Uptake of Orotate and Thymidine by Normal and Regenerating Rat Livers

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1. At 1 h after operation livers from partially hepatectomized rats showed a 60-100% increase in the capacity to concentrate ^3H radioactivity from orotate, thymidine or uridine with respect to the radioactivity in plasma. Uptake of [^3H]cytidine into liver was unaffected, as was entry of any precursor studied into any tissue other than liver.
2. This increase in intracellular radioactivity was detectable 10 min after operation with both orotate and thymidine. With orotate the augmentation had disappeared by 3 days, but with thymidine it was still evident 8 days after partial hepatectomy, when [^3H]thymidine incorporation into DNA was no longer increased. Competition studies established that orotate was not entering the liver by the same mechanism as thymidine.
3. In the soluble fraction of the liver all the ^3H radioactivity from orotate was present as uridine nucleotides. Thymidine was not phosphorylated, and was believed to be catabolized.

Increased uptake of nucleic acid precursors occurs in many tissues after hormonal stimulation and in cell cultures promoted into active growth (see Tata, 1970). Complex inter-relationships may exist between the entry of the precursor and the rate of nucleic acid synthesis, but from careful analysis of cell cultures the uptake of precursor may be a major determinant in the pattern of RNA synthesis (see Stambrook & Siskin, 1972). In regenerating liver uptake of orotate was increased 1 h after operation (Bucher & Swaffield, 1966, 1969; Ord & Stocken, 1972) and the entry of thymidine was also promoted. The increased penetration was not prevented by actinomycin, and with thymidine it occurred at least 12 h before [^3H]thymidine incorporation into DNA started to rise, so that the increased entries did not appear to be dependent on increased nucleic acid synthesis. Experiments have now shown that the augmented uptakes of orotate and thymidine after partial hepatectomy follow different time-courses and that the two precursors use different transporter systems. Although there are increases in some amino acids in liver and plasma by 1 h (Ferris & Clark, 1972; Ord & Stocken, 1972), these changes are not accompanied by corresponding changes in the rate of uptake of ^3H -labelled amino acid into the liver. The effects of partial hepatectomy on precursor entry are restricted to the liver and have so far been found to alter only the uptakes of orotate, and thymidine and uridine. No changes in the metabolism of orotate or thymidine have been reported by 1 h after partial hepatectomy (see Bresnick, 1971), nor were any detected in the experiments described here.

Methods

The animals were treated and the liver extracts prepared and analysed as described previously (Ord & Stocken, 1972).

Identification of pyrimidines, pyrimidine nucleosides and pyrimidine nucleotides

Liver extracts obtained after injection of [^3H]orotate or [^3H]thymidine were analysed by t.l.c. The method of Shimizu *et al.* (1969) was used to separate the free bases, nucleosides and nucleotides; in this procedure the phosphorylated compounds remained at the origin. The same gels were used to resolve the mono- and tri-phosphorylated nucleosides, by using the solvents employed by Lane (1963). With both methods recoveries of ^3H radioactivity and non-radioactive markers were better than 80%.

Radioactive precursors

These were obtained from The Radiochemical Centre, Amersham, Bucks., U.K. Their specific radioactivities were: [*carboxy*- ^{14}C]inulin, 9.5 mCi/mmol (mol.wt. 5175 ± 95); [$5\text{-}^3\text{H}$]cytidine, 29 Ci/mmol; [$5\text{-}^3\text{H}$]orotate, 23 Ci/mmol; [$6\text{-}^3\text{H}$]thymidine, 23 Ci/mmol; [$5\text{-}^3\text{H}$]uridine, 24 Ci/mmol; L-[$\text{G}\text{-}^3\text{H}$]aspartic acid, 178 mCi/mmol; L-[$2,5\text{-}^3\text{H}$]histidine, 500 mCi/mmol; L-[$4,5\text{-}^3\text{H}(\text{n})$]lysine, 7.5 Ci/mmol; L-phenyl[$2,3\text{-}^3\text{H}$]alanine, 1 Ci/mmol; L-[$2,3\text{-}^3\text{H}(\text{n})$]valine, 19 Ci/mmol.

