the other hand, symptoms appear as early as the fourth day after tri*para*ethylphenyl phosphate has been given but they increase more slowly and less steadily than in tri*ortho*cresyl phosphate poisoning. While some of the birds with severe disabilities have died, others have shown obvious improvement from the fourth to fifth week and in some less-affected hens recovery has been almost complete 7 weeks after dosing.

Although no claim is made on the basis of this work that tri*para*ethylphenyl and tri*ortho*cresyl phosphates produce their effects by a different biochemical pathway, the findings suggest that such a possibility should be considered. In view of this it seems important that workers in this field should describe their clinical observations more precisely than hitherto. It may be wrong to classify all organo-phosphorus-produced disabilities as 'Ginger Jake paralysis'.

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Glucagon : a Protein Catabolic Hormone in the Isolated Perfused Rat Liver

WE have reported that the isolated perfused rat liver from a fasted animal produces urea in linear fashion[1], at the expense of both liver and plasma proteins. Urea production occurs, and the blood amino-acid level is maintained in the absence of added extraneous amino-acids. When a free amino-acid supplement is added, urea production is greatly enhanced. The addition of glucose or fructose supplements is associated with a nitrogen-sparing effect manifest as a diminished production of urea. This nitrogen-sparing effect is seen in either the presence or absence of added amino-acids.

The production of urea by the isolated perfused liver may be regarded as a measure of the continuing or endogenous protein catabolism, and the isolated perfused liver affords a means of studying protein catabolism and the effects of various agents upon it.

This communication reports a remarkable effect of the hormone glucagon (generously supplied by the Eli Lilly Co.) in enhancing protein catabolism in the isolated perfused liver.

In typical experiments a 6-hr. liver perfusion is started and continued for a base-line period of 1½–2 hr. During this time, Ringer's solution is continuously infused. After this the continuous infusion is changed to one of Ringer's solution containing glucagon in such concentration that as little as 1 μgm. of glucagon is infused per hour.

Blood samples are removed at regular intervals, analysed for urea by Conway's method and for glucose by Nelson's method. The total amount of urea produced during each interval is computed after appropriate correction for the amount of urea removed by the sampling procedure itself.

Not only is prompt glycogenolysis produced by as little as 1 μgm. of glucagon per hour, but also, as Fig. 1 shows, the rate of urea production is greatly increased. Almost complete glycogenolysis occurs in the face of blood glucose-levels known to promote glycogen deposition[2] and also to spare protein[1].

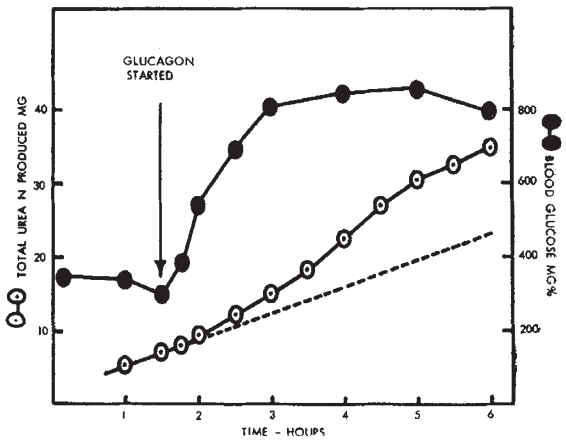

Fig. 1. Liver donor fed stock laboratory diet. Blood donors fasted 18 hr. before being bled to provide a total of 63 ml. of whole blood diluted with 35 mgm. heparin and Ringer's solution to 79 ml. at start of perfusion. Perfused liver weight, 14 gm.; glycogen content at 1½ hr. 2·64 gm. per cent, and at 6 hr. 0·11 gm. per cent. Over an interval of 1½–6 hr. glucagon was infused at the rate of 1 μgm. per hr. in 3 ml. of Ringer's solution

It is of some interest that the hormone hydrocortisone in the form of the soluble succinate given by continuous infusion in amounts up to 2 mgm. per hour produces no change in the output of urea by livers from either normal or adrenalectomized rats. Only when glucagon is infused into livers from the latter along with hydrocortisone is a maximal increase in protein catabolism elicited. Given alone, in perfusion of the adrenalectomized rat liver, glucagon causes a small but definite increase in protein catabolism.

The glycogenolytic effect of glucagon at 1 μgm. per hour on the liver is not altered by prior and continuous administration of insulin in amounts known to be sufficient to enhance glucose uptake and lipogenesis[3]. However, the protein catabolic effect of 1 μgm. per hour is abolished by the insulin.

Although relatively massive doses of glucagon given parenterally to intact rats have been associated with enhanced urinary nitrogen excretion[4], the site of action and the mechanism of the response have not been defined. Our experiments implicate the liver directly and point to glucagon as being a protein catabolic hormone *par excellence*, with adrenal corticoid hormone exerting a permissive action on this effect.

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