Original

Fetal and Neonatal Goiter in Cynomolgus Monkeys Following Administration of the Antithyroid Drug Thiamazole at High Doses to Dams During Pregnancy

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Abstract: To evaluate morphologic alterations in the thyroid gland in the second generation in cynomolgus monkeys, pregnant dams were exposed to high doses of thiamazole. In Experiment A, dams received thiamazole intragastrically via a nasogastric catheter from gestation day (GD) 50 to GD 150 or on the day before delivery. Initially, the dose level was 20 mg/kg/day (10 mg/kg twice daily); however, the dose level was subsequently decreased to 5 mg/kg/day (2.5 mg/kg twice daily), since deteriorated general conditions were observed in two dams. Six out of seven neonates died on the day of birth. The cause of neonatal death was tracheal compression and suffocation from goiter. The transplacental exposure to thiamazole affected the fetal thyroid glands and induced goiter in all neonates. The surviving neonate was necropsied 767 days after discontinuation of thiamazole exposure and showed reversibility of the induced changes. In Experiment B, dams were intragastrically administered thiamazole at 5 mg/kg/day (2.5 mg/kg twice daily) for treatment periods from GDs 51 to 70, 71 to 90, 91 to 110, 111 to 130 and 131 to 150. All fetuses showed enlarged thyroid glands but were viable. Histopathologically, hypertrophy and/or hyperplastic appearance of the follicular epithelium of the thyroid gland was observed at the end of each treatment period. The most active appearance of the follicular epithelium, consisting of crowded pedunculated structure, was demonstrated at end of the treatment period from GD 131 to 150. This is the first report on the morphology of fetal and neonatal goiter in the cynomolgus monkey. (DOI: 10.1293/tox.24.215; J Toxicol Pathol 2011; **24**: 215-222)

Key words: goiter, thiamazole, transplacental exposure, fetus, neonate, cynomolgus monkey

Introduction

Thiamazole, an antithyroid drug known as a synonym for methimazole, is a member of the thioamide group. It has been used for more than half a century to treat hyperthyroidism caused by Graves' disease[1], a condition in which the overactive thyroid gland produces excessive amounts of thyroid hormones. Thiamazole inhibits thyroid hormone synthesis stages, including the addition of iodine to thyroglobulin by the enzyme thyroperoxidase, which is essential to the synthesis of thyroxine. Thiamazole has been the drug of choice for treatment of hyperthyroidism during pregnancy and needs to be effectively managed and used to prevent maternal, fetal and neonatal complications. A literature review showed that infants born to mothers whose conditions had been managed with antithyroid drugs developed goiter[1–5]. However, there has been no report on the histopathology of goiter in nonhuman primate fetuses and neonates following administration of antithyroid drugs to dams. In the present study, we repeatedly administered relatively high doses of thiamazole to pregnant cynomolgus monkeys in the second and third trimesters of pregnancy to examine thyroidal morphological disorders in fetuses and neonates.

Materials and Methods

Animals and housing conditions

Adult female cynomolgus monkeys (*Macaca fascicularis,* age 3 to 8 years, body weight 2.6–5.4 kg, purpose bred) from China maintained in the primate facility of Drug Safety Research Laboratories, Shin Nippon Biomedical Laboratories, Ltd. (SNBL DSR), were used. Dams and offspring (after weaning) were individually provided with approximately 108 g (approximately 12 g × 9 pieces) and 72 g (approximately 12 g × 6 pieces), respectively, of solid food (Teklad Global Certified 25% Protein Primate Diet, Harlan Sprague Dawley, Inc., Madison, WI, USA) once daily between 14:30 and 16:00. Any remaining food was removed between 08:30 and 10:00 on the following day. Water conforming to the water quality standards required by the Japanese Waterworks Law was available *ad libitum* from an automatic supply (Edstrom Industries, Inc., Waterford, WI, USA). Stainless steel animal cages (Taiyo Stainless Co., Ltd., Kagoshima, Japan) conforming to USDA standards [690 mm (D) × 610 mm (W) × 750 mm (H)] were used. The number of animals per cage was one. Males and females were housed in pairs during the mating period. The animal rooms were maintained at a temperature of 23 °C to 29 °C and humidity of 35% to 75%, with artificial lightning for 12 hours/day (06:00 to 18:00). The use of animals in this study was approved by the Institutional Animal Care and Use Committee of SNBL DSR, and the study was performed in accordance with the ethics criteria contained in the bylaws of the committee.

