berg, 1951). However, in micro-organisms two distinct pathways of lysine biosynthesis are known (Meister, 1965; Rodwell, 1969). One is based on the formation and subsequent decarboxylation of α -diaminopimelate (Gilvarg, 1960), the other involves α -amino adipate as the key intermediary metabolite (Broquist, 1966).

From studies of patients with genetic defects in lysine metabolism it appears that lysine degradation in humans proceeds by a reversal of the α -amino-adipate pathway established for its biosynthesis in yeast and *Neurospora* (Kao *et al.*, 1964; Saunders & Broquist, 1967; Trupin & Broquist, 1965). 'Saccharopine dehydrogenase' [saccharopine-NAD⁺ oxidoreductase (hydrolysing)] has been isolated, purified and characterized (Hutzler & Dancis, 1970) from human liver. This enzyme reduces NAD⁺ in the presence of saccharopine, with the formation of glutamate and L-2-amino adipic δ -semialdehyde. Our evidence shows 'saccharopine oxidoreductase' to be distinct from 'saccharopine dehydrogenase'.

We have also studied the activity of 'saccharopine oxidoreductase' in the livers of different mammals. Our results show that herbivorous animals have the highest activity of the enzyme and that this activity is considerably less in omnivores and carnivores. Excessive amounts of saccharopine and lysine are observed in the plasma and urine of patients suffering from saccharopinuria (Carson, 1969; Carson *et al.*, 1968; Simell *et al.*, 1972). The high concentrations of lysine in the body fluids of these patients may result from repression or inhibition by saccharopine of 'lysine-oxoglutarate reductase'. Alternatively there may be an induction of 'saccharopine oxidoreductase', as indicated by our current findings.

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Regulation of L-Serine Dehydratase in Developing Rat Liver

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Previous workers have reported a peak of L-serine dehydratase activity in developing rat liver either at 2 (Yeung & Oliver, 1971) or at 20-26 days *post partum* (Vernon *et al.*, 1968; Evered & Roffe, 1971; Goswami *et al.*, 1972). In the present work L-serine dehydratase activity was assayed in unfractionated liver homogenates (5%, w/v) under the incubation conditions of Greengard & Dewey (1967) but by using a discontinuous procedure. Two peaks of activity, at 2 and 18 days *post partum*, both having essentially similar isoenzyme compositions (Inoue *et al.*, 1971), have thus been observed, and this developmental profile is similar to that of some other enzymes of amino acid metabolism (Snell & Walker, 1972).

L-Serine dehydratase activity was precociously induced 2 days before term by injection *in utero* of glucagon or dibutyryl cyclic AMP (6-*N*,2'-*O*-dibutyryladenosine 3':5'-cyclic monophosphate), but not by cortisol or thyroxine, and this induction, as with the natural postnatal increase, was blocked by cycloheximide or actinomycin D. Glucose administration to caesarian-delivered newborn rats partially blocked the postnatal increase in activity, but had no effect on glucagon-mediated induction at birth (see also Yeung & Oliver, 1971; Greengard & Dewey, 1967). Glucose may act indirectly to prevent postnatal hypoglycaemia and subsequent endogenous glucagon release.

The second postnatal rise in enzyme activity could be prematurely induced at 11 days by cortisol; tryptophan and an intragastrically-administered amino acid mixture were less effective, and induction by these agents was not additive to that by cortisol. Glucagon and dibutyryl cyclic AMP were completely ineffective at this age. Induction by cortisol or tryptophan was blocked by actinomycin D. Glucose also prevented the cortisol-stimulated increase in activity, and lowered the naturally elevated enzyme activity at 18 days.

At 21 days, after the second postnatal peak, L-serine dehydratase was stimulated equally by cortisol or tryptophan injection or by intubation of an amino acid mixture, and again the inductive effects were

not additive. The stimulation of activity by tryptophan or cortisol was not inhibited by actinomycin D.

It appears that around the time of weaning L-serine dehydratase synthesis is stimulated after cortisol release, but that then the increased dietary intake of glucose associated with weaning lowers the cortisol-stimulated activity. Subsequent increase of activity is effected by the increased intake of amino acids (perhaps specifically tryptophan) that is also associated with weaning (see Snell & Walker, 1972); this effect may operate at the translational level of enzyme synthesis.

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Enzyme Adaptation for Glycerol Utilization in Neonatal Rats

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The changes in hepatic glycerol kinase (EC 2.7.1.30) and glycerol 3-phosphate dehydrogenase (EC 1.1.1.8) activities during the development of the rat were described by Vernon & Walker (1970). Factors that regulate these changes and their relationship to the normal physiological events have now been investigated. Low activities of both enzymes are detected in the foetal liver at 18 days gestation, and these activities rise fourfold during the following 4 days and then continue to rise more rapidly after birth. The effect of starvation on prematurely delivered, full-term and 6h-old pups that have suckled once was examined, the animals being maintained in a humidicrib at 37°C for 24h and the hepatic activities then measured. These were 60% lower in the experimental animals than in normal suckled litter mates.

Increased activity of glycerol 3-phosphate dehydrogenase can be observed 5h after injection of thyroxine, cortisol or glycerol *in utero*, but glycerol kinase activity is increased only by thyroxine. In-

jections of neither glucagon nor dibutyl cyclic AMP (6-*N*,2'-*O*-dibutyladenosine 3':5'-cyclic monophosphate) have any effect on these enzymes. Administration of cortisol or glycerol to 5-day-old animals resulted in similar rises 24h later in both glycerol kinase and glycerol 3-phosphate dehydrogenase activities, but thyroxine had no effect.

Glycerol utilization in liver slices from animals of various ages incubated *in vitro* was examined by measuring the incorporation of ¹⁴C from [U-¹⁴C]-glycerol into CO₂, liver lipids and liver glucose + glycogen. Less than 0.5% incorporation into CO₂ was found for suckling rats, but this rises for weanling animals. Incorporation into glucose is by far the greatest in slices from animals 0-2h old. By 1 day *post partum* this has fallen through a minimum and then rises again to a new maximum at 15 days (Vernon & Walker, 1970). Incorporation of radioactivity into total liver lipids was very low throughout the whole suckling period.

These studies suggest that gluconeogenesis from glycerol may be important in the immediately newborn animal. Blood glycerol concentrations at this time measured by the method of Sheath (1970) are high, then decrease for several hours until normal suckling causes a fresh rise in them.

Prevention of the normal rise in glycerol kinase and glycerol 3-phosphate dehydrogenase activities by starvation and the failure of attempts at prenatal induction with glucagon suggest that postnatal hypoglycaemia is not involved in regulation of these enzymes, and that their development is related to as yet unknown suckling or associated factors.

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Enzyme Synthesis and Adaptation of Hepatic 'Malic' Enzyme

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The adaptive behaviour of rat hepatic 'malic' enzyme (EC 1.1.1.40) has been characterized sufficiently, both in the adult (Wise & Ball, 1964; Tarentino *et al.*, 1966) and in the developing postnatal animal (Vernon & Walker, 1968*a,b*; Hemon, 1968; Lockwood *et al.*, 1970), to indicate that similar physiological stimuli are involved in both adaptive and developmental phenomena.

A radio-immunological technique was developed to monitor changes in rate of hepatic 'malic' enzyme synthesis, relative to total soluble protein (Schimke & Doyle, 1970), during both adaptation and develop-