The Effect of Growth Hormone on Fibrinogen Synthesis

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A method described by McFarlane (1963a) for the measurement of the absolute rate of synthesis of liver-made plasma proteins was used to show that, within a few hours of giving bovine growth hormone to rats, fibrinogen synthesis increased significantly without a change in albumin synthesis.

Studies of the effect of growth hormone on the synthesis of plasma proteins have given conflicting results. Ulrich, Tarver & Li (1954) claimed that the administration of growth hormone enhanced albumin synthesis. In contrast, in liver perfusion studies (David & Miller, 1969), growth hormone did not seem to influence plasma protein synthesis significantly. Further, administration of growth hormone to both hypophysectomized (Warner, Weber, DeBodo & Kurtz, 1957) and normal animals (Campbell, Hausler, Munroe & Davidson, 1953) did not result in a significant increase in the concentration of serum albumin. Campbell *et al.* (1953) observed that administration of bovine growth hormone to dogs resulted in an early and marked increase in plasma fibrinogen concentrations and in the mass of circulating fibrinogen, without affecting the plasma albumin concentrations or the mass of circulating albumin, during a first series of injections (over 7 days).

McFarlane (1963a) described a method (elaborated by Reeve, Pearson & Martz, 1963) that can be used for the measurement of the synthesis of liver-made plasma proteins over short periods of time. This method has successfully measured the acute effects of endotoxin on fibrinogen synthesis (Koj & McFarlane, 1968).

The present study was designed to use McFarlane's (1963a) approach to observe the early effects of a single moderately small dose of bovine growth hormone on fibrinogen synthesis and to compare them with those on albumin synthesis.

The results of our study show that bovine growth hormone increases fibrinogen synthesis within 2-3 h of giving it to rats without affecting albumin synthesis.

MATERIALS AND METHODS

Animals. Male Wistar rats (body wt. 218-280 g) were used for these experiments.

Bovine growth hormone. This was a gift from Dr

Alfred E. Wilhelmi of Emory University, Atlanta, Ga., U.S.A., through the kindness of the Hormone Distribution Officer of the National Institute of Arthritis and Metabolic Diseases, Bethesda, Md., U.S.A. It met the specifications for bovine growth hormone NIH-GH-B15 with a mean relative potency of 0.88 USP unit/mg. [It had been prepared and characterized for the Endocrinology Study Section by Dr L. E. Reichert, jun., in 100g hypophysectomized female rats as described by Marx, Simpson & Evans (1942) with the subcutaneous injection modification of Parlow, Wilhelmi & Reichert (1965).] The batches contained negligible amounts of thyroid-stimulating hormone, luteinizing hormone and adrenocorticotrophic hormone.

Plan of experiment. Seven batches of four to six rats were used for control studies and four batches of six animals for the growth-hormone experiments.

The animals were placed on a diet containing 40% casein and providing 1700 kcal/m² surface area for 4-6 days before the study. According to Munro (1964) this intake of protein and calories provides optimum nutrition. Only animals eating the diet completely and gaining weight steadily were used for these studies. At 2-3 h before the injection of Na₂¹⁴CO₃ each rat was given 150 µg of bovine growth hormone intraperitoneally. A further two batches of rats were given bovine growth hormone for 3 days consecutively.

With the exception of the first two batches in the control series these animals received 25 µCi of Na₂¹⁴CO₃ intraperitoneally, followed by 5 µCi of either ¹²⁵I-labelled albumin or ¹²⁵I-labelled fibrinogen intravenously via the dorsal vein of the penis. The first two batches in the control series did not receive any ¹²⁵I-labelled protein. The second batch in the control series received 10 µCi of Na₂¹⁴CO₃.

After injection of the ¹⁴C- and ¹²⁵I-labelled compounds, blood was withdrawn under ether anaesthesia from the retro-orbital plexus into heparin 10 min, 20 min and hourly for 4 h after administration of the Na₂¹⁴CO₃. At the fifth or sixth hour the rats were anaesthetized and bled to obtain a large sample of blood. The samples were centrifuged and plasma was separated.

For each animal separately, the radioactivity (due to ¹²⁵I-labelled albumin or fibrinogen) of the 10 min plasma sample was determined to measure plasma volume (Jeejeebhoy *et al.* 1969). Subsequent blood samples were pooled before separation of the plasma.