Mating and pregnancy diagnosis

Females that showed regular menstrual cycles were mated with males of proven fertility for three days between the 11th and 15th days of the menstrual cycle. When copulation was confirmed visually, the median day of the mating period was designated as gestation day 0 (GD 0). On presumed GD 18, pregnancy was diagnosed by ultrasonography (SSD-4000, Hitachi-Aloka Medical, Ltd., Tokyo, Japan) under sedation from an intramuscular injection of 10 mg/kg of ketamine hydrochloride (Fuji Chemical Industry Co., Ltd., Saitama, Japan). Animal numbers were allotted in the order in which it was possible to confirm pregnancy (Experiment A or B). Thereafter, pregnant animals underwent treatment with one of the dosing regimens stated below.

Treatment of dams

Experiment A: Ten dams received thiamazole (Sigma-Aldrich Co., Ltd., Tokyo, Japan) intragastrically via a nasogastric catheter from GD 50 to GD 150 or on the day before delivery. Initially, the dose level was 20 mg/kg/day (10 mg/kg twice daily); however, the dose level was subsequently decreased to 5 mg/kg/day (2.5 mg/kg twice daily), since deteriorated general conditions were observed in two dams. Thiamazole was administered twice a day, and the second administration was 6 hours after the first. All dams were observed four times a day during the treatment period and once a day during the nontreatment period and were to be allowed to deliver naturally.

Experiment B: Two dams per group were administered thiamazole (Sigma-Aldrich) at 5 mg/kg/day (2.5 mg/kg twice daily) intragastrically via a nasogastric catheter for one of five different treatment periods. Thiamazole was administered twice a day, and the second administration was 6 hours after the first. Two or three animals were allocated to Groups 1, 2, 3, 4 and 5 as nontreated controls. The treatment periods for Groups 1, 2, 3, 4 and 5 were GDs 51 to 70, 71 to 90, 91 to 110, 111 to 130 and 131 to 150, respectively. All dams were observed four times a day during the treatment period and once a day during the nontreatment period. Cesarean section (CS) was performed on the day following the end of the relevant treatment period, and the treated fetuses were removed from the uterus.

Observations and examinations of second generation

All neonates were examined for viability, sex, body weight and external findings at birth. The offspring of Dam No. 7 in Experiment A was necropsied 767 days after birth. The thyroid glands collected from fetuses in Experiment B were weighed, and absolute and relative weights were calculated from the relevant fetal body weight. The fetal and neonatal thyroid glands from Experiments A and B were fixed in 10% neutral buffered formalin for histopathological examination. The specimens were embedded in paraffin, sectioned and stained routinely with Hematoxylin-Eosin (HE) stain. Slide specimens were examined microscopically. Neonates No.3 and No.7 in Experiment A and all treated fetuses and one nontreated fetus from each group in Experiment B were available for histopathological examination.

Examination of morphological parameters in the thyroid gland in Experiment B

Images of the thyroid were analyzed with analysis (Soft Imaging System GmbH, Muenster, Germany) software to determine the height of the follicular epithelium. The outer circumferences of the follicle and the lumen included in a one square millimeter section of each specimen were measured. The average radius and diameter of each were then calculated. The height of the follicular epithelium was calculated by subtracting the lumen radius from the follicular radius. Pairwise comparisons were performed for each parameter by t-test based on a one-way ANOVA model. A value of $p < 0.05$ was considered statistically significant.