Results

Investigation over a more extended range of rat tissues than in the previous experiments (Ord & Stocken, 1972) showed that the stimulation of uptake of [^3H]orotate into the acid-soluble intracellular fraction of liver detected 1 h after partial hepatectomy was not found in muscle, pancreas, salivary gland or thymus (Table 1). In contrast with liver, these tissues were not able to concentrate ^3H radioactivity into the acid-soluble fraction relative to plasma. Slices of kidney cortex were also examined and seemed to have a great capacity for uptake of [^3H]orotate, but since the amount of available tissue was small and the capacity of the kidney to filter off inulin led to apparently large corrections for extracellular radioactivity, difficulties of interpretation precluded further work with this tissue. In attempts to eliminate surgical trauma as a factor in the response, experiments with unilaterally nephrectomized rats 1 h after operation showed that this procedure did not increase uptake of [^3H]orotate into intact livers.

Some experiments were performed with livers from young rats which showed a greater capacity for uptake of [^3H]orotate than adult livers (Table 1), consistent with the higher growth rate for liver in these animals.

When the results were examined in greater detail

it was noted that although an approximately constant amount of [^3H]orotate was injected the amounts of ^3H radioactivity in the plasma varied at death (Table 2 and Fig. 1). However, the capacities of the livers to concentrate ^3H radioactivity with respect to plasma after a 0.5 h pulse were independent of the actual amount of ^3H radioactivity over a twofold range of concentration in both groups of rats, and the stimulus produced by the partial hepatectomy was constant.

Since doubling the concentration of ^3H radioactivity in the plasma did not affect the ability of the intact liver to take up [^3H]orotate, and since previous experiments (Ord & Stocken, 1972) had shown that still greater increases in plasma orotate concentration also had no effect on the liver/plasma ^3H ratio, the results (Table 2) suggested that the augmented uptake of orotate early in regeneration was not due to the decrease in the number of absorbing parenchymal cells relative to the volume of blood circulating through the liver.

Experiments in which the time of exposure to [^3H]orotate was varied showed that in animals killed 1 h after partial hepatectomy the stimulus to ^3H uptake was identical with pulses of 10, 20, 30 or 40 min. If the label was given intravenously immediately after hepatectomy and the animals were killed 10 min later, the stimulation of the liver/plasma

Table 1. *Uptake of [^3H]orotate into the intracellular acid-soluble fraction of rat tissues from normal and partially hepatectomized rats*

[^3H]Orotate ($5\mu\text{Ci}$) and [^{14}C]inulin ($2.5\mu\text{Ci}$)/100 g body wt. were injected intramuscularly 0.5 h after operation and the animals were killed at 1 h. The ratio is given of intracellular acid-soluble ^3H radioactivity in the tissues to that in plasma. The acid-soluble ^3H radioactivity of the plasma was about 5×10^4 c.p.m./ml. The results are expressed as means $\pm$ S.E.M., with the numbers of determinations in parentheses.

	Ratio of intracellular ^3H radioactivity in tissue to that in plasma	
	Sham-operated rats	Partially hepatectomized rats
Kidney cortex	13.9 ± 3.6 (5)	—
Liver (200 g body wt.)	5.9 ± 1.2 (37)	11.0 ± 3.0 (24)
Liver (40 g body wt.)	8.2 ± 0.4 (4)	—
Liver (8 g body wt.)	8.7 ± 0.6 (4)	—
Muscle	0.16 ± 0.01 (4)	0.12 ± 0.03 (4)
Pancreas	0.18 ± 0.01 (4)	0.16 ± 0.02 (4)
Salivary gland	0.21 ± 0.05 (6)	0.22 ± 0.02 (3)
Thymus	0.31 ± 0.04 (6)	0.29 ± 0.06 (4)

Table 2. *Effect of different concentrations of ³H radioactivity in plasma on the uptake of [³H]orotate into the intracellular acid-soluble fraction of livers from sham-operated and partially hepatectomized rats*

Animals were injected intramuscularly with 5 μ Ci of [³H]orotate and 2.5 μ Ci of [¹⁴C]inulin/100g body wt. at 0.5h and killed 1.0h after operation. The ratio is given of the acid-soluble intracellular ³H radioactivity in the liver to that in plasma at different ranges of radioactivity in plasma. Results are means $\pm$ S.E.M., with the numbers of rats in parentheses.

