	108	30	48	1.6	0.5	2.0	1.6
56	97	82			4.7	0.6		
	123	75			1.5	0.5		
110	184	110	55	43	2.9	2.5	1.1	2.9
28	83	70	21	20	1.6	1.3	1.5	1.5
156	168	371	207	111	4.8	5.7	6.0	4.8
111	86		125	162	4.7		4.1	5.4
100	94	166	79	61	0.7	3.8	1.5	0.9
74	73	63	42		1.7	0.7	1.0	
81	131	122	160	72	3.3	3.0	2.6	2.4
210	119		222	278		0.6	0.7	0.8
	82		243	117		5.3	8.2	9.4
	172	161				0.5		
		109	80			0.2	4.3	

receive penicillamine treatment.

colitis, died of bilateral pneumonia. Postmortem examination demonstrated chronic ulcerative colitis involving the entire colon and ileum, bilateral pneumonia, and moderate fatty metamorphosis of the liver.

*Case 5 (control).* C. P. J., an 18-year-old Chinese girl, died of high-output cardiac failure secondary to a pulmonary arteriovenous (A-V) fistula. Postmortem examination demonstrated a large A-V fistula and aneurysm in the right lower lobe.

### Methods

Necropsy specimens were collected soon after death with precautions to prevent contamination. The details of the technique<sup>11</sup> and methods for neutron activation analysis determinations for copper and zinc<sup>12</sup> and manganese<sup>13</sup> concentrations are reported elsewhere. Duplicate samples of each tissue were dried, weighed, and placed together with standards. They were rendered radioactive by neutron bombardment in a nuclear reactor. The copper, zinc, and manganese were then separated chemically and their radioactivity was identified with a gamma ray scintillation counter. The concentration of each element was then calculated from the relative amounts of radioactivity in the samples and standard. Duplicate samples agreed within 10 per cent; the average is reported in Table II.

### Results

The mean copper concentration in the central nervous system (CNS) tissues of the 3 patients with Wilson's disease was 9 to 18 times higher than that in the 2 controls (Table II). Hepatic copper concentration was markedly elevated, being as high as 792  $\mu\text{g}$  per gram of dry tissue in the patient who did not receive penicillamine therapy (Case 3). The mean splenic copper concentration was doubled in the treated patients (Cases 1 and 2) as compared with that of the controls (Cases 4 and 5), but for Case 3 the concentration was elevated by a factor of 65 (Table II). The copper concentration in renal tissue was not increased in Cases 1 and 2 who had received penicillamine, but was not determined in Case 3 who did not receive penicillamine therapy. Other tissues from these patients had slight elevations of copper, but Case 3 showed

marked increases, as for example, 102  $\mu\text{g}$  per gram of dry tissue from skeletal muscle.

The CNS tissue levels of zinc were increased in the patients suffering from Wilson's disease when compared with tissue zinc levels in the controls (Table II). The untreated patient's (Case 3) hepatic and splenic zinc levels were greater than those of the controls. Other tissues did not show any increase in zinc content. Differences in manganese levels between patients and controls were not present (Table II).

### Discussion

Case 5 had tissue copper,<sup>2-4, 6-9, 11-16</sup> zinc,<sup>3, 11, 16</sup> and manganese<sup>7, 16</sup> concentrations similar to values reported for normal controls in previous studies. Case 4 had lower tissue copper levels than reported elsewhere, except that copper concentration in the kidneys was about twice the values usually reported in normal subjects (Tipton and associates<sup>16</sup> reported similar values for renal copper concentration in normal subjects from the Far East). The somewhat lower tissue copper concentrations in Case 4 might be secondary to the chronic diarrhea and malnutrition associated with this patient's disease, chronic ulcerative colitis.

Tissue manganese levels were normal in our patients with Wilson's disease. The slight elevation of CNS tissue zinc concentration noted in the patients with Wilson's disease may not be significant. Harrison, Netsky, and Brown<sup>11</sup> have shown a wide variation in zinc concentration in adjacent samples taken from the brain; their results were similar to the values found in our Wilson's disease patients. The 11 patients dying from Wilson's disease reported by Butt and his colleagues<sup>3</sup> did not have significant differences in their tissue zinc and manganese concentrations from the controls.

It is of interest to compare the tissue copper levels in the 2 patients (Cases 1 and 2) who were treated with penicillamine (1.0 Gm. daily for 12 and 14 months, respectively) with those of Case 3 who received no penicillamine therapy. The copper levels in the CNS were all markedly elevated and did not differ among the 3 patients. The copper levels in the liver and other tissues studied were much higher in the untreated patient than in the treated patients. The concentration of copper in the spleen was strikingly high in the untreated patient. It is of interest to point out in this connection that the spleen has never been considered as a site for copper deposition.<sup>17</sup> The level of muscle copper in the untreated patient was almost 10 times higher than the mean value for muscle copper in the 2 treated patients.

Another interesting finding was that Cases 1 and 2 did not have increased kidney copper concentrations as has been reported by others.<sup>2, 16-18</sup> This suggested that penicillamine therapy rapidly decreased copper concentration in these organs and tended to agree with the rapid improvement in renal tubular function noted with penicillamine therapy.<sup>19, 20</sup>

As suggested by Osborne, Szaz, and Walshe,<sup>17</sup> and Osborne and Walshe,<sup>21</sup> the liver is saturated with copper deposits which overflow to the CNS and other tissues. In some untreated patients this could lead to marked elevations

in copper level than the liver. With penicillamine therapy, we studied that copper in peripheral tissues. Our finding that the CNS copper level was high in the untreated patient and that this finding was corrected by therapy.<sup>25</sup> Our study of neurologic symptoms in patients who had progressive neurologic symptoms with penicillamine therapy, had penicillamine abnormality; t

We are grateful to Lt. Colonel Blackwell, Ph.D. and Ping Yao for their assistance in this study.

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in copper levels in all tissues, however, copper concentrations in tissues other than the liver, CNS, and kidney to the degree noted in Case 3 must be unusual.<sup>11</sup> With penicillamine therapy, as in Cases 1 and 2, it appears from the tissues studied that copper is first removed from the kidneys, second from the liver and peripheral tissues, and last from the CNS. This does not agree with the clinical finding that the neurologic symptoms usually resolve first with penicillamine therapy.<sup>27</sup> Our impression is that the renal lesion has a major influence on the neurologic symptoms in Wilson's disease.<sup>19</sup> In fact, the patient in Case 1, who had progressive neurologic symptoms in spite of 14 months of penicillamine therapy, had severe renal tubular acidosis. Decoppering the kidneys with penicillamine may not be sufficient, as illustrated in her case, to reverse this abnormality; the use of supplemental potassium and bicarbonate is suggested.

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