Results

Experiment A

Clinical signs in dams and the viability outcomes for fetuses and neonates are shown in Table 1. Two dams (Nos. 1 and 2) showed convulsion, prone position, external genital bleeding and/or low food consumption, and one of these dams (No. 1) then died on GD 70 and the other dam (No. 2) aborted its fetus. Therefore, the dose level of thiamazole was decreased from 20 mg/kg/day (10 mg/kg twice daily) to
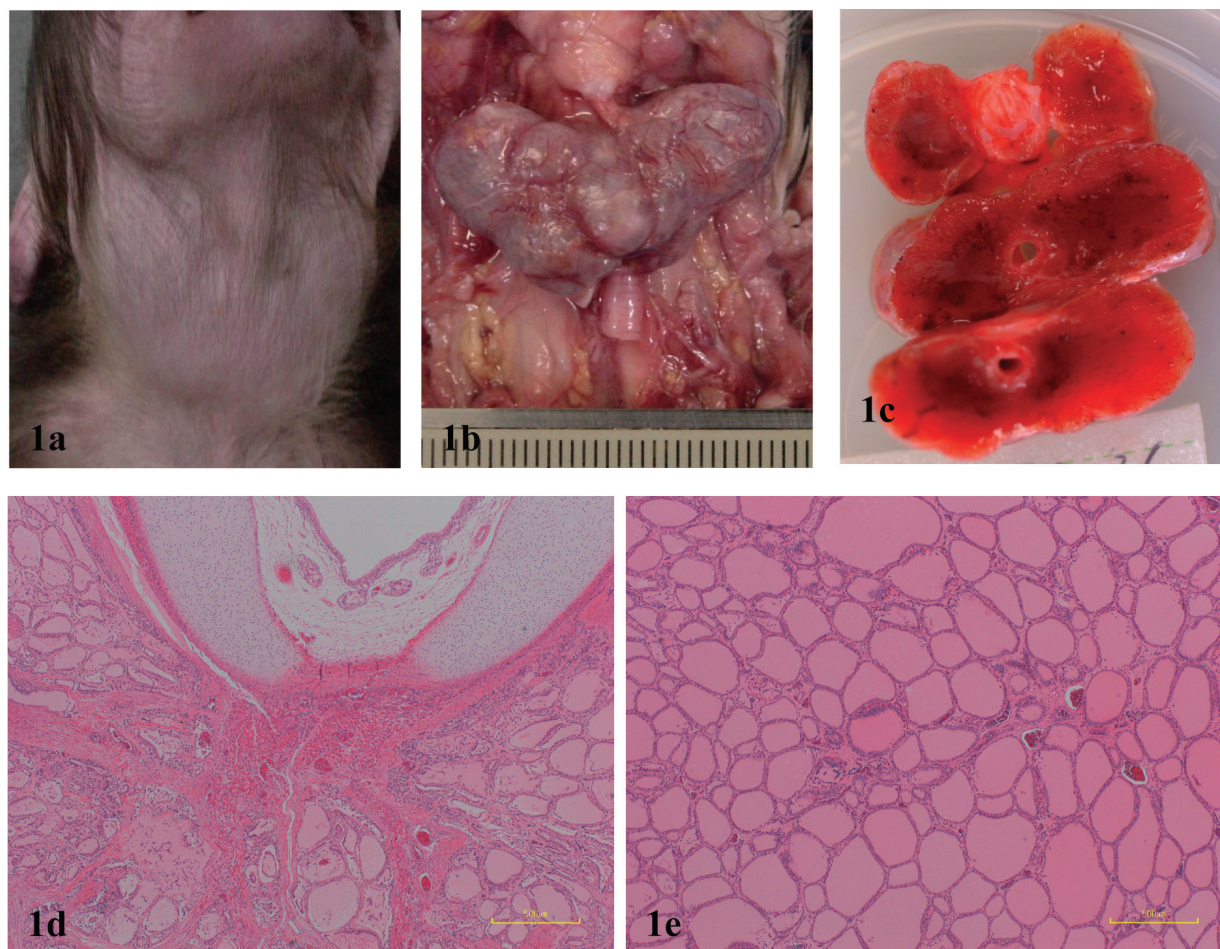
Fig. 1. Gross and histopathological findings in neonates in Experiment A. 1a: External appearance around the neck. 1b: Gross appearance of the thyroid gland. 1c: Cut surface of the thyroid gland. 1d: Thyroid gland reached the membranous wall of the trachea, HE stain. 1e: Follicles consisted of a flattened epithelium containing colloid, HE stain.

