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Changes in Nasal Mucosa of Monkeys (*Macaca rhesi*) and Humans by Male Hormone Substances.*

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A relation between certain nasal mucosal regions and sexual activity has long been known clinically,[1, 2] particularly with regard to nasal changes accompanying menstruation and pregnancy. Recently Mortimer and coworkers[3] have shown that in the monkey female sex hormones cause reddening and sometimes swelling of the "middle" and inferior conchae. The present data demonstrate that male sex substances, testosterone acetate† and testosterone propionate† effect changes in the nasal mucosa of monkeys and humans.

Thirty-one immature *Macaca rhesus monkeys* of 1.8 to 2.2 kg. were divided into the following groups which received daily subcutaneous injections:

Group	Animals	Hormone
I (a)	9 ♂	3-15 mg. testosterone acetate or propionate daily, 30 to 60 days
	4 ♀	
(b)	7 ♂	Doses graded, 1/64 mg. to 4 mg., 1-3 times weekly
II	1 ♀	3 mg. testosterone propionate and 3 mg. ketohydroxyoestrin†
III	6 ♂	Control
	4 ♀	

All injections were given in one cc. of peanut oil, since the amount and type of oil are known to influence the effect of the hormone.[4]

In the carrying out of nasal inspection an assistant entered the animal cages, selected each monkey in turn and held the animal against the mesh work of the cage in such a manner that the face fitted snugly against an opening in the mesh. Thus, with only moderate excitement of the monkeys, 3 observers, who remained outside of the cage, were enabled to examine the animals without knowledge beforehand of the monkey's identity.

* This work was in part supported by funds provided by Doctor George Walker.

1 Mackenzie, J., *Am. Med. Sci.*, 1884, **81**, 365.

2 Fliess, W., *Die Beziehungen zwischen Nase und weiblichen Geschlechtsorganen.* Franz Deuticke, Leipzig und Wien, 1897.

3 Mortimer, H., Wright, R., and Collip, *J. Can. Med. Assn.*, 1936, **35**, 503; 1936, **35**, 615.

† Testosterone acetate and testosterone propionate (Perandren) were furnished through the courtesy of Ciba Company, ketohydroxyoestrin (Theelin) through the courtesy of Parke, Davis and Company.

4 Parkes, A. S., *Lancet*, 1936, **2**, 674.

With a small otoscope study was made of the nasal cavity with reference to the amount of congestion, swelling and secretion. Inspection was also made of the sex skin and genital organs for comparison with nasal changes. Injection was given at completion of the observations. Drawings in color were made by an artist unacquainted with the problem.

Nasal inspection was done on a group of boys and men who were receiving testosterone propionate for various conditions such as cryptorchidism, impotence (absence of penile erection), hypogonadism and atrophic rhinitis. In this group were 5 boys ranging from 18 months to 15 years, a 27, a 29, and a 43-year-old man. Drawings in color were made as in the monkeys.

After a week or more there was seen in the animals receiving massive daily dosages of androgens a marked increase in the congestion, swelling and secretion of the mucosa covering the upper of the 2 conchae present in the macaque. Reddening of the circumgenital skin and development of the genitalia of both males and females[5] was observed, but the onset was not necessarily concomitant with the earliest appearance of nasal phenomena. Increased vaginal secretion was seen in the females but smears revealed neither cornification nor increase in the amount of free vaginal cells.

In monkeys receiving injections but 3 times weekly, nasal changes were not observed until after a longer period, appearing first in animals receiving doses of 4 mg., later in those receiving one mg., and failing to appear within 5 weeks in animals receiving 1/16 mg. or less. It is well to remember that in any quantitative measurement of response the condition of the animal is a significant factor. The monkey quarters used in the experiments are small, so that several shipments of animals were used at different times, hence the monkeys may well have varied in their capacity to respond to the hormones. Nevertheless, there was, beyond doubt, a longer latent period in the appearance of nasal changes when smaller dosages or infrequent administrations were employed.

Histologically, congestion and, in particular, perivascular edema were the most pronounced changes. Although considerable moisture was encountered during nasal inspection of the injected monkeys when they were alive, definite growth changes in the mucous glands were not observed. It may be possible that the fluid observed in the living state was in part associated with the congestion and edema of this region.

