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Testicular Lesions in Rats Treated for One Year with Ethambutol in Low Doses

G. P. Trentini, A. Botticelli and G. Barbolini

Istituto di Anatomia e Istologia Patologica dell'Università di Modena (Direttore: Prof. S. Battaglia), Modena, Italy

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Summary. EMB administered to albino rats in therapeutic doses for one year caused not only the loss of fertility but also evident regressive lesions in the testes. The phenomenon may be attributed to the chemical nature of dextrorotatory isomer of EMB or on the other hand to accumulation of the drug in the organism.

Introduction

In a previous note (Botticelli, Trentini and Barbolini, 1971) we described histological lesions in the testes of rats treated with ethambutol (dextrorotatory isomer) in doses of 300 and 600 mg/kg/day for three months.

The lesions were chiefly characterized by marked regressive changes and parenchymal atrophy with arrest of spermatogenesis.

The present study sets out to ascertain whether similar lesions can be induced by ethambutol (EMB) administered in therapeutic doses over a long period of time. We therefore limited doses to 35–50 mg/kg/day. It will be remembered in this context that the average dose used in human therapy is of 25–30 mg/kg/day.

Finally, in dogs treated with EMB for 6–12 months in doses of less than 100 mg/kg/day no regressive changes worthy of note were observed by Kaiser (1962), Cappiello and Layton jr. (1965), Diermeier, Kaiser and Yuda, (1966). However the AA did not consider the testis in their results.

Materials and Methods

20 albino male Wistar rats, aged on average 3 months and weighing 190 ± 10 were used.

The animals were kept under normal conditions and fed a completely standardized diet (pellets)[1] with water *ad libitum*. Of these, 10 served as controls (untreated); 10 were treated with EMB (dextrorotatory isomer, by gavage, daily for one year). The dose was 50 mg/kg/day for the first six months and 35 mg/kg/day for the remaining six months.

As from the 11th month of the experiment all the animals were placed in cohabitation with normal female adult rats.

At the end of the experiment the animals, now weighing on average $500\,g \pm 20$ were anaesthetized with ethyl ether and decapitated.

The testes were immediately removed, fixed in 1% calcium acetate—10% formalin and embedded in paraffin in the normal manner. The sections were stained with hematoxylin-eosin.

1 Morini, 42020 S. Polo d'Enza (RE), Italy.

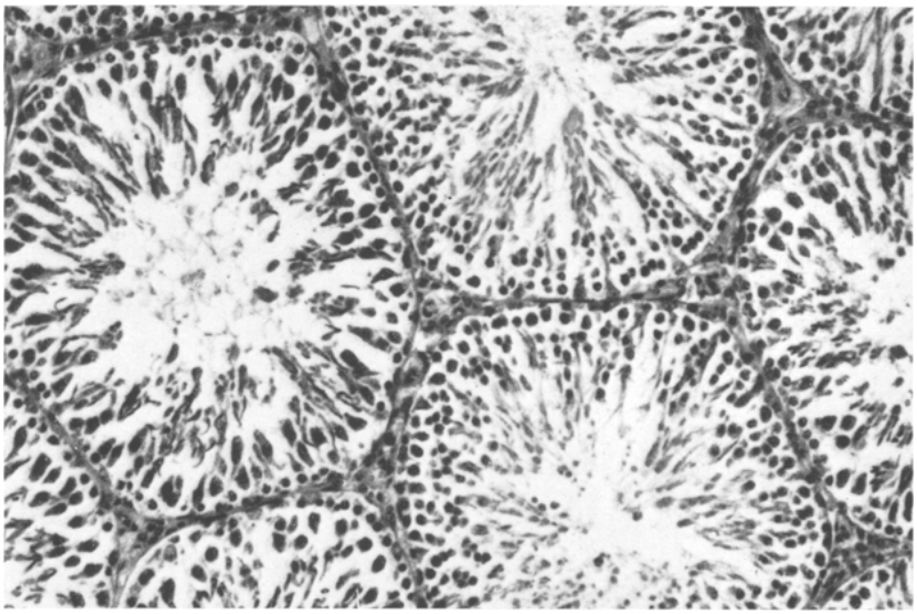

Fig. 1. Rat testis of 12 months: untreated control (× orig. 320)

Results and Discussion

1. Unlike the controls of the same age, the rats treated with EMB were not capable of fertilising the female.

2. The testes of the control rats did not exhibit any regressive changes worthy of note even after 12 months (Fig. 1).

3. The testes of the rats treated with EMB exhibit a whole series of regressive changes. The seminiferous tubules are generally dilated and hypotrophic with a lumen either optically empty or containing finely granular and eosinophilic material. At other times they appear atrophic with total disappearance of the cells of the seminal line (Fig. 2), with a wall consisting solely of the tunica propria and sometimes exhibiting necrosis and calcification (Fig. 3). Occasionally, seminiferous tubules are found which are lined with several layers of germinal cells but with arrest of meiosis in the acrosome-phase.