5 mg/kg/day (2.5 mg/kg twice daily). After the decrease in dose level, one other dam (No. 4) showed low body weight, low food consumption and emaciation; however, this dam was able to maintain its pregnancy until the end of the third trimester, and no abnormalities in clinical signs were observed in the other seven dams (Nos. 3 and 5 to 10). At around the end of the gestation period, fetal death (No. 6) was detected by ultrasonography on GD 170, and six other dams (Nos. 3, 4, 5, 7, 9 and 10) were able to deliver naturally. However, five out of the six neonates (Nos. 3, 4, 5, 9 and 10) died on the day of birth, and only one neonate (No. 7) survived. All fetuses and neonates that had been viable at the end of the third trimester showed swollen throat and presented palpable thyroid glands. Gross examination of this fetus and these neonates showed enlarged thyroid glands reaching the membranous wall of the trachea. Histopathologically, the thyroid showed colloid storage and a flattened follicular epithelium. Neither cellular atypia nor mitotic figures were seen (Figs. 1a-e). The offspring (No. 7) necropsied 767 days after birth showed no macroscopic abnormalities in the thyroid gland. Histopathologically, de-

position of brown pigment and proliferation of connective tissue were observed in this animal; however, no abnormal changes were observed in the follicular epithelium. Absolute and relative thyroid gland weights in this offspring were 1.42 g and 0.81 g/kg (body weight at necropsy: 1.76 kg), respectively.

Experiment B

The results of Experiment B are shown in Tables 2 and 3. No abortion or fetal death occurred during any thiamazole treatment period. All fetuses removed from uteri by cesarean section were viable. There was no difference in body weight between the control fetuses and the treated fetuses. All treated fetuses from Groups 1 to 5 showed enlarged thyroid glands (Fig. 2a–e). Absolute and relative thyroid weights in the treated fetuses were higher than those in the control fetuses. The follicular diameters, lumen diameters and the heights of the follicular epithelium were significantly higher in treated fetuses than control fetuses. Although the height of the follicular epithelium did not show any apparent increase, the follicular diameter and lumen di-

Table 1. Experimental Designs and Results of Experiment A

Thiamazole[a]		Dam animal No.	GD	Clinical signs of dams	Delivery status	Neonate animal No.	Body weight at birth (g)	Viability	Sex	External findings
20 mg/kg	5 mg/kg									
Treated period (days)										
20	-	1	-	Prone position (GD69), external genital bleeding (GD70), dam death (GD70)	Abortion (GD70)	1	NE	Dead	NE	NE
33	-	2	-	Convulsion (GD69-71), prone position (GD69), low food consumption (GD70~)	Abortion (GD83)	2	NE	Dead	NE	NE
7	108	3	165	No abnormal changes	Neonatal death	3	245	Dead	M	Swelling, throat
7	111	4	168	Low body weight, low food consumption, emaciation	Neonatal death	4	249	Dead	M	Swelling, throat
3	127	5	180	No abnormal changes	Neonatal death	5	320	Dead	F	Swelling, throat
2	118	6	-	No abnormal changes	Fetal death (GD170)	6	NE	Dead	F	Swelling, throat
-	118	7	168	No abnormal changes	No abnormal changes	7	331	Alive	F	Swelling, throat
-	40	8	-	No abnormal changes	Abortion (GD90)	8	NE	Dead	NE	NE
-	120	9	170	No abnormal changes	Neonatal death	9	302	Dead	F	Swelling, throat
-	92	10	142	No abnormal changes	Neonatal death	10	197	Dead	M	Swelling, throat

[a] Dose 20 mg/kg/day → 5 mg/kg/day. Thiamazole was administered on GD 50 to 150 or on the day before delivery. The dose level was decreased to 5 mg/kg/day, since deteriorated general conditions were observed in two dams (Animal Nos. 1 and 2). GD: Gestation day. NE: Not examined. M: Male. F: Female.

ameter tended to increase as gestation progressed.

