depletion of pituitary GH (group 2 vs. 1). No changes of blood glucose were noticed after administration of cyclic AMP or theophylline, or both compounds at the doses used. The second series of experiments are summarized in Table II. The administration of formalin to normal rats did not elicit a significant depletion of pituitary GH (group 2 vs. 1), but was effective in this sense in animals pretreated 1 h before with theophylline (group 4 vs. 1 and 2). Blood glucose levels found in formalin or theophylline plus formalin treated rats were significantly higher than controls.

Discussion. Our results confirm and extend the previous observations of SCHOFIELD[2]. In fact the intraventricular administration of theophylline, which through inhibition of phosphodiesterase presumably enhances endogenous levels of 3′,5′-AMP, brings about a clear GH release. On considering this result, the lack of effect of the intraventricular injection of 3′,5′-AMP appears surprising but is probably due to the low entry into cells of the nucleotide[6], even if by using the dibutyrate derivative a greater rate of entry into cells would be expected[6]. To allow the appearance of an effect sustained by the low amounts of 3′,5′-AMP able to penetrate into cells, a contemporary inhibition of phosphodiesterase seems to be required. This is suggested by the observation that theophylline, although ineffective in releasing GH when given by s.c. injection, favours the appearance of a GH-releasing effect in animals treated intraventricularly with 3′,5′-AMP. It is relevant to this point that GAGLIARDINO and MARTIN[7] observed a sharp rise in the circulating levels of GH in monkeys treated i.v. with 3′,5′-AMP alone. Recently LEVINE[8] has demonstrated in the human clearcut increase of plasma levels of GH after perfusion with dibutyril 3′,5′-AMP. These data fit in well with our results in the rat and in addition point to differences among species with respect to the ability of 3′,5′-AMP to penetrate cell membranes[6]. The action of theophylline in the processes of GH release depends upon the ability of this xanthine to inhibit the cyclic nucleotide phosphodiesterase that hydrolizes cyclic AMP in the pituitary and/or hypothalamus. In the light of the results of VERNIKOS-DANELLIS and HARRIS[9], who have shown that in vivo caffeine and theophylline markedly reduced the phosphodiesterase activity of the anterior pituitary while being quite ineffective on the enzyme activity of the hypothalamic median eminence; and the in vitro work of SCHOFIELD[2], it would appear that theophylline given intraventricularly releases GH, since it is capable of reaching the pituitary by diffusion into the portal vessels. The observation that a stress ineffective in releasing GH in the rat, such as formalin administration[4], induces this effect when animals are pretreated with theophylline, is reminescent of data reported by VERNIKOS-DANELLIS and HARRIS[9], who noticed that pretreatment of rats with theophylline resulted in a potentiation of the stress-induced secretion of ACTH. Apparently the level of 3′,5-AMP in the pituitary mediates the secretion of the gland in response to impulses conveyed by different nervous pathways.

Riassunto. Il 3′,5′-AMP dibutirrato (5 μg) iniettato nel ventricolo laterale del cervello di ratto, provoca una spiccata liberazione dell'ormone somatotropo soltanto in animali pretrattati con teofillina (50 mg/kg s.c.). La teofillina per via s.c. (50 mg/kg) si dimostra inattiva, ma libera ormone somatotropo quando è iniettata per via endoventricolare (5 μg). Uno stimolo usualmente incapace di liberare somatotropo (formalina) provoca deplezione dell'ormone dall'ipofisi in ratti pretrattati s.c. con teofillina. I risultati sono in favore di una partecipazione del 3′,5-AMP nel meccanismo di liberazione di ormone somatotropo.

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Growth of the Endocrine Organs of Female Hamsters Blinded at 25 Days of Age[1]

Light deprivation from adult female hamsters (*Mesocricetus auratus*) either by exposure to darkness or by blinding leads to gonadal atrophy within 8 weeks; the gonadal inhibitory effects of darkness are prevented if the pineal gland is removed[2,3]. The pineal gland, or epiphysis cerebri, in the hamster lies just beneath the confluence of sinuses between the cerebral hemispheres and is attached to the epithalamus by a tenuous stalk. To test the effect of the absence of light on the neuroendocrine axis of female hamsters blinded before puberty the following experiment was performed.

Materials and methods. Growth of the endocrine and reproductive organs were compared in the following groups of hamsters: (1) normal; (2) blinded and sham-pinealectomized; (3) blinded and pinealectomized. Anesthetized animals were operated on using techniques previously established[4,5]. Since the pineal gland lies directly under the confluence of sinuses it can be extirpated easily after removing a circular piece of bone overlying the area[4]. Animals were maintained under controlled temperature (24 ± 2 °C) and lighting (14 h light per 24 h period) conditions. 8–10 hamsters from each of the 3 groups were killed at 25 day intervals after the operations

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to 150 days of age; the endocrine and reproductive organs were weighed and retained for histological study. 10 hamsters were killed at 25 days of age and the reproductive organs were weighed; these mean weights are used as the 25-day valves in Figures 1 and 2. A total of 154 animals were used.

