

MATERNAL IODINE DEFICIENCY AND
PRENATAL BRAIN DEVELOPMENT

by

IAN DAVID HAY

B.Sc., M.B., Ch.B., M.R.C.P.

University Department of Medicine,
Royal Infirmary, Glasgow

VOLUME II

A thesis in two volumes submitted for the degree of
Doctor of Philosophy to the University of Glasgow
June 1978

TABLE OF CONTENTS**VOLUME II**

Title page	i
Table of contents	ii
List of figures	iii
List of tables	v
Figures	1-38
Tables	1-61

LIST OF FIGURES

1. Josef Warkany and "The Poor in Iodine".
2. The clinical spectrum of endemic cretinism.
Modified from Delange et al. (64).
3. Principal features of endemic cretinism.
4. Iodisation and deaf-mutism in Switzerland.
Drawn from data of Wespi (284).
5. Prevention of endemic cretinism in the Jimi Valley.
6. Relation of serum T_4 to serum TSH in endemic goitre.
After Chopra et al. (38).
7. Development of the HPT axis in man.
Modified from Fisher et al. (115).
8. Development of the HPT axis in the rat.
Modified from Fisher et al. (115).
9. Effect of LID on 4 hour RAIU.
10. Effect of LID on relative thyroid weight.
11. Effect of LID on serum T_4 concentration.
12. Comparison of effects of diet I and diet II on serum T_4 concentration.
13. Effect of LID on serum T_3 concentration.
14. Varying degrees of iodine deficiency.
15. Postnatal brain development in the rat.
Drawn from data of Donaldson and Hatai (86).
16. Quantitative changes in DNA and protein during brain growth in the rat. After Winick and Noble (289).
17. Quantitative changes in DNA during forebrain growth in man.
After Dobbing and Sands (79).
18. Method of dissection of rat forebrain.
19. Biochemical analysis of rat forebrain.
20. Typical standard curve for DNA assay.
21. Typical standard curve for protein assay.

22. Quantitative changes in DNA and protein during postnatal forebrain growth.
23. Design of experiments 1-4.
24. Growth of rats on LID for 4 weeks.
25. Changes in serum T_4 and T_3 concentrations of animals mated after 4 weeks on LID.
26. Comparison of serum T_4 concentrations in test and control animals after 8 weeks on LID. Broken line denotes the lower limit of the normal range. The means \pm 1 S.D. are shown for the animals selected for mating after 10 weeks.
27. Changes in serum T_4 and T_3 concentrations of animals mated after 10 weeks on LID.
28. Changes in serum T_4 and T_3 concentrations of animals mated after 6 months on LID.
29. Comparison of growth rate in test and control pups during first three postnatal weeks.
30. Changes in serum T_4 and T_3 concentrations during pregnancy and lactation in Experiment 5.
31. Changes in thyroid hormone concentrations during pregnancy in Experiments 2, 3 and 4.
32. Changes in serum T_4 concentration due to pregnancy in Experiment 6.
33. Changes in serum T_3 concentration due to pregnancy in Experiment 6.
34. Effect of mild iodine deficiency on serum T_4 and T_3 changes during pregnancy.
35. Changes in serum T_4 and T_3 concentrations in mildly iodine deficient mothers during the last seven days of gestation.
36. Changes in serum T_4 concentration during pregnancy and lactation in Experiment 7.
37. Changes in serum T_3 concentration during pregnancy and lactation in Experiment 7.
38. Effect of moderate iodine deficiency on serum T_4 , T_3 and T_3/T_4 ratio during pregnancy and lactation.

LIST OF TABLES

1. Effect of diet I for periods up to 4 weeks on relative thyroid weight and radioactive iodine uptake.
2. Effect of diet I for periods up to 4 weeks on serum thyroxine and tri-iodothyronine levels.
3. Effect of diet I for periods up to 24 weeks on relative thyroid weight and radioactive iodine uptake.
4. Effect of diet I for periods up to 24 weeks on serum thyroxine and tri-iodothyronine levels.
5. Effect of diet II for periods up to 4 weeks on relative thyroid weight and radioactive iodine uptake.
6. Effect of diet II for periods up to 4 weeks on serum thyroxine and tri-iodothyronine levels.
7. Effect of diet II for periods up to 12 weeks on relative thyroid weight and radioactive iodine uptake.
8. Effect of diet II for periods up to 24 weeks on serum thyroxine and tri-iodothyronine levels.
9. Comparison of effects of diets I and II on serum thyroxine levels.
10. Comparison of wet weight and chemical composition of forebrain in neonates and 22 day old weanling pups.
11. Effect of LID introduced at mating on neonatal body and forebrain weights (all pups).
12. Effect of LID introduced at mating on neonatal body and forebrain weights (male pups).
13. Effect of LID introduced at mating on DNA and protein content of neonatal forebrain.
14. Effect of LID introduced at mating on thyroid parameters of mothers in immediate post-partum period.
15. Effect of LID introduced at mating on serum thyroid hormone levels of post-partum mothers.
16. Effect of LID fed to mothers from 4 weeks before mating and throughout gestation on litter size and perinatal mortality.