The histopathological appearances of the thyroid glands from each group are shown in Figs. 3a to 3e'. Mitotic figures were sporadically observed in the follicular epithelium in treated fetuses from all groups. Hypertrophy and/or hyperplasia of the thyroid follicular epithelium were diffusely observed in treated fetuses from all groups. Follicular size was distinctly larger in the treated fetuses than in the control fetuses, with narrowed lumens. The follicular cells were more columnar than normal. Control thyroid glands examined at GD 72 and GD 91 consisted of a number of small follicles thought to be immature. Projections into the follicular lumen as a result of proliferation of the follicular epithelium were observed at GD 91. Large follicles lined by a low cuboidal follicular epithelium were observed at GD 131. The follicular epithelium showed an active appearance with proliferated papillary projections into the follicular lumen and pedunculated structure at GD 151.

Discussion

Experiment A, thiamazole was administered at relatively high doses for an antithyroid drug to pregnant cynomolgus monkeys during pregnancy to investigate morphologic changes in fetuses and neonates. In Experiment B, morphologic changes in the fetal thyroid glands during the second and third trimesters were investigated sequentially with five different treatment periods to examine the effect of thiamazole. It has been reported that the drug induced hypertrophy of the follicular epithelium in the thyroid glands of common marmosets (*Callithrix jacchus*)[6]. However, there has been no report of histopathological changes in nonhuman primate fetuses and neonates until now. The thyroid glands from fetuses exposed to thiamazole during the second and third trimesters of pregnancy were compared morphologically with those from control fetuses.

The thyroid gland is one of the organs most susceptible to various intrinsic and extrinsic factors[7], and the hypothalamus-pituitary-thyroid axis and its hormonal feedback system involving TSH, triiodothyronine (T3) and thyroxine (T4) is well established.

Thiamazole, an antithyroid drug, is a member of the thioamide group. Thiamazole (1-methy-1*H*-imidazole-2-thiol), whose chemical formula is $C_4H_6N_2S$ and whose molecular mass is 114.17 g/mol has been used for more than half a century to treat hyperthyroidism caused by Graves' disease[1], a condition in which the overactive thyroid gland produces excessive amounts of thyroid hormones. The working mechanism of thiamazole is based on inhibition of the addition of iodine to thyroglobulin by the enzyme thyroperoxidase, an essential step in the synthesis of T3 and T4.

It has been reported that thionamide compounds are
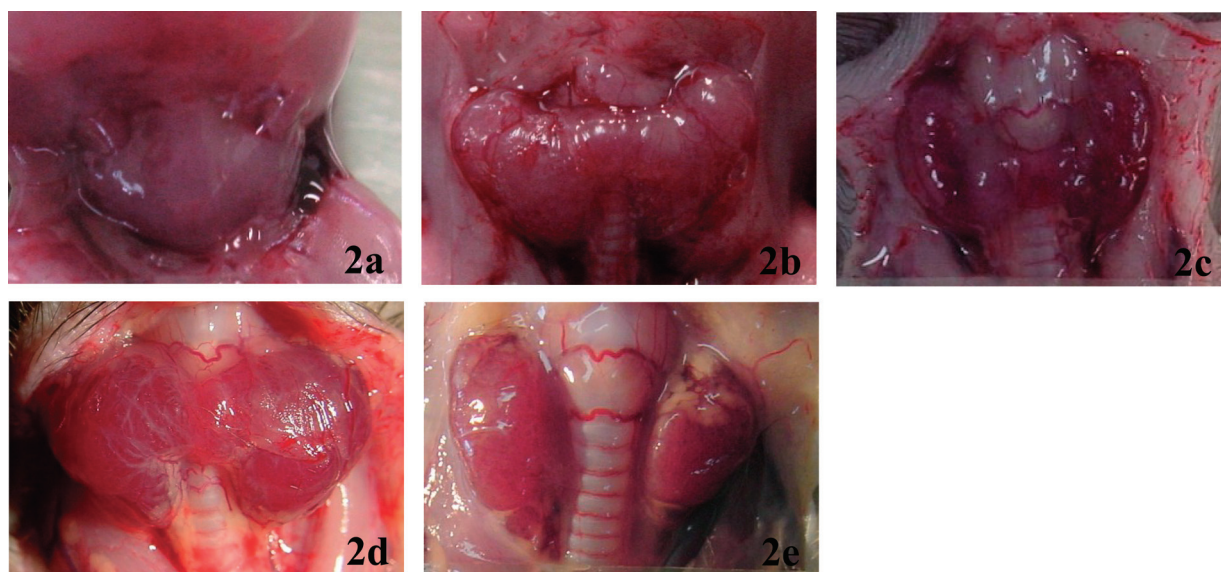
Fig. 2. Gross appearance of changes in the thyroid glands of fetuses in Experiment B with 5 different treatment periods. All fetuses in thiamazole exposure Groups 1 to 5 showed swollen throats. 2a: Treatment period GD 51 to 70; fetuses removed on Day 71. 2b: Treatment period was GD 71 to 90; fetuses removed on Day 92. 2c: Treatment period GD 91 to 110; fetuses removed on Day 111. 2d: Treatment period GD 111 to 130; fetuses removed on Day 131. 2e: Treatment period GD 131 to 150; fetuses removed on Day 151.

