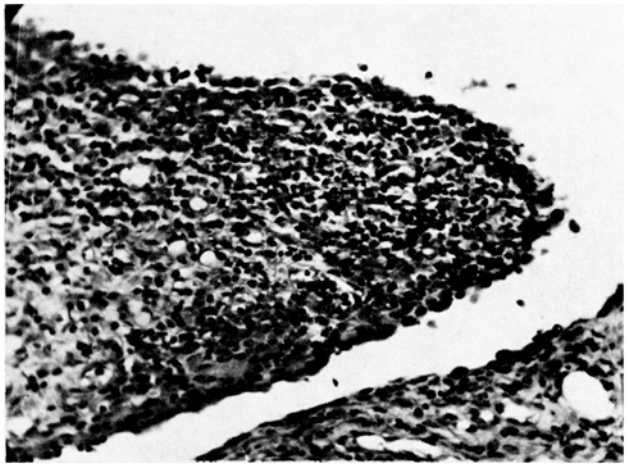

Fig. 3. Swollen synovial villous of a rabbit joint killed 20 days following intraarticular injection of 5 mg SEP. The villous is infiltrated by predominantly mononuclear inflammatory cells. The synovial lining cells are prominent. × 270.

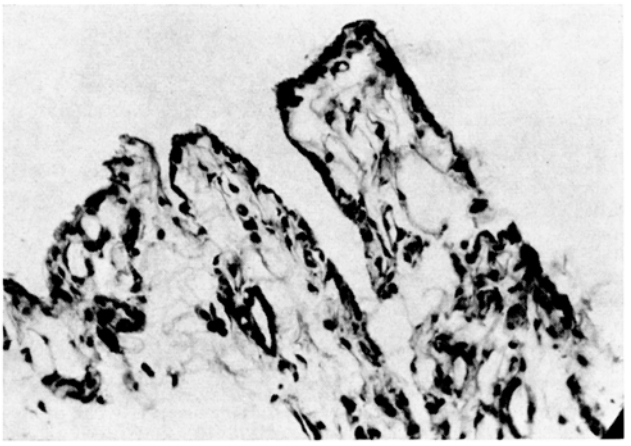

Fig. 4. Normal appearing synovia in a rabbit killed 7 days following an intraarticular injection of SEP heated to 100 °C. Note the delicate subsynovial connective tissue. × 270.

polysaccharides[7], the effect of the various streptococcal products (SLS, sonicates and SEP) on the synovial membrane are but 1 example of agents capable of injuring the joints. The sera of the rabbits used did not contain any detectable antibodies reactive with SEP. Thus, since the first synovial lesions become manifest as early as 16 h following injection, the possibility that the synovial alterations are due to an immune response should be considered only to be excluded[8].

*Zusammenfassung.* Intraartikuläre Injektion von Streptolysin-S-freien extrazellulären Produkten der Streptokokken Gruppe A verursacht eine zunächst akute, in der Folge aber subkutane Synovitis. Die Veränderungen gleichen denjenigen nach Injektion von Streptololensonikaten, so dass angenommen wird, ausser Streptolysin S bedingen auch andere streptokokkale Faktoren eine Arthritis.

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*19 October 1967.*

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## Effect of Alloxan Diabetes and Insulin Administration on the Incidence of Pituitary Necrosis Caused by Hexadimethrine Bromide in Rats

According to obduction data necrosis of anterior pituitary occurs more frequently in diabetic patients[1]. As administration of hexadimethrine bromide to rats causes necrosis in the anterior lobe of the pituitary gland[2–4], the possibility arose of studying whether the incidence and extent of adenohypophysial necrosis due to hexadimethrine bromide (HB) is modified in rats with alloxan diabetes and in those injected with insulin.

The experiments were carried out on female albino rats of the same strain weighing ca. 200 g and kept on a standard diet. One group of rats received HB (Polybrene®, Abbott) alone in a dose of 5 mg/rat i.v. Three groups of rats were given a single i.v. injection of 40 mg/kg body weight alloxan monohydrate. Two, 6 and 30 days later they were i.v. injected with 5 mg/rat of HB. Blood sugar levels were determined before the administration of HB and only the rats having hyperglycaemia were used. Other groups fasting for 12 h were given 1.0 IU/100 g body weight aqueous insulin (Richter, Budapest) i.p. simultaneously with HB.

The results are shown in the Table. It can be seen that, contrary to our expectation, the rats with alloxan diabetes did not become more sensitive to the effect of HB; their survival time was not shorter, mortality and incidence of adenohypophysial necrosis did not increase. On the other hand, insulin administration strikingly sensitized the rats to the effect of HB; most of the rats died within 48 h, survival time was shortened and adenohypophysial necrosis more often appeared.

