not directly proportional to changes in MI during the 24-hour period. It can accordingly be concluded that the cell composition of the G_2 population differs in the course of the 24-hour period, as reflected in the response to adrenalin. Considering the important role of adrenalin in the control of cell proliferation, the fact that the number of cells sensitive to adrenalin increases during the 24-hour period in a proportion different from that of mitotic activity during the circadian rhythm can be interpreted as evidence that mechanisms regulating the rhythms of mitosis exist at the cell population level.

The results of this investigation show that the degree of inhibition of mitosis depends directly on the dose of adrenalin. The size of the cell population reacting to adrenalin is thus related to the strength of action of the hormone. This is evidence that cells in the G_2 phase which respond to adrenalin differ from one another in their sensitivity to the hormone. Nevertheless, the general rule expressed in the words that significant saturation of the G_2 population by cells sensitive to adrenalin takes place during an increase in MI, is observed with all doses of the hormone.

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ANDROGENIC FUNCTION OF STEROID-PRODUCING GLANDS DURING THE METOPIRONE TEST ON BABOONS

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KEY WORDS: baboon (*Papio hamadryas*); metopirone; hormonal reaction.

Substances with an oriented effect on the level of function of particular endocrine glands are nowadays finding increasing application in clinical and experimental endocrinology. One such substance, used to study the functional reserves of the pituitary gland, is metopirone [2-methyl-1,2-bis-(pyridyl)-propan-1-one] (metyrapone), which has a selective inhibitory action mainly on 11β-hydroxylase [5]. The result of this is to block synthesis of key corticosteroids, mainly hydrocortisone. A fall in the blood hydrocortisone level leads to marked activation of the adrenocorticotrophic function of the pituitary, the degree of which is estimated by the rise in the level of steroid precursors in the blood or urine.

However, despite much research into the effect of metopirone on pituitary and adrenal function, there is practically no reference to the study of the endocrine function of the gonads during the metopirone test in the world literature. Yet this is a most important aspect, particularly in the study of functional reserves of the adenohypophysis in children. According to the most widely approved scheme, within a short time interval the child receives several grams of metopirone, and this may have untoward consequences.

Baboons were chosen as the model in which to study the effect of metopirone on gonadal function because, as previous investigations showed [2], of all the lower monkeys baboons are closest to man in thier endocrine parameters.

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TABLE 1. Dynamics of Testosterone and Δ^4-Androstenedione Levels in Peripheral Blood Plasma (in ng/ml) of Immature and Adult Male Baboons before and after Injection of Metopirone (M ± m)

Group of animals	Steroid	Before injection	Time after injection of metopirone, h				
			3	6	24	48	72
Immature	Testosterone	0,2±0,1	0,3±0,1	0,4±0,1	0,3±0,1	0,3±0,1	0,3±1,6
	Androstenedione	1,2±0,1	6,3±0,7	9,0±1,5	2,4±0,3	1,8±0,3	1,6±0,1
Adult	Testosterone	7,7±0,9	10,3±2,0	10,8±3,5	10,6±3,6	7,5±1,8	—
	Androstenedione	1,5±0,2	3,1±0,4	3,1±0,4	1,7±0,6	1,3±0,2	—

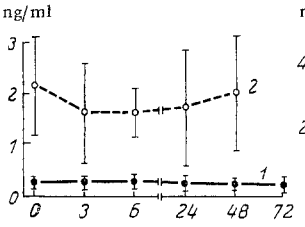

Fig. 1

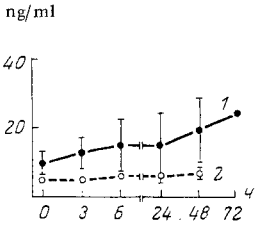

Fig. 2

Fig. 1. Dynamics of 5α-dihydrotestosterone level in peripheral blood plasma of immature (1) and adult (2) male baboons during metopirone test. Abscissa, time after injections of metopirone (in h). 0) Time of injection of metopirone; ordinate, concentration of 5α-dihydrotestosterone (in ng/ml). Each point on graph represents mean concentration in group of baboons at corresponding times after injection of metopirone.