Labelled compounds. $\text{Na}_2^{14}\text{CO}_3$ (specific radioactivity $>50\text{mCi/mmol}$) was supplied by Amersham/Searle, Don Mills, Ont., Canada. Rat albumin was prepared by DEAE-cellulose chromatography and labelled with ^{125}I by the method of McFarlane (1964). Fibrinogen was separated from rat plasma by $(\text{NH}_4)_2\text{SO}_4$ precipitation and labelled with ^{125}I (McFarlane, 1963b).

Experimental procedure. The methods used for the determination of plasma urea, ^{14}C urea, albumin and fibrinogen concentrations and arginine guanidine ^{14}C specific radioactivity were as described by Jeejeebhoy *et al.* (1969).

Calculation of results. The results were calculated from the formula proposed by Koj & McFarlane (1968): fractional synthesis rate of the given protein = (fractional synthesis rate of urea) $\times$ (hypothetical specific radioactivity of arginine guanidine carbon)/(hypothetical specific radioactivity of urea carbon).

Hypothetical specific radioactivity of urea carbon. This is defined as the specific radioactivity of urea that would be observed if all the labelled urea were distributed in the body water instantaneously. It can be calculated either by extrapolating the slope of the urea ^{14}C specific-radioactivity curve to t_0 or by an area method (Koj & McFarlane, 1968). Since we did not find any significant reutilization of $^{14}\text{CO}_2$ in our studies the extrapolation method of Koj & McFarlane (1968) was used. Under these circumstances extrapolation gives results that are almost the same as those obtained by the area method (Koj & McFarlane, 1968). We are aware that an error in the value obtained by extrapolation has an effect in the denominator of the equation for calculation of the synthesis rate. However there is some innate balancing of errors due to the fact that a higher extrapolation value is associated with a steeper slope.

Hypothetical specific radioactivity of arginine guanidine carbon. This is defined as the specific radioactivity of guanidine carbon that would be observed if all the active

protein had been distributed instantaneously in the plasma compartment. It is calculated by correcting the observed plasma protein arginine guanidine carbon specific radioactivity at any given time for radioactivity lost into the extravascular compartment and by catabolism. These losses were computed separately for albumin and fibrinogen by using the disappearance curves for ^{125}I -labelled albumin and fibrinogen. The method used for correction was the analogue-computer method described by Koj & McFarlane (1968).

Fractional synthesis rate of urea. The fractional synthesis rate of urea is given by the ratio of $\ln 2$ to t_1 of the slope of the graph of specific radioactivity of ^{14}C -urea in the plasma against time.

RESULTS

Plasma volume. The results are noted in Table 1. The plasma volume was 3.81 ± 0.289 and $4.34 \pm 0.496\text{ml}/100\text{g}$ in control and growth-hormone-treated animals respectively. This increase in plasma volume after administration of growth hormone was statistically significant ($0.02 > P > 0.01$).

Plasma albumin, plasma fibrinogen, total circulating albumin and total circulating fibrinogen. The results are given in Table 1. The concentration of plasma albumin was 2.90 ± 0.300 and $2.69 \pm 0.191\text{g}/100\text{ml}$ in control and growth-hormone-treated animals respectively. The decrease in plasma albumin concentration after administration of growth hormone was statistically significant ($0.02 > P > 0.01$). However, the values for total circulating albumin (plasma volume $\times$ plasma concentration of albumin) in control and growth-hormone-treated animals were not significantly different, being

Table 1. Comparison of plasma volume, plasma albumin and fibrinogen concentrations and the slope of ^{14}C urea specific radioactivity and urinary urea excretion, in control and growth-hormone-treated rats

Mean values are listed with standard deviation for the samples. Numbers in parentheses refer to the number of rats for the measurement concerned save for the mean slope of ^{14}C urea sp. radioactivity where the numbers refer to the number of batches (of about 6 rats each).

