Failure of folic acid to influence mortality of rats with acute tubular necrosis caused by mercury

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ONE of the hypotheses advanced to explain the anuria or oliguria of acute tubular necrosis is that the glomerular filtrate is passively reabsorbed through the tubules which have been stripped of epithelium. Moreover, it has been suggested that the rise in urine volume in the early diuretic phase results from a relining of the tubules by division of surviving cells (Oliver, 1954). This process is well demonstrated in mercury poisoning. Noltenius, Schellhas & Cehlert (1963), using radioactive thymidine to mark the synthesis of new DNA, found that the regeneration commenced after a latent period of 72 hr from the mercury poisoning and spread upwards from the lowest end of the proximal convoluted tubule.

If this hypothesis to explain the anuria or oliguria is correct and if one could hasten the process of relining of the tubules, one might shorten the period of oliguria and improve the prognosis in mercury poisoning and in other varieties of acute tubular necrosis.

In this connection the work of Haddow (1954) and Taylor, Threlfall & Buck (1966) is of special interest. Certain pteridines such as folic acid given intravenously to rats causes a marked and rapid increase in kidney weight. This increase in weight is associated with an outburst of mitotic activity and an increase of cell numbers. It therefore seemed worth while to test the effect of folic acid on the speed of regeneration of tubules in animals suffering from acute tubular necrosis induced by mercury and on their survival.

Methods

Rats of both sexes and weighing between 180 and 230 g were used. These were divided into the following five groups:

1. Five untreated animals.

2. Five animals received 25 mg folic acid/100 g body weight intravenously dissolved in isotonic NaHCO_3 solution.

3. Twenty-five animals received intraperitoneally 0.25 ml/100 g body weight of an 0.1% solution of HgCl_2 .

4. Fourteen animals received the same dose of mercury as in (3) and either 24 or 48 hr later an intravenous injection of isotonic dextrose.

5. Eight animals received the same dose of mercury as in (3) and 24 hr later an intravenous injection of an isotonic solution of NaHCO_3 .

6. Twenty-seven animals received the same dose of mercury as in (3) and either 24 or 48 hr later received the same dose of folic acid intravenously as in (2).

The kidneys of all animals were collected as soon after death as possible, weighed and examined histologically. (Animals surviving after mercury poisoning were killed on the 14th day.)

Results

Five animals in group 2 which received folic acid alone were killed 48 hr after the injection. The results are shown in Table 1 compared with group 1.

TABLE 1
Effect of folic acid injection on kidney weight in normal rats

	Control (g)	F.A. treated (g)
	1.240	2.279
	1.307	2.496
	1.477	2.490
	1.186	2.064
	1.230	2.027
Mean weight	1.394	2.276
SD	± 0.226	± 0.218

$P < 0.001$.

The kidney weights and the histological examination confirm the findings of Taylor *et al.*

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(1966) of a marked increase in kidney weight and an increase in mitoses of tubular cells.

The mortalities in the animals receiving HgCl_2 are shown in Table 2.

TABLE 2
 HgCl_2 injected animals

	Folic acid treated groups			Control groups given dextrose or NaHCO_3		
	No. of animals	Survived	Died	No. of animals	Survived	Died
I	8	4	4	4	2	2
II	9	4	5	10	5	5
III	10	2	8	8	4	4

- I. F.A. or dextrose injected 48 hr after HgCl_2 poisoning.
 II. F.A. or dextrose injected 24 hr after HgCl_2 poisoning.
 III. F.A. or NaHCO_3 injected 24 hr after HgCl_2 poisoning.

On summed figures for Control and Treated Groups

$$\chi^2 = 0.39 \text{ for 1 d.f.}$$

$$0.7 > P > 0.5.$$

It will be seen that approximately 50% of animals died and that there was no significant difference between those receiving folic acid and a control solution of either dextrose or NaHCO_3 .

The kidney weights of animals examined are shown in Table 3. (The numbers of animals dying on days other than the fourth were so small as to make comparison of kidney weights difficult. Therefore weights derived from deaths on day 4 only are shown in the table.)

Although the mean weights of the kidneys of animals receiving folic acid and mercury were greater than those receiving a control solution and mercury, the differences were not significant.

Moreover, histological examination did not reveal any difference between these groups in respect of mitotic activity or appearance of the tubule cells.

TABLE 3
Mean kidney weights of rats (g)

		Died on 4th day	Survived 14 days
Non-treated normal kidney	1.301		
Folic acid injected kidney	2.276		
HgCl_2 poisoned kidney		2.361	1.861
HgCl_2 poisoned + folic acid treated kidney		2.915	2.004

Discussion

This study confirms the findings of Taylor *et al.* (1966) and Haddow (1954) that folic acid causes an increase in kidney weight and a multiplication of tubule cells in normal animals. However, when it was administered to rats poisoned with mercury, no such effect could be demonstrated and, moreover, the survival of animals so treated was unaffected.

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Synalbumin insulin antagonism

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USING the technique of the isolated rat diaphragm to measure insulin activity and antagonism, our initial studies on untreated or uncontrolled insulin-requiring diabetic patients showed that their plasma inhibited the activity of insulin *in vitro* (Vallance-Owen, Hurlock & Please, 1955). It was then found that this antagonism to insulin was associated with the

albumin fraction of the plasma proteins (Vallance-Owen, Dennes & Campbell, 1958a). Whole plasma from normal subjects and from obese maturity-onset diabetics, who ordinarily do not require insulin therapy, has no measurable insulin antagonism. Nevertheless, when normal plasma is broken down into its various constituents, insulin antagonism can be detected in the