Table 2. Experimental Designs and Results of Experiment B

Group	Dam animal No.	Dose (mg/kg)	Dosing days (GD)	CS* day	Neonate animal No.	Viability	Sex	Fetal weight (g)	Organ weight (Thyroid) Absolute weight (mg)	Organ weight (Thyroid) Relative weight (mg/g)
1	Control-1	-	-	72	Control-1		F	33.1	13.0	0.39
	Control-2	-	-	72	Control-2		M	22.3	5.4	0.24
	101	5	51–70	71	101		F	33.8	135.0	3.99
	102			71	102		F	32.4	180.0	5.56
2	Control-3	-	-	91	Control-3		M	84.2	18.0	0.21
	Control-4	-	-	91	Control-4		M	77.1	27.6	0.36
	201	5	71–90	91	201		M	61.0	185.4	3.04
	202			92	202		M	89.7	531.8	5.93
3	Control-5	-	-	110	Control-5		M	165.0	64.0	0.39
	Control-6	-	-	110	Control-6		M	157.5	48.3	0.31
	Control-7	-	-	111	Control-7	Alive	M	150.5	30.3	0.20
	301	5	91–110	110	301		F	170.0	360.0	2.12
	302			111	302		M	162.0	316.0	1.95
4	Control-8	-	-	131	Control-8		M	228.5	56.0	0.25
	Control-9	-	-	131	Control-9		M	273.2	123.2	0.45
	401	5	111–130	131	401		F	256.3	840.0	3.28
	402			131	402		M	260.5	341.0	1.31
5	Control-10	-	-	151	Control-10		M	307.4	50.0	0.16
	Control-11	-	-	155	Control-11		F	363.0	147.0	0.40
	501	5	131–150	152	501		M	332.4	560.0	1.68
	502			151	502		F	363.9	533.5	1.47

GD: Gestation day. M: Male. F: Female. *: Caesarean section.

among the most potent inhibitors of thyroid hormones and that they have induced hyperplasia of the thyroid gland in experimental animals[8]. This effect occurs when the administration of the drug reduces thyroid hormones to subnormal levels and the resultant increase in circulating TSH stimulates enlargement of the thyroid gland.

The cynomolgus monkey, a widely used nonhuman primate model, has similar reproductive physiology, endo-

Table 3. Morphological Parameters in the Thyroid Gland in Experiment B

Group	1		2		3		4		5	
Dose (mg/kg)	-	5	-	5	-	5	-	5	-	5
Dosing days (GD)	-	51–70	-	71–90	-	91–110	-	111–130	-	131–150
Follicular diameter (µm)	36.09	89.53*	44.25	115.71*	69.35	123.45*	96.85	156.16*	65.90	164.13*
Lumen diameter (µm)	27.29	56.15*	35.47	83.49*	54.75	86.17*	77.99	123.96*	47.36	128.19*
Height of follicular epithelium (µm)	4.40	16.69*	4.39	16.11*	7.30	18.64*	9.43	16.10*	9.27	17.97*

GD: Gestation day. Values are expressed as averages. *: Significantly different from the control (P<0.05).