	Control	Growth-hormone-treated ($150\mu\text{g} \times 1$)
Plasma volume (ml/100g body wt.)	3.81 ± 0.289 (19)	4.34 ± 0.496 (14)
Plasma albumin concentration (g/100ml)	2.90 ± 0.300 (21)	2.69 ± 0.191 (12)
Total circulating albumin (mg/100g body wt.)	111 ± 12.5 (19)	117 ± 16.4 (14)
Plasma fibrinogen concentration (mg/100ml)	254 ± 31.3 (21)	261 ± 32.3 (12)
Total circulating fibrinogen (mg/ 100g body wt.)	9.75 ± 1.16 (19)	11.29 ± 1.88 (12)
Mean slope of ^{14}C urea sp. radio- activity ($0.693/t_1$):		
After injection of $\text{Na}_2^{14}\text{CO}_3$	0.393 (7)	0.433 (8)
After injection of ^{14}C urea	0.372 (6)	0.454 (3)
Urinary urea excretion (mg/h) (during the day following injection)	14.36 ± 1.315 (8)	8.423 ± 2.152 (6)

Fig. 1. Mean relative arginine guanidine ^{14}C specific radioactivity in albumin of control (O) and growth-hormone-treated (●) rats. The ordinate represents the arginine guanidine ^{14}C specific radioactivity expressed as a percentage of the highest specific radioactivity obtained.

Fig. 2. Mean relative arginine guanidine ^{14}C specific radioactivity in fibrinogen of control (O) and growth-hormone-treated (●) rats. The ordinate represents the arginine guanidine ^{14}C specific radioactivity expressed as a percentage of the highest specific radioactivity obtained.

111 ± 12.5 and 117 ± 16.4 mg/100 g body wt. respectively. Hence the decrease in plasma albumin concentration was due to dilution of the circulating albumin by the increased plasma volume.

The concentration of plasma fibrinogen was not significantly different in control and growth-hormone-treated animals, being 254 ± 31.3 and 261 ± 32.3 mg/100 ml respectively, and correspondingly the total circulating fibrinogen was higher ($P=0.05$) in the growth-hormone-treated animals, being 11.29 ± 1.88 mg/100 g body wt. compared with the control value of 9.75 ± 1.16 mg/100 g body wt.

Arginine guanidine ^{14}C specific radioactivity and hypothetical specific radioactivity of the arginine guanidine carbon. The mean relative arginine guanidine ^{14}C specific radioactivities for albumin

and fibrinogen are given in Figs. 1 and 2. Growth hormone had no effect on the curve for fibrinogen arginine guanidine ^{14}C specific radioactivity. In contrast, after administration of growth hormone the albumin arginine guanidine ^{14}C specific radioactivity reached a peak earlier than in controls. The fractional loss of arginine guanidine ^{14}C radioactivity into the extravascular compartment and through catabolism was obtained by analogue-computer analysis of the corresponding disappearance curves for ^{125}I and is given, for different time-intervals, in Table 2. Growth hormone did not change significantly the total loss of arginine guanidine ^{14}C radioactivity for both albumin and fibrinogen at any given time after the injection of $\text{Na}_2^{14}\text{CO}_3$, although the loss of fibrinogen was about 10% higher than that of albumin. Table 2 shows that the total arginine guanidine ^{14}C radioactivity (column 3) remained constant for any time-interval from 3 h onwards after injection of $\text{Na}_2^{14}\text{CO}_3$, showing that all the labelled protein had been delivered from the liver by that time. Hence arginine guanidine ^{14}C specific radioactivities from 3 h onwards were used to calculate synthesis. (Constancy was noted from 2 h onwards in the case of albumin alone.)

The observed and hypothetical specific radioactivities are given in Tables 3 and 4. Syntheses, calculated from arginine guanidine ^{14}C specific radioactivities obtained at any two intervals of time from 3 to 6 h after injection of $\text{Na}_2^{14}\text{CO}_3$, were compared in the control animals and agree with each other. In growth-hormone-treated animals the values were calculated from the single large specimen of blood drawn at the end of the experiment.

Comparison of [^{14}C]urea specific radioactivity obtained by injecting sodium [^{14}C]carbonate with that after injecting [^{14}C]urea. In control animals, the mean k factor ($0.693/t_1$) for [^{14}C]urea specific radioactivity after injection of $\text{Na}_2^{14}\text{CO}_3$ varied between 0.322 and 0.576 with a mean of 0.393 compared with a range and mean of 0.301–0.434 and 0.372 respectively after injection of [^{14}C]urea. In growth-hormone-treated animals the corresponding mean k values were 0.433 and 0.454 for rats injected with $\text{Na}_2^{14}\text{CO}_3$ and [^{14}C]urea respectively. The differences between the k values for [^{14}C]urea curves after injection of $\text{Na}_2^{14}\text{CO}_3$ and for those after the injection of [^{14}C]urea were not considered to be significantly different in either control or growth-hormone-treated animals.