The above findings emerged in various combinations in about half of the animals examined. Tubular atrophy is almost always accompanied by localised hyperplasia of the Leydig cells. Cytological examination revealed in one animal a bulky cell which was trinucleate, endotubular and classifiable under the cell "association pattern" previously described by us (Botticelli, Trentini and Barbolini, 1971).

4. It is seen, therefore, that EMB causes obvious histological lesions in the testes of rats even when the dosage level approaches that used in therapy, provided treatment is continued over a long period of time. The phenomenon might depend either on pharmaco-biological properties connected with the destrorotatory isomer or on the accumulation in the organism of the drug itself. (Lucchesi *et al.*, 1966).

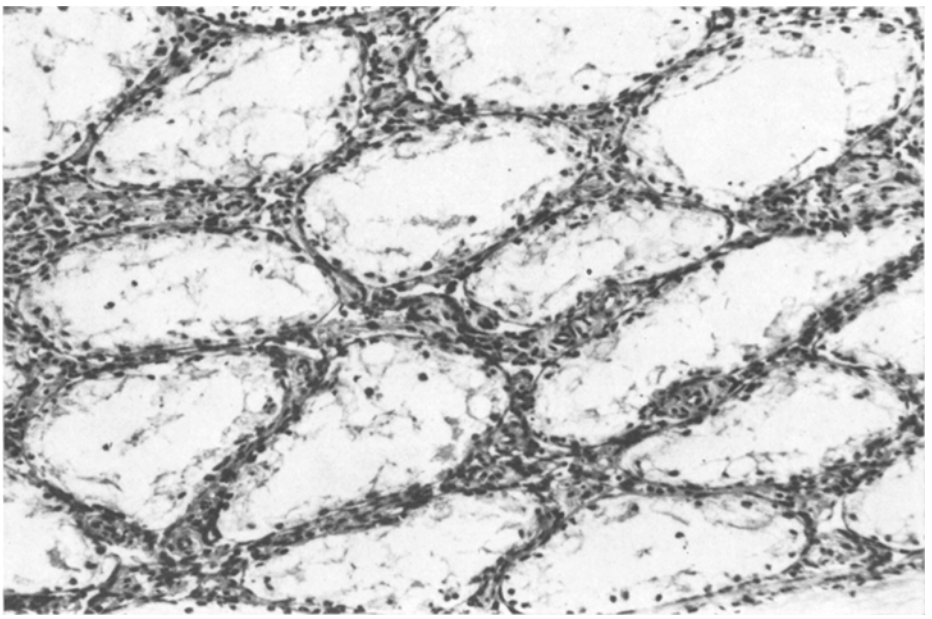

Fig. 2

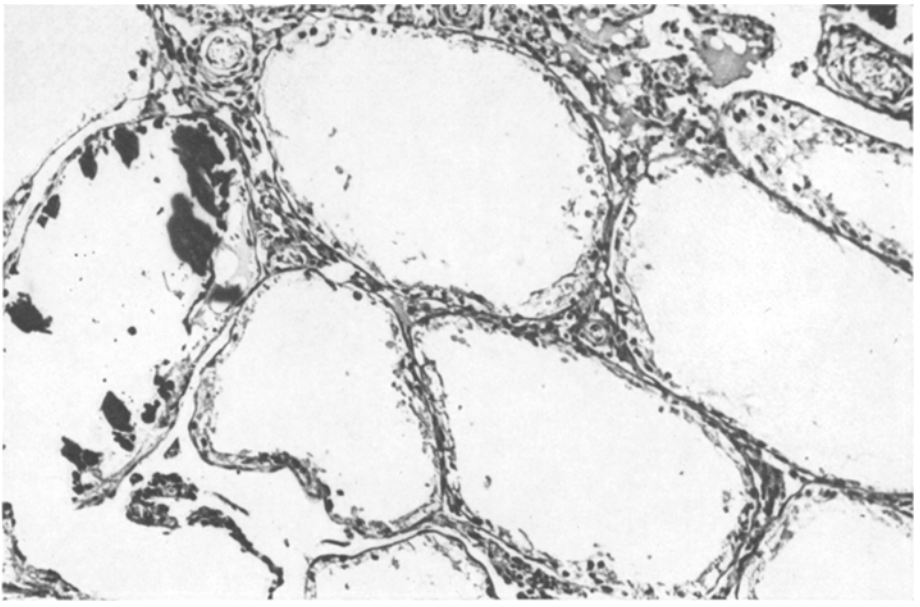

Fig. 3

Figs. 2 and 3. Testis of rat treated with EMB for 12 months ($\times$ orig. 125)

5. Should the last possibility be confirmed, the present study stresses the opportunity in human therapy of periodically interrupting administration of the drug so as to avoid possible damage to the testes.

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Dr. G.P. Trentini
Istituto di Anatomia
e Istologia Patologica
Universita di Modena
Via Berengario 4
I-41100 Modena/Italy