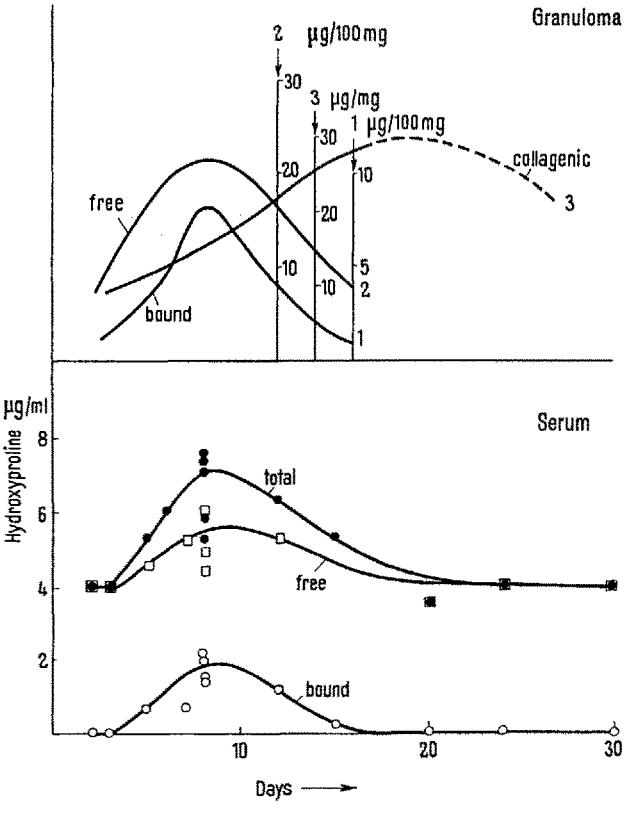
40th day. At the time of the resorption of collagen structure in granuloma, the level of the compounds studied in serum was within the bounds of the norm.

Discussion. The age changes in ultrafiltrable HYPRO in serum are, according to our experience, parallel with the decrease of the level of these substances in different organs (not yet published)[13].

The HYPRO containing peptides which we did not find in the serum of adult animals increased again during the development of carrageenin granuloma. The increase of serum HYPRO compounds could theoretically be expected in three periods of the development of fibrotic granuloma: (1) at the time of the infiltration of the subcutis of the polymorphonuclear leucocytes when an increased proteolytic activity occurs, (2) at the time of collagen formation or its precursors, (3) at the time of the degradation of collagen at the phase of the resorption of the granuloma. Our results favour the second possibility. Although the morphologically provable accumulation of polymorphonuclears precedes the increase of ultrafiltrable HYPRO in granuloma tissue, and also the serum and peptidic HYPRO correlate rather with the accumulation of fibroblasts, our results are not a direct proof that peptides are precursors of collagen. According to HOUCK and JACOB[14], who found an increase of serum HYPRO during inflammation of the skin induced by croton oil, we expected a second peak of ultrafiltrable serum HYPRO at the phase of the resorption of collagen. Our negative finding could perhaps be explained by the different mechanism of destruction of collagen during croton inflammation, perhaps in the carrageenin granuloma.

As the increase of the serum ultrafiltrable HYPRO occurs in the early stage of the fibroplastic inflammation, we suppose that the study of these substances could serve for an early diagnosis of fibrotic diseases (precirrhosis, presilicosis)[15].



Time correlation of serum and granuloma changes in ultrafiltrable—free and conjugated—and collagen hydroxyproline. The upper part describes schematically tissue changes, for details see [7–9].

Zusammenfassung. Die Konzentration des ultrafiltrierbaren Oxyprolins im Serum der Ratten und Meerschweinchen senkt sich während des Alterns. Bei erwachsenen Tieren ist peptidisch gebundenes ultrafiltrierbares Oxyprolin nicht mehr nachweisbar. Während des 6.–10. Tages der Entwicklung des Carrageeningranuloms bei Meerschweinchen steigt die Konzentration des freien und peptidisch gebundenen Oxyprolins im Serum gleichlaufend mit der Erhöhung dieser Stoffe im Bindegewebe des Granuloms.