The above results indicated that in the 218–280 g rats, taken as a group, there was no significant reutilization of $^{14}\text{CO}_2$ after injection of carbonate. Hence the k values used for the calculation of synthesis were obtained from the [^{14}C]urea curve generated endogenously by the injected $\text{Na}_2^{14}\text{CO}_3$.

Table 2. *Losses of radioactivity from the plasma compartment [analogue-computer estimates as percentage of maximum value in plasma (pool 1); see Koj & McFarlane (1968)]*

Synthesis interval (h)	Control					Growth-hormone-treated				
	Pool 1 (plasma)	Pool (3+4) (catabolism + extravascular)		Total radio- activity (pools 1 + 3 + 4)		Pool 1 (plasma)	Pool (3+4) (catabolism + extravascular)		Total radio- activity (pools 1 + 3 + 4)	
Albumin										
1	82	+	13	=	95	100	+	16.5	=	116.5
2	100	+	34	=	134	94	+	34	=	128
3	88	+	47	=	135	90	+	44	=	134
4	84	+	54.5	=	138.5	82	+	50	=	132
5	71	+	60	=	131	78	+	55	=	133
Fibrinogen										
1	80	+	10.5	=	90.5	83	+	10	=	93
2	98	+	29	=	127	92	+	32	=	124
3	100	+	43	=	143	100	+	47	=	147
4	92	+	53	=	145	92	+	57	=	149
6	82	+	60	=	142	77	+	68	=	145

Fibrinogen and albumin synthesis. The results are listed in Tables 3 and 4. The fibrinogen synthesis in control animals was 6.39 ± 0.838 mg/day per 100g body wt. In growth-hormone-treated rats fibrinogen synthesis had increased to 10.36 ± 2.374 mg/day per 100g body wt. The difference was easily significant ($P \approx 0.005$). Albumin synthesis, however, showed the opposite trend, being 84.21 ± 12.14 and 73.16 ± 16.15 mg/day per 100g body wt. in control and growth-hormone-treated rats respectively, but the difference was not statistically significant ($0.2 > P > 0.1$). In the two batches studied after administration of growth hormone for the longer period of 3 days, the fibrinogen synthesis again was higher than in controls but within the range obtained with animals treated with a single injection of growth hormone. However, the albumin synthesis this time had not decreased but increased, though marginally, in one of the two batches, to 156 mg/100g body wt per day.

Fibrinogen and albumin concentrations in the plasma of rats given 150 μ g of growth hormone for 3 days consecutively. The plasma albumin and fibrinogen concentrations were 2.87 ± 0.186 g/100 ml and 432 ± 64.1 mg/100 mg respectively in five rats given growth hormone for 3 consecutive days. Although the concentration of plasma albumin had remained unchanged, that of plasma fibrinogen had risen significantly after injection of growth hormone on 3 successive days.

Effect of growth hormone on urea excretion. This is listed in Table 1. It is noted that growth-hormone-treated rats as a group, showed an increased plasma volume and a very significantly ($0.001 > P$) decreased urinary urea excretion. These effects are compatible with the preparation used in our studies being effective as growth hormone in our animals.

Moreover the preparation supplied had been standardized and found effective (as growth hormone) in rats, as noted in the Materials and Methods section.

DISCUSSION

The results show clearly that in the intact animal bovine growth hormone increased the synthesis of fibrinogen within a few hours of administration to a rat. This increase in fibrinogen synthesis indicates a specific effect of growth hormone on the synthesis of one protein without affecting that of another (albumin). Our finding of an acute increase in fibrinogen synthesis is supported by the observed increase in total circulating mass of plasma fibrinogen (Table 1) which was even more marked in rats given growth hormone for 3 days (Table 3) contrasted with the unchanged plasma albumin pool size (Table 4).

These results are in accord with the findings of Campbell *et al.* (1953), who observed that administration of growth hormone to dogs increased plasma fibrinogen concentrations within 24 h of administration to 2.5–8 times the control value, without any increase in albumin concentrations. Further indirect support for the above results comes from the observations of both Warner *et al.* (1957), who showed that administration of growth hormone to hypophysectomized dogs increased the plasma concentration of globulin without changing that of albumin, and of Levin & Leatham (1942), who observed that the hypoalbuminaemia of hypophysectomy was almost completely reversed by adrenal corticoids without administration of growth hormone. Our findings, taken together with the studies mentioned above, suggest that growth