Range of plasma radioactivity (c.p.m./ μ l)	Sham-operated rats		Partially hepatectomized rats	
	Mean radioactivity of plasma (c.p.m./ μ l)	Liver/plasma ³ H ratio	Mean radioactivity of plasma (c.p.m./ μ l)	Liver/plasma ³ H ratio
35-44	40.4	6.65 $\pm$ 1.26 (9)	40.0	10.6 $\pm$ 3.6 (4)
45-54	49.2	6.3 $\pm$ 0.94 (12)	50.9	10.3 $\pm$ 2.0 (5)
55-65	60.6	6.25 $\pm$ 0.72 (4)	60.7	11.2 $\pm$ 3.1 (6)

Fig. 1. *Time-course of the disappearance of ³H radioactivity from the plasma and the uptake of ³H radioactivity into the intracellular acid-soluble fraction of the liver in sham-operated and partially hepatectomized rats*

Groups of four rats received 5 μ Ci of [³H]orotate and 2.5 μ Ci of [¹⁴C]inulin intramuscularly/100g body wt. They were killed 1h after operation, having been exposed to the radioisotopes for 10, 20, 30 or 40 min. —, Intracellular soluble ³H radioactivity; ----, ³H radioactivity in the plasma. ○, Partially hepatectomized rats; ●, sham-operated rats. The points represent mean values and the bars represent $\pm$ S.E.M.

concentration ratio was the same as that 50-60min after operation, indicating that the effect on the uptake was immediate.

The time-course of uptake of [³H]orotate into

livers of sham-operated rats was different from that reported in Fig. 2 of Bucher & Swaffield (1966), where with young rats injected intravenously with 0.5 μ Ci of [6-¹⁴C]orotate (specific radioactivity

4.2 $\mu\text{Ci}/\mu\text{mol}$) the specific radioactivity of the UTP in control and sham-operated rats declined from 3 min until the end of the experiment at 16 min. In our adult rats, with intramuscular injections, ^3H radioactivity/g of liver increased in both sham-operated and partially hepatectomized rats over the period examined (10–40 min, Fig. 1); during this time the ^3H radioactivity in the plasma of both groups of rats decreased, but not very sharply. Bucher & Swaffield (1966, 1969) have established that the amounts of UTP/g of liver do not change in fed rats 45 min after partial hepatectomy and that 80% of ^{14}C radioactivity in their uridine nucleotides was in UTP. In their experiments, in which young rats were given orotate by continuous infusion over 15 min, the specific radioactivities of UTP increased linearly for both groups of rats, those in the partially hepatectomized animals being about 60% higher than the controls. Bucher & Swaffield (1969) suggested that in their rats the higher amounts of radioactivity from orotate in livers of partially hepatectomized animals were due to the decrease in liver mass, so that each cell was exposed to a more abundant supply of label.

To determine whether uptake in our sham-operated adult rats was being limited by the availability of the orotate experiments were performed with sham-operated and partially hepatectomized rats. To compensate for the differences in liver weights the sham-operated rats were given three times the dose of orotate as that given to the partially hepatectomized animals. These doses were chosen to be either below or approximately equal to the concentrations of orotate that were believed to saturate the transporter sites. The concentration ratio in livers of the sham-operated rats was not affected by the amounts of unlabelled orotate administered (Table 3), in agreement with our previous results (Ord & Stocken, 1972). When the effects of partial hepatectomy were

compared, with rats given orotate in proportion to their liver weights, the stimulus was still the same. Sham-operated and partially hepatectomized rats were also compared which had received the same amount of orotate/body wt. and again the same augmentation was found. It was therefore concluded that in these sham-operated adult rats receiving orotate intramuscularly the lower radioactivity in the intracellular soluble pool in the livers was not due to inadequacies in the availability of the orotate.

Next the specificity of the effect with respect to precursors was studied. Previously orotate, thymidine and uridine were found to have an enhanced uptake 1 h after partial hepatectomy, but adenine transport showed no change (Ord & Stocken, 1972). When [^3H]cytidine was used no evidence for increased uptake of cytidine could be found. Orotate and the three nucleotides showed similar ratios of ^3H uptake into thymus with respect to plasma after a 30 min exposure to the label, and these ratios were unchanged after partial hepatectomy.