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[13] The discrepancy of our results and of KIVIRIKKO and LIESMAA[10] could be explained by analysing younger and older rats in our experiments where the decreasing trend is evident (Table).

[14] R. JACOB and J. C. HOUCK, Surg. Gynec. Obstet. *109*, 85 (1959).

[15] The carrageenin was the gift of Mr. L. STOLOFF of Seaweed Chemicals Inc., New Brunswick, to whom we express our thanks.

Induced Increase of Meprobamate Metabolism in Rats Pretreated with Phenobarbital or Phenaglycodol in Relation to Age

In a previous work a remarkable increase of meprobamate metabolism in rats pretreated with phenobarbital or phenaglycodol was reported[1]. The mechanism which produces an increase of meprobamate metabolism is not yet clear but some sort of enzymatic adaptation of the liver of the pretreated animals was supposed[2–4]. In the work reported here, a possible difference in the induction capacity of increased metabolism of meprobamate between different ages of rats was examined.

Rats of Sprague-Dawley strain, weighing 300 g and 180 days old (adult rats), weighing 160 g and 60 days old (young rats), weighing 70 g and 32 days old (immature rats) were used. The determination of meprobamate concentrations in serum and brain was carried out according to the method of HOFFMAN and LUDWIG[5]. Phenobarbital and phenaglycodol were injected intraperitoneally in doses of 80–100 mg/kg, 48 h before the injection of meprobamate (150 mg/kg i.p.).

Figure and Table show that metabolism of meprobamate in phenobarbital or phenaglycodol pretreated rats markedly increased, and, on the other hand, younger rats can metabolize meprobamate more rapidly than older rats. For example: *in vivo* metabolisms of meprobamate by 100 g of body weight for 2 h after the injection were as follows: 3.5 mg for adult rats, 5.3 mg for young rats and

[1] R. KATO, Med. exp. *3*, 95 (1960).

[2] A. H. CONNEY, C. DAVISON, R. GASTEL, and J. J. BURN, J. Pharm. exp. Therap. *130*, 1 (1960).

[3] R. KATO, Jap. J. med. Sci. Pharmacol., in press.

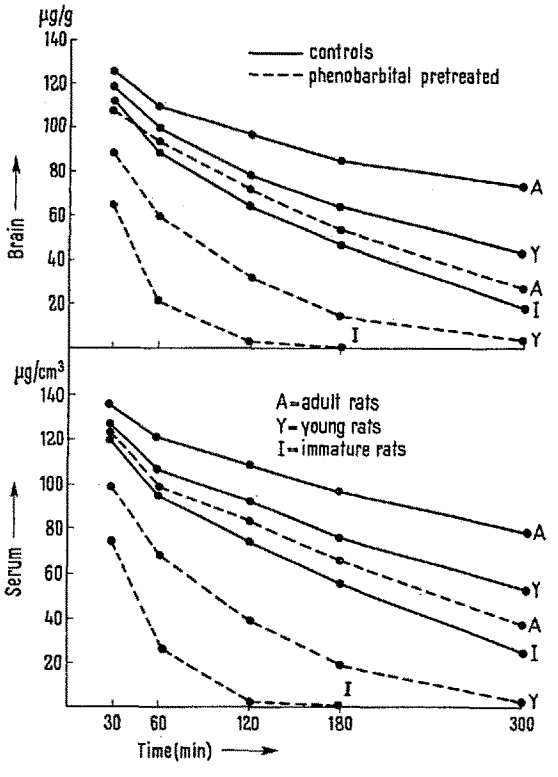
[4] R. KATO, Neuro-psychopharmacology (Ed. Rethlin) *2*, 57 (1936).

[5] A. J. HOFFMAN and B. J. LUDWIG, J. Amer. pharm. Assoc. *68*, 740 (1959).

