

BASAL COPPER EXCRETION IN WILSON'S DISEASE

BY

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The clinical manifestations of Wilson's disease are believed to be due to the accumulation of toxic amounts of copper within the body. The primary aim of treatment is to remove these, usually by giving chelating agents that will combine with the copper and be excreted in the urine. The most effective of these therapeutic agents is penicillamine (Walshe, 1960), and clinical improvement follows in a high proportion of cases treated with this compound. When the more obvious clinical signs and symptoms have improved or disappeared it is difficult to judge the effectiveness of long-term treatment or to control dosage, and an objective method of assessing the degree of copper depletion is needed. This would be particularly valuable in those cases that are diagnosed from the biochemical findings and the family history, and may be treated with chelating agents before the typical signs have developed.

Warren and Broughton (1962) described a case of Wilson's disease that had been successfully treated with D-penicillamine for four years, and they found that the best biochemical index of long-term response to treatment was the basal copper excretion measured on urines collected after penicillamine had been stopped for several days. This paper describes some further basal copper excretion results on this case, and on five others with Wilson's disease, before and after treatment with D-penicillamine.

Methods

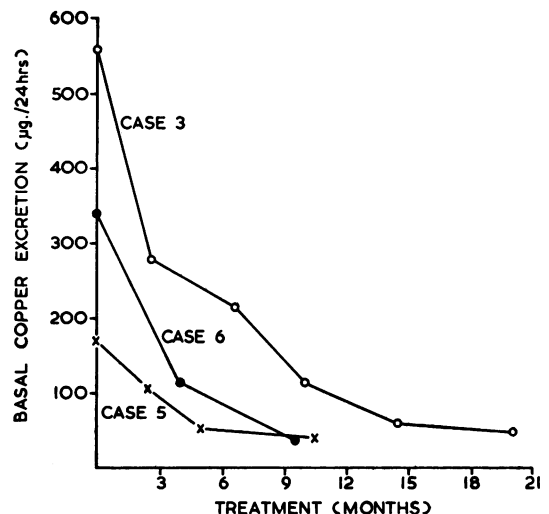
At least two consecutive 24-hour urine collections were made into polythene bottles before penicillamine treatment was started, and these were analysed for copper by a modification of the method of Earl (1954), after ashing an aliquot of the urine with sulphuric and perchloric acids. The test was repeated at intervals after penicillamine therapy, the drug having been stopped for at least three days before and during each period of urine collection.

The basal copper excretion was defined as the 24-hour output in the urine, measured on at least two consecutive specimens, after all cupruric therapy had been discontinued for at least three days.

Results and Discussion

The daily copper excretion of patients with Wilson's disease varies considerably, and on successive days may differ by as much as 100%. This may be due to fluctuations in the amount of copper in the diet, but will also depend on the intake of amino acids (Matthews, Milne and Bell, 1952) and of protein (Bearn and Kunkel, 1954). Copper excretion is also likely to be influenced by oestrogenic (German and Bearn, 1961) and adrenocortical activity (Bearn and Kunkel, 1954) and by renal function. But the analysis of duplicate specimens, at regular intervals, as in the cases reported here, reduces the effect of the variables, and enables the trend of the results to be clearly seen (Fig. 1).

The basal copper excretion of all six cases reported here showed a significant fall after penicillamine treatment (Table 1); and in those cases with symptoms, there has been a corresponding clinical improvement. A number of published reports



FIGURE—Changes in basal copper excretion during treatment.

TABLE 1
BASAL COPPER EXCRETION RESULTS

Case No.	Age (yr.)	Presentation	Duration of Penicillamine Treatment	Basal Copper Excretion ($\mu\text{g./24 hr.}$)	
				Before Treatment	After Treatment
1*	{ 7 11 12 18	Jaundice Neurological symptoms Diagnosis; penicillamine started Well	5½ years	290	50
2*	{ — 6 9 12	Brother of Case 1 Asymptomatic Liver biopsy: cirrhosis + Cu; penicillamine started Well	2½ years	470	80
3	{ 12 14 18 21 22 24	Jaundice Neurological symptoms Diagnosis. BAL treatment Relapse Penicillamine started Well	2 years	560	50
4	{ — 8 9	Elder sister died aged 11 yr. with Wilson's disease Asymptomatic; biochemical diagnosis Penicillamine started Well	17 months	200	53
5	{ 7 11½ 12	Hepatitis Liver failure; diagnosis; penicillamine started Well	10 months	170	40
6	{ — 8 9	Younger sister of Case 5 Asymptomatic; biochemical diagnosis Penicillamine started Well	9 months	340	35

* Cases 1 and 2 were described more fully by Warren and Broughton (1962).

include similar figures (Table 2), although previous authors do not seem to have commented upon these changes in copper excretion.

In an earlier report (Warren and Broughton, 1962), it was found that remission of the symptoms in Case 1 occurred by the time the basal copper excretion had fallen to approximately 100 $\mu\text{g./24 hr.}$; when treatment became intermittent, symptoms began to reappear when the excretion increased much above 100 $\mu\text{g./24 hr.}$ We have therefore aimed at reducing the basal copper excretion to below this figure. The

time taken to bring it down to this relatively safe level will presumably depend upon the size of the initial copper pool and the dosage of penicillamine used. The speed of this biochemical remission in these six cases has varied from six months (Case 1 of Warren and Broughton, 1962) to two years (Case 2), and did not appear to be related either to the initial severity of the disease or to the basal copper excretion before treatment.

When there is no renal disease the basal copper excretion is probably an index of the total body copper pool. The copper content of the liver is presumably another such measure, and Sherlock (1961) and Sternlieb and Scheinberg (1963) have found that this is reduced following penicillamine treatment, with accompanying clinical improvement. The amount of copper in the body is probably a relative, and not an absolute, measure of the severity of the disease, and many other factors, including the variable sensitivity of organs to copper, will determine when clinical signs and symptoms appear.

Because of the wide range of clinical effects in Wilson's disease it is difficult to find an objective measure, applicable to all cases, which records their progress. The basal copper excretion appears to be promising in this respect, and the test is simpler than regular liver copper analysis advocated by Sternlieb

TABLE 2
SOME BASAL COPPER EXCRETION RESULTS
REPORTED PREVIOUSLY

Reference	Duration of Penicillamine Treatment	Basal Copper Excretion ($\mu\text{g./24 hr.}$)	
		Before Treatment	After Treatment
Boulding (1961)	1½ years	257	less than 80
Garland and Sumner (1961)	2 years	590	250
Lange (1961)	3½ years	1,061	202
Sherlock (1961)	9 months	409	200
	2-3 years	529	77
		309	71
Walshe (1961)	1 year	360	43
		0.5*	0.15*

* $\mu\text{g. per minute}$

and Scheinberg (1963). It remains to be seen whether this index can be used to control the long-term dosage of penicillamine in patients who have shown a good initial clinical improvement.

It is noteworthy that three of these six cases were diagnosed when they were asymptomatic and had no Kayser Fleischer rings. This emphasizes the importance of full investigation of all sibs of patients with Wilson's disease.

Summary

The basal copper excretion of six cases of Wilson's disease has been estimated before and after treatment with penicillamine. In all cases a striking fall was demonstrated after several months.

These results suggest that this test may be a relatively simple method of assessing the extent to which the body has been depleted of copper and may thus be a useful guide to the choice of long-term maintenance dosage of penicillamine.

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