Uptakes of ^3H -labelled amino acid into the tissues of partially hepatectomized rats were also investigated. Previous experiments had shown (Ord & Stocken, 1972) that ornithine and lysine were increased in liver and plasma 1 h after operation whereas amounts of the non-essential amino acids were unchanged. Measurements of intracellular soluble amino acids in liver showed big differences in the extent to which they were concentrated with respect to plasma (Ord & Stocken, 1972). In spite of these differences the entries of ^3H -labelled amino acids into acid-soluble fractions of the liver were very similar for four out of five of the amino acids studied and in no case did partial hepatectomy affect the concentration ratios (Table 4).

The lack of correlation between uptake of ^3H -labelled amino acid and concentration of the amino

Table 3. *Uptake of [^3H]orotate into livers of sham-operated and partially hepatectomized rats 1 h after operation: effects of administration of amounts of unlabelled orotate proportional to the liver weight*

Rats (body wt. 200 g) were given 10 μCi of [^3H]orotate and 5 μCi of [^{14}C]inulin intramuscularly 40 min after operation. Some sham-operated rats additionally received 0.3 or 0.9 mg of unlabelled orotate intramuscularly at 40 min and some partially hepatectomized rats were given 0.1 or 0.3 mg of unlabelled orotate. The ratios of intracellular acid-soluble ^3H radioactivity in the livers to that in plasma and also the relative increase in this ratio produced by partial hepatectomy are given. Each result was obtained from one rat.

Sham-operated animals		Partially hepatectomized animals		Stimulus produced by partial hepatectomy
Dose of unlabelled orotate (mg/kg)	Liver/plasma ^3H ratios	Dose of unlabelled orotate (mg/kg)	Liver/plasma ^3H ratios	
0	4.9, 4.8	0	9.7, 10.1	2.0
1.5	4.9	0.5	8.5, 9.1	1.8
4.5	4.3, 5.5	1.5	7.4, 8.8	1.7

Table 4. Uptake of ^3H -labelled amino acid into livers from normal and partially hepatectomized rats 0.5–1 h after operation

The labelled compounds were given as described in the previous tables. The ratio of the amino acid concentrations in the intracellular acid-soluble fraction of the livers to those in plasma are taken from previous results (Ord & Stocken, 1972). Groups consisted of three to seven rats. Results are means $\pm$ S.E.M.

^3H -labelled amino acid administered	Liver/plasma ratio of amino acid concentration		Liver/plasma ratio of uptake of ^3H -labelled amino acid	
	Sham-operated rats	Partially hepatectomized rats	Sham-operated rats	Partially hepatectomized rats
Asp	52.7	60.5	0.3 ± 0.03	0.3 ± 0.05
Val	1.1	1.5	0.2 ± 0.05	0.1 ± 0.01
Phe	1.5	7.4	0.4 ± 0.04	0.4 ± 0.04
His	11.6	10.2	0.9 ± 0.1	1.0 ± 0.02
Lys	1.9	2.1	0.2 ± 0.05	0.2 ± 0.07

Table 5. Competition studies *in vivo* on uptakes of [^3H]orotate, [^3H]thymidine and [^3H]uridine into regenerating rat livers 1 h after operation

[^3H]Orotate, [^3H]thymidine or [^3H]uridine ($5\mu\text{Ci}$) and [^{14}C]inulin ($2.5\mu\text{Ci}$)/100g body wt. and, where indicated, unlabelled precursors, were injected intramuscularly into the rats 0.5 h after operation and the animals were killed at 1 h. Each result was obtained from one rat.

Precursor	Ratio of intracellular acid-soluble ^3H radioactivity to that in plasma		
	Ratio with ^3H precursor	Ratio with added non-labelled precursor	
		(2mg of orotate/kg)	(10mg of thymidine/kg)
Orotate	13.7, 14.3	8.8, 8.1, 8.1	11.4, 15.2
Thymidine	8.3, 7.3, 9.0, 11.3	7.0, 10.2	9.0, 12.0
Uridine	1.1, 1.1	1.1, 1.3	1.1, 1.1

acid in liver with respect to plasma emphasizes that the rate of uptake of ^3H -labelled precursors does not necessarily give any indication of the nature of the transport process. Mortimore *et al.* (1972) have made a detailed study of the uptake of [^{14}C]valine into perfused rat liver and found that at valine concentrations in the perfusate identical with those in rat plasma (0.1 mM) the ratio of intracellular to extracellular valine was less than 0.5. There was probably an intracellular valine pool which would be included in determinations of the intracellular acid-soluble amino acids but which was not in ready equilibrium with extracellular valine.