crinology and development to the human[9,10]. The human gestation period is around 40 weeks, while that of the cynomolgus monkey is around 160 days[10]. Organogenesis occurs during the first trimester in both the cynomolgus monkey and the human, between GDs 21 and 50 and GDs 18 and 60, respectively[9,10]. It has been reported that the development of the human thyroid gland begins from GD 21[11], and that the human thyroid gland is well developed by GD 70 in the first trimester and begins concentrating iodide and producing thyroid hormones at this time[11]. Compounds with a molecular weight greater than 1000 Da do not cross the placenta easily, whereas those of less than 600 Da, including thiamazole, freely cross the placenta[2–4,12–14]. In the present study, an excessive dosage of thiamazole affected the fetal thyroid glands through the placenta, inducing goiter in fetuses or neonates.

Fetal, neonatal or maternal death or abortion occurred in Experiment A. It was considered that the cause of death was respiratory impairment following severe compression of the trachea by an enlarged thyroid gland, as has been reported in humans[1,2]. Compression of the cervical region by an excessively enlarged thyroid gland is considered potentially lethal to neonates.

One offspring (No. 7), which showed a swollen throat at birth, was necropsied on Day 767. Although no abnormal changes were observed macroscopically, its absolute thyroid gland weight was above the range of the control background data (unpublished data) of our laboratories. This organ weight result in this animal showed that even at the age of two years, thyroid gland weights had not returned to normal, a finding similar to that reported in rats[15]. Moreover, there were no abnormal changes in the follicular cells. Histopathological changes observed in the interstitium of the thyroid gland were considered traces of goiter at birth. Regression of goiter induced in fetuses was observed when antithyroid compounds including propylthiouracil (PTU) were withdrawn, enabling reversibility of the induced changes[2,15,16].

In Experiment B, there were no nonviable outcomes for fetuses or abnormalities in fetal body weight. All treated fetuses from each group that underwent treatment for one of five periods showed goiter. The detection of fetal goiter during pregnancy in a mother on antithyroid drug therapy by ultrasonography is an indication of fetal hypothyroidism[1–3].

High absolute and relative thyroid organ weights were noted in treated fetuses in all groups when compared with control fetuses. These high organ weights were considered to be due to the increase in size of the follicle and the colloid, since both the follicular and lumen diameters increased as gestation progressed.

Although the mean height of the follicular epithelium in the treated groups did not show any apparent increase in morphometry examinations, both diffuse hyperplasia and hypertrophy of the thyroid follicular epithelium were observed in the histopathological examination. In Group 4 (GD 111 to 130 treatment period), around the midpoint of the third trimester, an inactive appearance of the follicular epithelium was seen. This was considered to indicate that the susceptibility to thiamazole in this group was not as great as in the other groups. In contrast to those from Group 4 (GD 111 to 130 treatment period), the fetal thyroids from Group 5 (GD 131 to 150 treatment period) demonstrated the most characteristic appearance of thiamazole treatment-related changes. The follicular epithelium appeared active, consisting of papillary projections into the follicular lumens that had become pedunculated. This observation suggests that administration of thiamazole to dams just before delivery strongly induces histopathological changes in the follicular epithelium of the thyroid gland in the fetal cynomolgus monkey. Although TSH and thyroid hormones were not assessed in the present study, the morphologic features of the thyroid glands from treated fetuses were consistent with enhanced resorption of colloid through TSH stimulation[17].

In conclusion, this is the first report on macroscopic and histopathological investigations of goiter in cynomolgus monkey fetuses and neonates when dams received relatively high doses of thiamazole during the second and third trimesters of pregnancy.