Table 3. *Fibrinogen synthesis*

The hypothetical specific radioactivity of plasma, fibrinogen arginine guanidine ^{14}C (column 4) and the plasma [^{14}C]urea sp. radioactivity at time t_0 (column 5) were calculated in the manner shown in the text. Total circulating fibrinogen (column 7) = concentration of fibrinogen in plasma $\times$ plasma volume. The fractional synthesis rate of fibrinogen (column 8) was computed according to Koj & McFarlane (1968) (see the text). The absolute synthesis rate for fibrinogen (column 9) was calculated thus: column 8 $\times$ column 7 = column 9.										
	Synthesis interval (h) (1)	Batch no. (2)	Plasma fibrinogen arginine guanidine ^{14}C sp. radioactivity		Plasma [^{14}C]urea sp. radioactivity		Total circulating fibrinogen (mg/100 g body wt.) (7)	(% of intra-vascular pool/day) (8)	Synthesis	
			Actual (d.p.m./mg of C) (3)	Hypothetical (d.p.m./mg of C) (4)	At time t_0 (d.p.m./mg of C) (5)	Slope 'E' (0.693/ t_1) (6)			(mg/100 g body wt. per day) (9)	
(a) Control	4	5	8400	13000	1.7×10^5	0.346	10.4	63.5	6.60	
	5	5	7120	12050	1.7×10^5	0.346	9.2	59.0	5.42	
	4	6	8540	13300	1.7×10^5	0.346	10.5	65.0	6.82	
	4	7	7400	11500	2.1×10^5	0.576	10.7	69.6	7.45	
	6	2	872	1560	2.4×10^4	0.322	—	50.5	—	
	3	2	1082	1542	2.4×10^4	0.322	—	50.0	—	
	5	3	7100	12000	2.0×10^5	0.470	8.4	67.6	5.67	
										6.39 ± 0.898
(b) Growth-hormone-treated ($150 \mu\text{g} \times 1$)	4	1	7120	11500	1.6×10^5	0.433	11.6	74.5	8.64	
	4	2	7633	12300	1.6×10^5	0.434	11.0	80.0	8.80	
	4	3	11241	18250	1.6×10^5	0.433	11.8	118.5	13.98	
	4	4	10103	16400	1.6×10^5	0.433	12.0	106.7	12.80	
	5	5	5400	10150	1.6×10^5	0.433	15.5	66.0	10.23	
	6	6	5762	10850	1.6×10^5	0.434	11.3	70.5	7.96	
	6	7	5995	11300	1.6×10^5	0.433	11.0	73.5	8.08	
	6	8	8503	16000	1.6×10^5	0.433	11.9	104.0	12.37	
										10.36 ± 2.374
(c) Growth-hormone-treated ($150 \mu\text{g}/\text{day} \times 3$)	5	2	8689	15350	2.9×10^5	0.601	15.7	76.5	12.02	
	4	3	8176	13200	3.0×10^5	0.601	17.5	63.5	11.13	

Table 4. *Albumin synthesis*

The notes for Table 3 apply here except that albumin is read for fibrinogen.