Since the effects of partial hepatectomy on uptake of precursors into liver seemed restricted to orotate, thymidine and uridine, simple competition studies were made to see if more than one transporter site was involved. The previous work (Ord & Stocken, 1972) had indicated saturation kinetics for the entries of orotate and thymidine into intact livers. Experi-

ments were now made with partially hepatectomized livers 1 h after operation. A marked difference in behaviour was detected between orotate and thymidine. In partially hepatectomized rats administration of 2mg of unlabelled orotate/kg decreased the capacity of the residual liver to accumulate ^3H radioactivity with respect to plasma. In contrast 10mg of unlabelled thymidine/kg did not detectably affect the uptake of radioactivity from [^3H]thymidine (Table 5). When 2mg of orotate/kg was given to rats receiving either [^3H]thymidine or [^3H]uridine no effects on the entries of these precursors were detectable, and conversely 10mg of unlabelled thymidine/kg had no effect on uptake of [^3H]orotate.

The results indicate that orotate does not compete with thymidine or uridine for entry into regenerating rat liver. Other evidence distinguishing between orotate transporters and those for thymidine comes from differences in the duration of the accelerated entry after partial hepatectomy. Experiments with

orotate (results not shown) indicated that the increased uptake of this precursor was no longer detectable 72 h after partial hepatectomy, but at this time the uptake of [^3H]thymidine was still increased, although [^3H]thymidine incorporation into DNA was past its peak (Table 6). By 8 days, DNA synthesis was not different from that in control rats, but the uptake had still not returned to normal. When tested at 15 days, uptake of [^3H]thymidine was in the control range; at this time the liver weights in the partially hepatectomized rats were 82% of those of unoperated rats of the same body weight.

Studies on pyrimidine metabolism (see Hartman, 1970) have established that in normal rats thymidine is catabolized via carbamoyl- β -aminoisobutyrate and β -aminoisobutyrate. It is not until about 12 h after partial hepatectomy that these catabolizing enzymes begin to decline in activity as thymidine kinase and the enzymes involved in the endogenous production of thymidine nucleotides begin to increase (see Bresnick, 1971). Orotate can be catabolized but is normally incorporated into uridine nucleotides after ribosylation with 5-phosphoribosyl pyrophosphate. The distribution of ^3H radioactivity was therefore

Table 6. Uptake of [^3H]thymidine into livers of partially hepatectomized rats at various times after operation

Unless otherwise stated, [^3H]thymidine and [^{14}C]inulin were injected intramuscularly 0.5 h before death. Other procedures are as described in Table 1. Values are means $\pm$ S.E.M., with the number of rats in parentheses.

Time of death after operation	Ratio of intracellular acid-soluble ^3H radioactivity to that in plasma	Stimulus produced by partial hepatectomy	Specific radioactivity of DNA relative to sham-operated rats
Sham-operated rats (10 min)*	1.4 ± 0.1 (3)	—	—
Sham-operated rats (0.5 h)	4.5 ± 0.2 (3)	—	1.0 ± 0.1 (9)
10 min*	2.3 ± 0.2 (4)	1.6	—
1 h	9.2 ± 1.6 (3)	2.0	—
22 h	8.9 ± 1.4 (14)	2.0	14.4 ± 3.5 (9)
3 days	8.0 ± 2.1 (3)	1.8	5.9 ± 1.2 (3)
8 days	7.4 ± 1.0 (4)	1.6	0.9 ± 0.2 (4)
15 days	3.8 ± 0.5 (3)	0.8	—

* Precursors given intravenously for 10 min only.

Table 7. Distribution of ^3H radioactivity in the acid-soluble fraction of livers from normal and partially hepatectomized rats

^3H -labelled precursor ($5\mu\text{Ci}$) and [^{14}C]inulin ($2.5\mu\text{Ci}$)/100 g body wt. were injected intramuscularly 0.5 h before death. The extracts were analysed by t.l.c. (Shimizu *et al.*, 1969) as described in the text. The results of one or two experiments are given.