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| Group | No. of rats | Body weight g | Died within 6 h | 24 h | 48 h | Average survival time h | Incidence of pituitary necrosis |
|---|---|---|---|---|---|---|---|
| Untreated control | 20 | 205 ± 2.7[a] | 0 | 0 | 0 | – | 0[b]/0[c] |
| Hexadimethrine bromide (HB) | 20 | 208 ± 3.2 | 0 | 1 | 4 | 46 ± 1.3 | 7/20 |
| Alloxan + 2 days later HB | 18 | 228 ± 4.3 | 0 | 1 | 2 | 46 ± 1.5 | 4/18 |
| Alloxan + 6 days later HB | 13 | 171 ± 7.8 | 0 | 1 | 1 | 45 ± 2.8 | 2/13 |
| Alloxan + 30 days later HB | 9 | 187 ± 3.9 | 0 | 2 | 2 | 40 ± 5.3 | 2/9 |
| Insulin | 20 | 204 ± 2.8 | 0 | 0 | 0 | 48 | 0/20 |
| Insulin + HB | 40 | 199 ± 3.3 | 32 | 32 | 34 | 12 ± 2.9 | 7/8 |
| Heparin + insulin + HB | 10 | 205 ± 0.9 | 0 | 0 | 0 | 48 | 0/10 |
| Pipolphen + insulin + HB | 11 | 190 ± 3.7 | 3 | 9 | 11 | 15 ± 4.4 | 2/8 |
| Polymyxin-pretreatment + insulin + HB | 10 | 201 ± 2.7 | 4 | 4 | 4 | 30 ± 7.2 | 2/6 |
| Compound 48/80-pretreatment + insulin + HB | 18 | 200 ± 4.0 | 5 | 5 | 8 | 35 ± 4.7 | 1/13 |

[a] Standard error. [b] No. of rats with pituitary necrosis. [c] No. of investigated rats.

HB is an antiheparin agent and causes disruption of mast cells thus inducing histamine and serotonin release[5–7]. It was therefore further examined whether administration of heparin (Richter, Budapest) and Pipolphen (promethazine, E.Gy.T., Budapest) as well as pretreatment with polymyxin (polymyxin B sulphate, Pfizer, Brussels) and compound 48/80 (Wellcome Research Laboratories, Langley Court, Beckenham) to deplete histamine stores may modify the potentiating effect of insulin on that of HB. Heparin (10 mg of heparin i.p. 15 min prior and 4 h later to HB and insulin administration) offered complete protection. This, however, did not throw any light on the pathogenesis of the process as heparin neutralizes HB in vitro and in vivo. Pipolphen (10 mg of pipolphen i.p. 15 min prior and 1, 2, 3 h later to HB and insulin administration) did not significantly influence mortality and survival time, whereas frequency of adenohypophysial necrosis was reduced. Pretreatment with polymyxin (2 × 0.5 mg for 2 days, 2 × 1.0 mg for 2 days, 2 × 1.5 mg for 2 days i.p.; on the seventh day HB and insulin administration) and compound 48/80 (2 × 0.1 mg on the first day, 2 × 0.2 mg on the second day, 2 × 0.3 mg on the third day, 2 × 0.4 mg on the fourth day, 2 × 0.5 mg on the fifth day i.p.; on the sixth day HB and insulin administration) was effective; survival time was fairly well extended, mortality and frequency of pituitary necrosis decreased.

Further experiments are needed to elucidate the exact mechanism of the sensitizing effect of insulin (or hypoglycaemia). It is known that HB releases histamine and, as the potentiating action of insulin does not occur in rats depleted of their histamine stores due to polymyxin and compound 48/80 pretreatment, it can be supposed that histamine plays an important role in the potentiating effect of insulin. This assumption is not contradicted by the fact that pipolphen possessed only a weak protective effect; obviously it could not be administered in such a large dose to accumulate in an effective amount on the receptor sites. Other authors[8–10] demonstrated that insulin hypoglycaemia potentiated also the effect of other histamine releasers and increased their toxicity. Insulin may promote the release of histamine or sensitize the capillaries to the effect of histamine, or it may intensify in the presence of histamine the vascular changes caused by HB leading to an arrest of adenohypophysial circulation and subsequently ischaemic infarction.

*Zusammenfassung.* Während Alloxan Diabetes die Sensitivität der Ratten für die Wirkung des Hexadimethrin-Bromid (HB) nicht steigert, bewirkt Insulinbehandlung eine starke Erhöhung der HB-Empfindlichkeit. Die Mehrzahl der mit Insulin + HB simultan behandelten Ratten starb innerhalb von 2 Tagen, und in den Adenohypophysen zeigten sich häufig Nekrosen. Da die potenzierende Wirkung des Insulins bei Ratten, deren Histamin-Depots durch Vorbehandlung mit Polymyxin und Substanz 48/80 depletiert worden waren, nicht zur Geltung kam, wird angenommen, dass beim HB-potenzierenden Effekt des Insulins auch das Histamin eine Rolle spielt.

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## La Rigenerazione del testicolo atrofico da Fluoroacetamide

In una precedente pubblicazione[1] abbiamo descritto una distruzione dell'epitelio germinativo nel testicolo di ratti trattati per os con fluoroacetamide (FAA).

Tale risultato è stato da noi attribuito ad un'azione selettiva esercitata dalla sostanza sull'epitelio germinale.

Nella presente nota riferiamo con quali modalità ed in quale lasso di tempo sia possibile ottenere, sospendendo la somministrazione della FAA, una ripresa della funzionalità dell'organo.

Le nostre indagini sono state condotte su 25 ratti albini, del peso oscillante fra 160–180 g, a cui la FAA è

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