Synthesis interval (h) (1)	Batch no. (2)	Plasma albumin arginine guanidine ¹⁴ C sp. radioactivity		Plasma [¹⁴ C]urea sp. radioactivity		Total circulating albumin (mg/100 g body wt.) (7)	Synthesis	
		Actual (d.p.m./mg of C) (3)	Hypothetical (d.p.m./mg of C) (4)	At time t ₀ (d.p.m./mg of C) (5)	Slope 'k' (0.693/t ₁) (6)		(% of intra-vascular pool/day) (8)	(mg/100 g body wt. per day) (9)
(a) Control								
3	1	12500	19200	1.9 × 10 ⁵	0.346	—	83.5	—
5	1	9750	18000	1.9 × 10 ⁵	0.346	—	83.5	—
3	2	1400	2160	2.4 × 10 ⁴	0.322	—	69.6	—
3	3	9050	13900	2.0 × 10 ⁵	0.470	124.9	78.5	97.0
5	3	7220	13300	2.0 × 10 ⁵	0.470	108.9	75.0	81.0
6	4	6822	13300	1.5 × 10 ⁵	0.346	97.1	74.0	71.7
3	5	9114	14000	1.7 × 10 ⁵	0.346	117.1	68.0	79.5
2	5	10901	14600	1.7 × 10 ⁵	0.346	129.9	71.2	92.6
5	5	8152	15100	1.7 × 10 ⁵	0.346	97.6	73.9	72.2
4	6	9355	15400	1.7 × 10 ⁵	0.346	106.6	75.0	80.0
5	6	6759	12500	1.7 × 10 ⁵	0.346	120.0	61.0	73.1
3	7	10487	14100	2.1 × 10 ⁵	0.576	93.0	92.8	86.0
4	7	9000	14800	2.1 × 10 ⁵	0.576	112.1	97.4	109.0
							84.21 ± 12.14	
(b) Growth-hormone-treated (150 μg × 1)								
4	1	7960	12800	1.6 × 10 ⁵	0.433	126.3	83.0	105.0
4	2	6050	9740	1.6 × 10 ⁵	0.434	114.4	63.4	72.0
4	3	5080	8200	1.6 × 10 ⁵	0.433	121.7	53.3	64.5
4	4	7160	12300	1.6 × 10 ⁵	0.433	111.5	80.0	89.0
5	5	5400	9240	1.6 × 10 ⁵	0.433	90.0	60.0	54.0
6	6	5265	9460	1.6 × 10 ⁵	0.434	107.5	61.5	65.8
6	7	4820	8660	1.6 × 10 ⁵	0.433	121.9	56.2	68.0
6	8	3775	6800	1.6 × 10 ⁵	0.433	152.9	44.2	67.0
							73.16 ± 16.15	
(c) Growth-hormone-treated (150 μg/day × 3)								
5	2	11129	19100	2.9 × 10 ⁵	0.601	104.5	95.5	100.0
4	3	18504	30000	3.0 × 10 ⁵	0.601	108.0	144.0	156.0

hormone has a greater effect on 'globulin' and fibrinogen synthesis than on albumin synthesis. Some reservation in interpretation and application of our observations is necessary in view of our dose of growth hormone being hyperphysiological, although it is considerably less than that used in some other rat studies (Sellers, Bonoris & Katz, 1969). Because of the dose size and specificity (bovine growth hormone used in rat) and because it was given to growing animals, it is possible (although perhaps not likely) that the changes we have noted may in fact not represent physiological effects. It is thought to be improbable that the artificial, high-protein diet has any significant bearing upon the observed differential effect on plasma protein synthesis. The diet was so chosen for reproducibility and in order that plasma protein synthesis rates might be maximal and changes therein more readily demonstrable.

In opposition to the above-mentioned studies, Bartlett & Gaebler (1952), using ^{15}N -labelled amino acids, showed that growth hormone increased the ^{15}N specific radioactivity of both albumin-rich and globulin-rich plasma protein fractions obtained by Cohn's fractionation, and inferred that albumin synthesis had increased. However, their results do not necessarily suggest an increase in albumin synthesis because the albumin-rich protein fractions obtained by Cohn's fractionation also contain significant amounts of globulin, which may alter the specific radioactivity of albumin in this fraction. Our findings are also in contrast with the findings of Ulrich *et al.* (1954). However, in their studies growth hormone was injected for several days before measurement of synthesis. During prolonged administration of growth hormone, other factors such as increase in nitrogen retention or increase in food intake could have affected plasma protein synthesis. Further, although our results show an early and specific increase in fibrinogen synthesis, it is quite possible that with continued administration of growth hormone albumin synthesis may increase eventually, as in fact is suggested by the increase in synthesis of albumin in one of the two batches to which we gave growth hormone for 3 days. In this context Campbell *et al.* (1953) found no change in albumin mass during the first set of growth-hormone injections (7 days) but observed an increase during the subsequent series of injections. In studies with perfused liver David & Miller (1969) did not find any significant effect of growth hormone on plasma protein synthesis unless cortisol was removed from the perfusing medium, findings that are different from those observed *in vivo*. In other studies with perfused liver (Sellers *et al.* 1969) where growth hormone was thought to augment albumin synthesis, there is some difficulty in interpreting the data for lack of

evidence of constancy of the proportional production of urea and albumin.

The observation that growth hormone influences plasma globulin concentrations and fibrinogen synthesis may have a bearing on the albumin/globulin ratio in malnutrition. Plasma growth-hormone concentrations are increased in protein malnutrition (Marks, Howorth & Greenwood, 1965), and it is tempting to speculate that the growth-hormone-induced hyperglobulinaemia observed by Campbell *et al.* (1953), and the increased fibrinogen synthesis in our studies, may be relevant to the mechanism of hyperglobulinaemia in states of malnutrition.

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