Fig. 3. Histologic appearance of changes in the thyroid glands of fetuses in Experiment B with 5 different treatment periods, HE stain. 3a: Induced change in the thyroid gland at GD 71. 3a': Control thyroid gland at GD 72. 3b: Induced change in the thyroid gland at GD 91. 3b': Control thyroid gland at GD 91. 3c: Induced change in the thyroid gland at GD 111. 3c': Control change in the thyroid gland at GD 111. 3d: Induced change in the thyroid gland at GD 131. 3d': Control thyroid gland at GD 131. 3e: Induced change in the thyroid gland at GD 151. 3e': Control thyroid gland at GD 151.
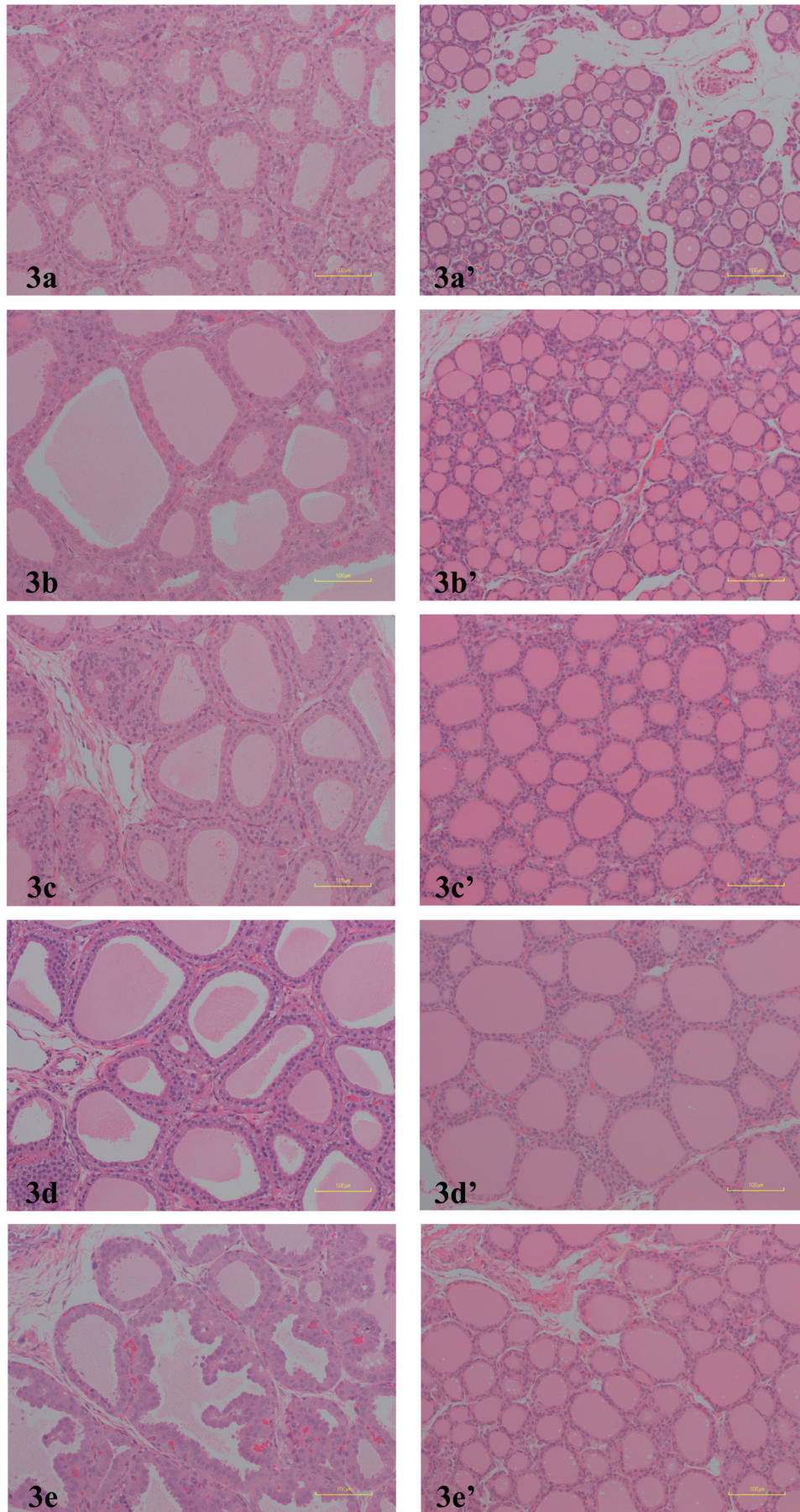
Fig. 3.

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