17. Effect of LID fed to mothers from 4 weeks before mating and throughout gestation on body and forebrain weights of newborn.
18. Effect of LID fed to mothers from 4 weeks before mating and throughout gestation on neonatal forebrain chemical composition.
19. Effect of iodine supplementation on thyroid function of animals fed LID for 4 weeks prior to mating.
20. Results of thyroid function tests performed after 7 weeks of LID on animals mated after 4 weeks.
21. Effect of LID on body weights of animals fed ad libitum for 10 weeks prior to mating.
22. Effect of iodine deprivation for 8 weeks on total serum T_3 and T_4 levels and T_3/T_4 ratio.
23. Comparison of total serum T_3 and T_4 levels and T_3/T_4 ratio in control and test animals selected for mating.
24. Effect of iodine supplementation on thyroid function of infertile animals fed LID for 13 weeks.
25. Effect of LID fed to mothers from 10 weeks before mating and throughout gestation on litter size and incidence of postmaturity.
26. Effect of LID fed to mothers from 10 weeks before mating and throughout gestation on body and forebrain weights of newborns.
27. Effect of moderate iodine deficiency on body and forebrain weights of pups born on day 22 of gestation.
28. Effect of LID fed to mothers from 10 weeks before mating and throughout gestation on neonatal forebrain chemical composition.
29. Effect of moderate iodine deficiency on forebrain content of DNA and protein in pups born on day 22 of gestation.
30. Effect of moderate iodine deficiency on cell size in forebrains of pups born on day 22 of gestation.
31. Effect of LID fed for 24 weeks on serum T_4 and T_3 concentrations.
32. Comparison of levels of serum T_4 and T_3 in animals selected for mating.

33. Effect of LID fed for six months prior to mating and throughout gestation on litter size and perinatal mortality.
34. Effect of severe prenatal iodine deficiency on body and forebrain growth and development.
35. Effect of severe prenatal iodine deficiency on neonatal forebrain chemical composition.
36. Effect of severe iodine deficiency on thyroid function of animals sacrificed in the immediate post-partum period.
37. Effect of combined prenatal and postnatal iodine deficiency on body weights of pups during the period of maternal lactation.
38. Effect of combined prenatal and postnatal iodine deficiency on body and forebrain weights of 22 day old weanlings.
39. Effect of male or female sex on body and forebrain weights of test pups at 22 postnatal days.
40. Effect of combined prenatal and postnatal iodine deficiency on body and forebrain weights of 22 day old male weanlings.
41. Effect of combined prenatal and postnatal iodine deficiency on forebrain content of DNA and protein in 21 day old weanlings.
42. Effect of combined prenatal and postnatal iodine deficiency on forebrain content of DNA and protein in 22 day old male weanlings.
43. Effect of male or female sex on forebrain content of DNA and protein in test pups at 22 postnatal days.
44. Effect of LID for 16 weeks and lactation during 3 weeks on in vitro thyroid function at 21 postnatal days.
45. Effect of moderate iodine deficiency on serum thyroxine concentrations before and after successful pregnancy.
46. Effect of moderate iodine deficiency on serum tri-iodothyronine concentration before and after successful pregnancy.
47. Effects of pregnancy and lactation on serum thyroid hormone concentrations of control mothers.
48. Effects of pregnancy and lactation on serum thyroid hormone concentrations of test mothers.

49. Effect of combined prenatal and postnatal iodine deficiency on thyroid function in the 22 day old weanling.
50. Comparison of thyroid function in control weanlings and their mothers at time of weaning.
51. Comparison of thyroid function in test weanlings and their mothers at time of weaning.
52. Effects of pregnancy and mild iodine deficiency on maternal serum T_4 concentrations.
53. Effects of pregnancy and mild iodine deficiency on maternal serum T_3 concentrations.
54. Effect of pregnancy on serum T_3 , T_4 and T_3/T_4 ratio in control animals fed LID with iodine supplements for 10 weeks prior to mating.
55. Effect of pregnancy on serum T_3 , T_4 and T_3/T_4 ratio in test animals fed LID for 10 weeks prior to mating.
56. Effect of moderately severe iodine deficiency on changes in maternal serum T_4 during pregnancy and lactation.
57. Effect of moderately severe iodine deficiency on changes in maternal serum T_3 during pregnancy and lactation.
58. Effect of moderately severe iodine deficiency on changes in maternal serum T_3/T_4 ratio (x 1000) during pregnancy and lactation.
59. Changes in maternal serum T_4 concentrations during the second week of pregnancy.
60. Changes in maternal serum T_3 concentrations during the last seven days of pregnancy.
61. Changes in maternal serum T_4 concentrations during the period of lactation.