^3H -labelled precursor administered	Metabolite	Distribution of radioactivity in extracts (%)	
		Sham-operated rats	Partially hepatectomized rats
Orotate	UMP + UTP	92, 86	91, 90
	Orotate	8, 10	9, 5
	Uridine	0, 4	0, 5
	Uracil	0, 0	0, 0
Thymidine	TMP + TTP	0, 0	0
	Unknown catabolite	100, 100	100
	Thymidine	0, 0	0
	Thymine	0, 0	0

analysed in extracts from sham-operated and partially hepatectomized rats killed 1 h after operation, which had received [^3H]orotate or [^3H]thymidine (Table 7). All the acid-soluble ^3H radioactivity from orotate was present as uridine nucleotides, the 8–10% of the counts in orotate being due to the extracellular fluid present in the portions of the liver examined. Predictably, with [^3H]thymidine given 0.5–1.0 h after partial hepatectomy no radioactivity was detected in thymidine phosphates. The radioactivity moved on the plates similarly for samples from sham-operated and partially hepatectomized rats, occupying a position similar to that taken up by marker orotate. The radioactivity was assumed to be due to thymidine catabolites. When the distribution of ^3H radioactivity from orotate between UMP and UTP was examined only 25% was in UTP, probably due to the sub-optimum conditions used for maintenance of high UTP concentrations (cf. Bucher & Swaffield, 1966). The concentration of ATP was $1.4\text{ }\mu\text{mol/g}$ wet wt. as compared with the value of 2.9 found by Bucher & Swaffield (1966), but it was considered desirable to bleed out the animals at death to minimize contamination of the liver extracts by radioactivity from the extracellular fluid.

Discussion

The competition studies and the difference in time-course of the response to partial hepatectomy indicate, as might be expected, that orotate and thymidine enter the liver by different mechanisms. Whether uridine uses the same system as thymidine is not clear from these results, but with L_{1210} murine leukaemia-cell cultures (Kessel & Shurin, 1968), chick embryo cells (Steck *et al.*, 1969) and human erythrocytes (Oliver & Paterson, 1972) there is evidence for a common transporter for ribonucleosides and deoxyribonucleosides. The behaviour in liver is complicated by the rapid metabolism of both orotate and thymidine; at the tracer concentrations administered no ^3H radioactivity remaining in these two precursors could be detected in the extracts. It seems probable that the great capacity of the liver to take up orotate and thymidine is due to the efficiency with which the compounds are utilized or catabolized. The absence of any stimulation of uptake of cytidine into livers after partial hepatectomy is consistent with results of Bucher & Swaffield (1969) who showed little change in [$2\text{-}^{14}\text{C}$]cytidine incorporated into CTP 45 min after operation.

The experiments described here and those with orotate reported by Bucher & Swaffield (1966, 1969) do not suggest that the increased intracellular ^3H radioactivity from orotate and thymidine in partially hepatectomized livers is due to any alteration in their pattern of metabolism. No changes in amounts of the

enzymes involved have been described by 1 h after partial hepatectomy.

In our adult rats the effect of partial hepatectomy on orotate entry seems to be independent of the amount of precursor provided that the circulatory concentration does not exceed that at which the overall mechanism becomes saturated ($1.5\text{--}2.0\text{ mg/kg}$ for partially hepatectomized rats, which is about $10\text{ }\mu\text{M}$). In the overall mechanism two stages must be distinguished: the translocation of the precursor across the membrane and its subsequent metabolism. This mechanism, which does not become saturated in normal rats until amounts of administered orotate exceed 5 mg/kg ($33\text{ }\mu\text{M}$), should be more than adequate to cope with the concentrations of orotate (2 nM) that are present in partially hepatectomized rats after administration of ^3H -labelled precursor. It does not therefore seem necessary to postulate that partial hepatectomy activates existing enzymes metabolizing orotate. Similar arguments obtain for thymidine entry.

Increased uptakes of cytidine and uridine occur in sea-urchin eggs immediately after fertilization (Piatigorsky & Whitely, 1965; Mitchison & Cummins, 1966). With uridine the greater uptake was inhibited by dinitrophenol. Both groups of workers suggested that fertilization activated pre-existing mechanisms that were linked to metabolism. In regenerating liver it is likely that the immediate activation is of the membrane transporters and that the existing intracellular enzymes have sufficient capacity to metabolize the substrates normally.

The physiological significance of the increased removal of orotate from plasma by regenerating liver is not clear, since this substance presumably does not usually circulate. With uridine and thymidine increased uptake of these compounds from the circulation might be a factor in the induction of their kinases, which occurs about 12 h after partial hepatectomy.

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