Fig. 2. Dynamics of dehydroepiandrosterone levels in peripheral blood plasma of immature (1, with confidence limits) and adult (2) male baboons during metopirone test. Legend as to Fig. 1.

The aim of the investigation was to compare the androgenic function of the steroid-producing glands in immature and mature male baboons *(Papio hamadryas)* during the metopirone test.

EXPERIMENTAL METHOD

Five prepubertal (aged 3 years) and five adult (aged 10-14 years) male baboons were used for the experiments. The average weight of the immature animals was half that of the adults, and accordingly the former received a single peroral dose of 250 mg metopirone, the latter a dose of 500 mg. Blood for determination of steroids was taken from the cubital vein before injection of metopirone, and again 3, 6, 24, 48, and 72 h after injection. Blood plasma steroid levels were determined by radioimmunoassay after preliminary chromatographic separation of individual compounds on columns with Celite [1]. Concentrations of the following steroids were determined simultaneously in 0.8 ml of plasma: testosterone, 5α-dihydrotestosterone, dehydroepiandrosterone, and Δ^4-androstenedione.

EXPERIMENTAL RESULTS

As Table 1 shows, 3-6 h after injection of metopirone the blood testosterone concentration was appreciably raised in baboons of both age groups. In the adult animals, however, the average increase was only 30%, whereas in the immature baboons the testosterone concentration was doubled.

The dynamics of blood levels of 5α-dihydrotestosterone, a biologically active metabolite of testosterone, is shown in Fig. 1. In the course of the experiment the blood level of 5α-

dihydrotestosterone remained virtually unchanged in the immature monkeys whereas in the adults it showed a moderate fall, although this was not statistically significant.

The blood level of androstenedione, a sex hormone precursor, was considerably raised in baboons of both age groups. In the immature animals, however, the androstenedione level rose by 8 times, whereas in the adults it was only doubled (Table 1). The blood androstenedione concentration in adult baboons returned to its initial level 24 h after the beginning of the experiment, whereas in the immature animals, even 3 days after injection of metopirone it was still 1.5 times higher than the basal level.

The effect of metapirone on the blood level of dehydroepiandrosterone, an important intermediate in the system of sex hormone synthesis, is interesting. The dehydroepiandrosterone concentration in blood plasma of the immature baboons rose gradually and on the 3rd day after injection of metopirone it was 2.5 times higher than initially ($P < 0.05$). The mean dehydroepiandrosterone level in adult animals remained unchanged throughout the period of investigation.

Consequently, the hormonal response of immature and adult baboons to metopirone injection differs considerably. This is due, on the one hand, to differences in the initial blood levels of androgenic steroids in monkeys of different ages and, on the other hand, to differences in the sensitivity of the endocrine glands of baboons to metopirone in the course of postnatal development. The blood testosterone concentration in adult male baboons was about 20 times higher than in the immature animals, whereas after injection of metopirone the testosterone level rose by a greater degree in the prepubertal baboons. Since metopirone exerts its action through pituitary ACTH, the question arises: What is the effect of ACTH on gonadal function in primates at different age periods? According to data in the literature injection of ACTH caused an increase in the blood testosterone concentration in boys before the period of testicular hormonal activity, i.e., at a prepubertal age, whereas in early childhood, during puberty, and also in adult men injection of ACTH lowered the blood testosterone level [7]. In the opinion of the author cited, the inhibitory effect of ACTH on testosterone production in the testes may be exerted through glucocorticoids, and its magnitude depends on the blood hydrocortisone level. It has also been shown that whereas injection of ACTH caused a marked decrease in the blood testosterone concentration, after injection of metopirone the testosterone level rose moderately [9]. This also is evidence that the change in the testosterone level was due to a change in the hydrocortisone concentration rather than to the concentration of ACTH itself. The present results agree with this view because the rise in the plasma testosterone level of the baboons during the metopirone test coincided in time with the minimal hydrocortisone concentration due to blocking of 11β-hydroxylase activity. Besides the facts described above, it must also be remembered that a certain quantity of testosterone, in both immature and adult animals, is formed in the adrenals, the functional activity of which is directly dependent on the blood ACTH concentration. The blood level of the biologically active testosterone metabolite, 5α-dihydrotestosterone, in adult male baboons is 3-5 times lower than the testosterone concentration itself. Statistically significant changes in the blood 5α-dihydrotestosterone level were not found in baboons of either age group, although in the immature animals it showed a tendency to fall. Synthesis and secretion of 5α-dihydrotestosterone in the steroid-producing glands of baboons are evidently not sensitive to the influence of metopirone.