Results and discussion. The results showed that body weights were unaffected by blinding, by sham pinealectomy or by real pinealectomy throughout the duration of the experiment. Similarly, ovarian weights were unchanged by either removal of the eyes alone or in combination with pinealectomy (Figure 1). On the other hand, uterine weights were markedly affected. Blinded, sham-operated hamsters killed at 75 days of age (50 days after blinding) had uteri that were significantly smaller ($P < 0.001$) than those of untreated animals of the same age. Thereafter the uteri of eyeless hamsters remained regressed and at 150 days of age they averaged 92 mg per 100 g of body weight compared with a mean of 364 mg for uteri of normal hamsters (Figure 2). By comparison, uterine weights of blinded pinealectomized animals at each interval were similar in size to those of untreated animals and at 150 days of age they weighed 375 mg per 100 g of body weight. The sizes of typical uteri from animals of the 3 groups are compared in Figure 3. Adrenal and thyroid gland weights were unaffected by blinding, sham or real pinealectomy. Pituitary weights of eyeless hamsters killed at 125 and 150 days of age were significantly smaller ($P < 0.05$) than those of the other 2 groups. Histologically, the uteri and ovaries of blinded non-pinealectomized animals were atrophic suggesting a decreased hormonal stimulation. Follicular development in ovaries of eyeless hamsters was impaired as judged by the paucity of vesicular follicles; in addition the amount of interstitial tissue was greatly increased in these ovaries similar to that seen in ovaries of females blinded after puberty[6]. Uterine structure was generally infantile in appearance with few endometrial glands and low columnar or cuboidal epithelia lining the lumina.

The results indicate that blinding prepuberal female hamsters severely curtails the growth of the reproductive organs after adulthood is achieved although it does not seem to restrict the initial maturation of the reproductive organs. If animals are also pinealectomized, however, the gonads and accessory organs grow at the same rate as those of untreated control animals.

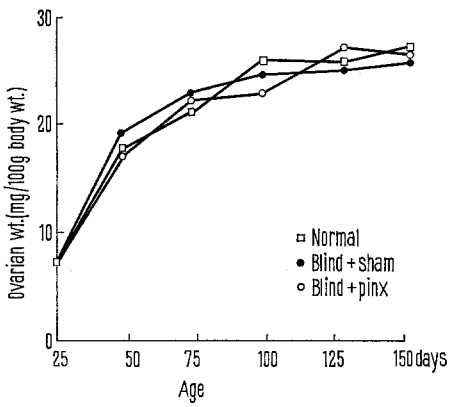

Fig. 1. Mean ovarian weights of 3 groups of hamsters (normal; blinded and sham-pinealectomized; blinded and pinealectomized) killed at 25-day intervals after the operations. Since none of the mean weights differed significantly from the mean of any group killed at the same interval and since the standard errors of the means were so small that they could not be accurately drawn of the figure, vertical lines signifying standard errors (such as in Figure 2) are not included. Each point represents 8–10 animals.

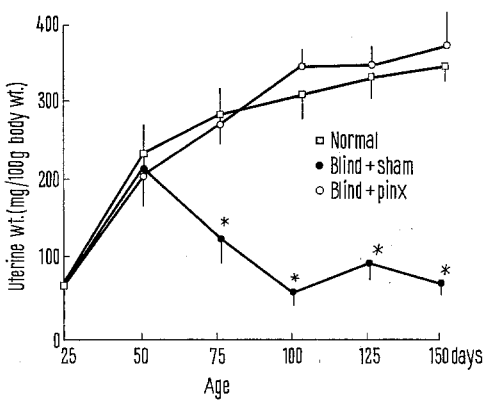

Fig. 2. Mean uterine weights of 3 groups of hamsters (normal; blinded and sham-pinealectomized; blinded and pinealectomized) killed at 25-day intervals after the operations. Vertical lines signify standard errors. Asterisk indicates mean weights that are significantly different ($p < 0.001$) from mean of normal animals. Each point represents 8–10 animals.

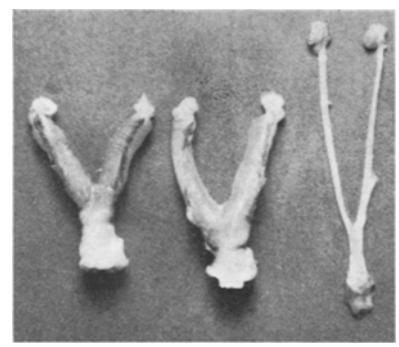

Fig. 3. Uteri, with attached ovaries, of one animal from each of the experimental groups. From left to right, a uterus of a normal hamster, a blinded pinealectomized hamster and a blinded hamster that had a pineal gland but had been sham-operated. All animals were 125 days old when killed. × 1.

Zusammenfassung. Blendung von 25 Tage alten, geschlechtsunreifen weiblichen Goldhamstern führt zur Atrophie der Geschlechtsorgane im Erwachsenenalter. Wenn zusätzlich die Epiphyse entfernt wird, wird eine durch die Blendung verursachte Gonadenatrophie verhindert.

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