Effect of phenobarbital or phenaglycodol pretreatment on metabolism of meprobamate in relation to age of rats

Age	Pretreatment	Meprobamate concentration serum (μg/ml)	brain (μg/ml)	*In vivo* metabolism (μg/100 g/2 h)	Variation (%)	Biological half-life (min)	Variation
Adult	–	108 ± 4.1 (12)	97 ± 3.7 (12)	35		345	
Adult	Phenobarbital	84 ± 3.5 (8)	72 ± 3.5 (8)	60	+ 71	150	× 0.44
Adult	Phenaglycodol	96 ± 4.0 (8)	84 ± 3.4 (8)	49	+ 40	–	
Young	–	92 ± 3.4 (15)	79 ± 2.9 (16)	53		195	
Young	Phenobarbital	40 ± 2.1 (8)	31 ± 2.3 (8)	104	+ 96	58	× 0.30
Young	Phenaglycodol	59 ± 3.4 (8)	59 ± 3.5 (7)	75	+ 41	–	
Immature	–	77 ± 2.9 (16)	65 ± 2.7 (16)	67		130	
Immature	Phenobarbital	3 ± 0.9 (8)	4 ± 1.1 (8)	141	+110	31	× 0.24
Immature	Phenaglycodol	28 ± 2.2 (4)	21 ± 1.8 (4)	117	+ 75	–	

Meprobamate concentration was determined 2 h after the injection of meprobamate (150 mg/kg). Metabolism *in vivo* is represented by metabolized meprobamate during 2 h after the injection of meprobamate (150 mg/kg) per 100 g body weight. The numbers in brackets show number of the determination.



Influence of different ages of rats on the induction of increase of meprobamate metabolism. Meprobamate (150 mg/kg) was injected intraperitoneally at 0 time. The abscissas show serum and brain meprobamate concentration.

6.7 mg for immature rats; the biological half-life of meprobamate was 345 min in adult rats, 195 min in young rats and 130 min in immature rats.

It is also demonstrated that the induction of increased meprobamate metabolism is more remarkable in younger rats than in older rats. For example, the meprobamate metabolism in adult rats was increased 71% by the pretreatment with phenobarbital, while in young rats and in immature rats, the metabolism was increased 96% and 110% respectively, and also biological half-life of meprobamate was shortend 56% in adult rats, 70% in young rats and 76% in immature rats by the pretreatment with phenobarbital. It is not yet known why the liver of younger rats is more sensitive than that of older ones in response to the phenobarbital pretreatment. On the other hand, recently it was reported that no difference in the induction of liver tryptophanperoxydase exists in the different ages of the rats used[6].

According to our results, the regenerating liver of the adult rats was still less sensitive than the liver of young rats in the induction, therefore the factors which determine the sensitivity of liver in the induction of the enzyme by phenobarbital are not related to the age of the liver but it might be related to some humoral factors in these animals.

Riassunto. Si è osservato che il metabolismo del meprobamato è tanto più rapido quanto più giovani sono i ratti usati ed anche che l'induzione dell'aumento del metabolismo *in vivo* è tanto più intensa quanto più giovani sono i ratti usati.

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[6] R. I. Gregerman, Amer. J. Physiol. *197*, 63 (1959).

Effect of Amygdaloid Lesions on Plasma Corticosterone Response of the Albino Rat to Emotional Stress

The rich projection of the amygdaloid nucleus to the hypothalamus (Gloor[1]), suggests that this limbic structure may modulate the hypothalamic-hypophysial response to stress. Experiments undertaken to date have supported this assumption. Mason[2] found in the monkey that partial or complete bilateral amygdalectomy temporarily inhibited the plasma 17-hydroxycorticosteroid response to emotional stress (bar-pressing to avoid electric shock), delaying peak output as much as 6 h. This effect was only obtained, however, at 4 weeks following the operation. This work suggests that the amygdala normally boosts ACTH secretion in the monkey. Martin[3] et al. found high adrenal venous corticosteroid output in dogs

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[2] J. W. Mason, Amer. Psychosom. Soc., Montreal, March 26 (1960); Psychosom. Med., in press.
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