The dynamics of the blood dehydroepiandrosterone level, which in immature monkeys on the 3rd day of the experiment was considerably higher than initially, during the metopirone test, whereas the blood dehydroepiandrosterone level in the adult male baboons remained virtually unchanged, deserves special attention. The results of experiments with incubation of the fetal and definitive zones of the human embryonic adrenals [10] will shed some light on the causes of age differences in the dynamics of the blood dehydroepiandrosterone level in monkeys. It has been shown that under the influence of ACTH, dehydroepiandrosterone sulfate synthesis was increased in the fetal (embryonic) zone, whereas in the definitive zone this was not observed under identical conditions. According to data in the literature [3, 4], remains of the embryonic zone are found during the postnatal development of several mammals: tigers, elephants, etc. The higher initial dehydroepiandrosterone level in the peripheral blood plasma of immature male baboons aged 3 years compared with that in adult animals is evidently indirect evidence that isolated areas of the embryonic zone still persist in them in a state of functional activity.

The androstenedione concentration in the blood of immature and adult male baboons is at approximately the same level, namely about 2 ng/ml. It has been shown [8] that most androstenedione in adult male baboons is synthesized in the adrenals. Probably the high blood level of androstenedione in the monkeys is the result of activation of adrenocortical function by pituitary ACTH; the sensitivity of the adrenals, moreover, is much higher in immature than in adult animals [6].

To conclude, even a single injection of metopirone into immature primates causes marked and persistent disturbances of the steroid hormonal balance, which can be observed for 3 days or more.

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REGENERATION OF HEMATOPOIESIS DURING LOCAL IRRADIATION

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KEY WORDS: thymus; bone marrow; stem cells; irradiation; proliferation.

During local irradiation of part of the body lymphocytosis develops in the depopulated bone marrow [2], mainly as a result of accumulation of lymphocytes of thymic origin [11]. T cells stimulated postirradiation regeneration of erythropoiesis [3]. The development of lymphocytosis preceded an increase in the number of hematopoietic stem cells, capable of forming colonies in the spleens of lethally irradiated recipients, in the bone marrow [1, 3].

The object of this investigation was to study the effect of T lymphocytes on proliferative activity of hematopoietic stem cells during local irradiation.

EXPERIMENTAL METHOD

Experiments were carried out on 600 BALB/c mice weighing 18-20 g. Local irradiation of the right hind limb of the mice was given in a dose of 7.0 Gy on the RUM-17 x-ray apparatus (dose rate 0.65 Gy/min). Thymectomy or mock thymectomy was performed on some mice 1 month before irradiation. On the 5th-8th day after irradiation the mice were killed by destruction of the cervical spinal cord. The total number of myelokaryocytes was determined in the bone marrow of the irradiated femora. The myelogram was studied in bone marrow films. The population of hematopoietic stem cells (CFU-C) in the bone marrow was studied by the exogenous cloning method [9] in lethally irradiated (7.5 Gy) syngeneic recipients. Colonies were counted

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