As in the monkeys, swelling and congestion were obvious in the

[5] Hamilton, J. B., *Anat. Rec.*, 1937, **67** (Supplement), 22.

humans. Some of the patients reported an increased amount of secretion during the period of treatment with a disappearance of secretion after cessation of injections. Upon nasal inspection fluid was observed. Although coryza and other complicating factors are found much more commonly in humans than in monkeys, the nasal mucosa was seen to be definitely affected by adequate dosages of testosterone acetate or testosterone propionate in all 5 boys and the 3 men under observation. Of particular interest is the 29-year-old patient with a condition of atrophic rhinitis of several years' duration. Change in the nasal condition did not occur when control injections were given of oil solution which lacked the androgenic substance, but improvement was obtained following periods of treatment with 6 injections (3 per week), each containing 20 mg. testosterone propionate in one cc. of peanut oil. This improvement lasted from 2 to 4 weeks after a period of administration. Such symptomatic treatment has maintained the nasal mucosa of this patient in a satisfactory condition for the past 9 months. Histological studies have not been done in humans.

A definite relationship between the function of specialized regions of the nasal passages and the presence of the female sex hormone has been conclusively shown by Mortimer and coworkers.[3] The present data demonstrate that male hormone substances also influence the state of this region, both in the female as well as in the male monkey, in boys and in men. Possibly clinical treatment of under-development or hypofunction of this nasal region with hormonal substances may be of use. The 27-year-old man with hypopituitaryism, the immature children and the adult men all exhibited pronounced nasal responses following administration of androgenic substances. At present estrogenic[3] and androgenic substances are being employed in further study of atrophic rhinitis. Caution should be observed, however, in the use of androgens in females, for they inhibit menstruation and also exert a direct masculinizing effect, particularly upon homologues of those organs which in the male respond to male substances.[5] This is especially marked in the development of Skene's ducts into a prostatic type of organ[6] and the clitoris into a penis-like structure.[5]

The narrowing, congestion and secretion of the nasal passageway is significant in regard to infectious processes and also the warming of inspired air. It is well-known that there is normally a sheet of fluid material which is continually passed back by ciliary

[6] Hamilton, J. B., and Wolfe, J. M., PROC. SOC. EXP. BIOL. AND MED., 1937, **36**, 465.

action to the pharynx, a phenomenon considered significant in preventing lodging of material on nasal areas. It would seem worthwhile to study the effect of gonadal hormones upon the formation and movement of this nasal sheet.

Summary. 1. In 15 monkeys and 8 humans testosterone propionate effected changes in specialized nasal areas. These changes produced by androgens occurred in both male and female monkeys. 2. In monkeys and in humans congestion, swelling and fluid formation were observed grossly. Histologically, perivascular edema was pronounced in the monkeys. 3. The nasal areas affected are similar to those which exhibit vicarious menstruation. Discussion is given as to possible physiological significance of gonad-controlled function of these areas with regard to warming of inspired air, the prevention of infection, and therapeutic use of gonadal substance in conditions of atrophic rhinitis and nasal hyposecretion.

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Effect of Sodium Chloride Therapy on Oestrous Cycle and Hypophysis of Bilaterally Suprarenalectomized Rats.

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Complete suprarenalectomy in rats results in a suppression or irregular appearance of the oestrous cycle.[1, 8] This has been attributed to an intermediate factor, the impaired gonad stimulating function of the hypophysis. Rubin and Krick,[9] and Gaunt,[3, 4] and other investigators have established the efficacy of salt therapy in maintaining the life of adrenalectomized rats. Experiments were conducted in this investigation to determine the influence of sodium chloride administration in restoring (1) gonadotropic function of the hypophysis and (2) the normal oestrous rhythm. Reference to

1 Corey, E. L., and Britton, S. W., *Am. J. Physiol.*, 1934, **107**, 207.

8 Martin, S. J., *Am. J. Physiol.*, 1932, **100**, 180.

9 Rubin, M. I., and Krick, E. T., PROC. SOC. EXP. BIOL. AND MED., 1933, **31**, 228.

3 Gaunt, R., Tobin, C. E., and Gaunt, J. H., PROC. SOC. EXP. BIOL. AND MED., 1934, **32**, 134.

4 Gaunt, R., Tobin, C. E., and Gaunt, J. H., *Am. J. Physiol.*, 1935, **111**, 321.