Fig. 1 **Josef Warkany and "The Poor in Iodine".**



The Poor in Iodine

Warkany

.....That such a complicated disorder as endemic cretinism could be wiped out without explanation of the intricate mechanisms involved in its pathogenesis may be disappointing to some scientific purists but consoling to those who like shortcuts in the prevention of congenital disorders.

Josef Warkany (1971)

**Fig. 2 The clinical spectrum of endemic cretinism.
Modified from Delange et al. (64).**

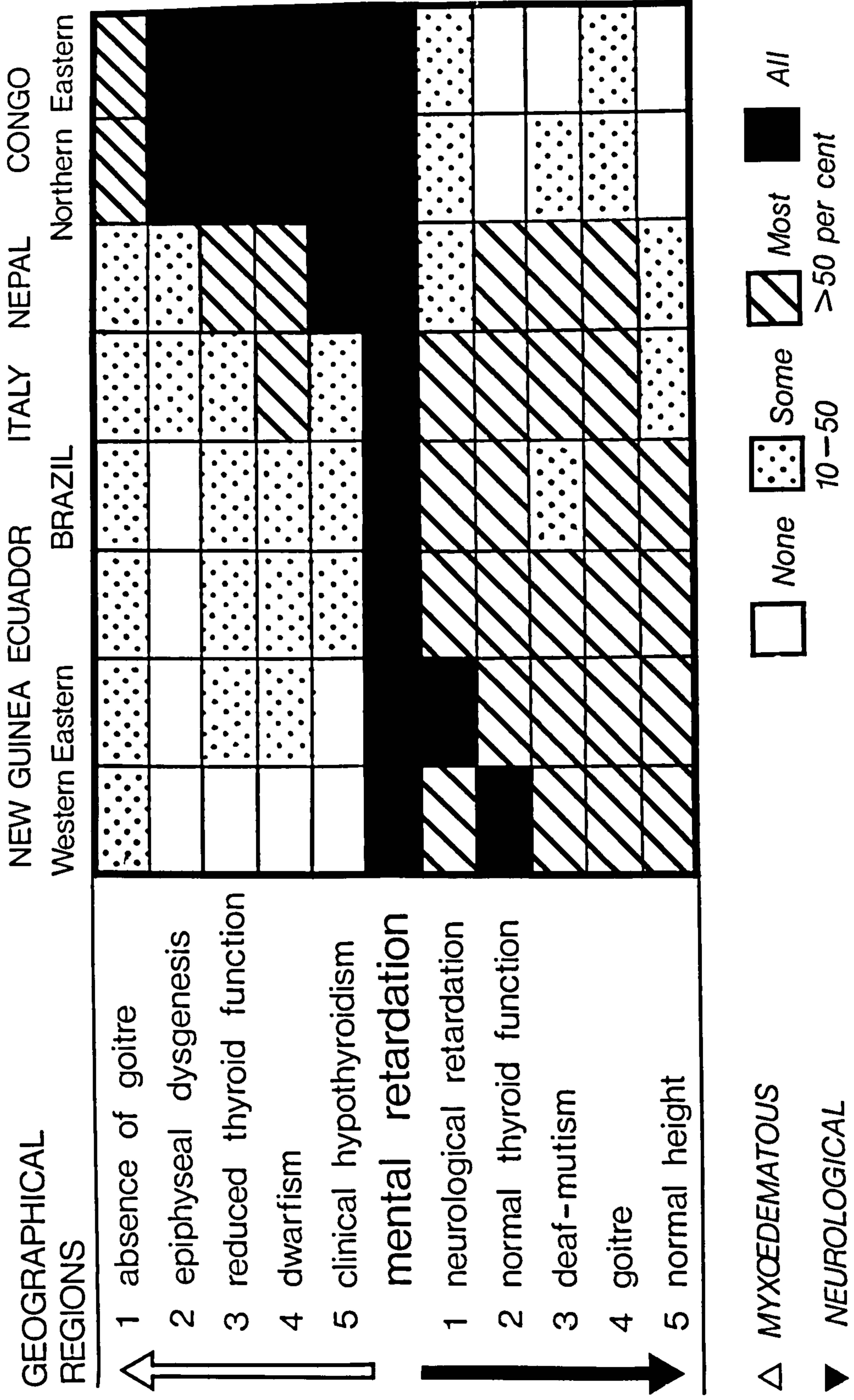


Fig. 3 Principal features of endemic cretinism.

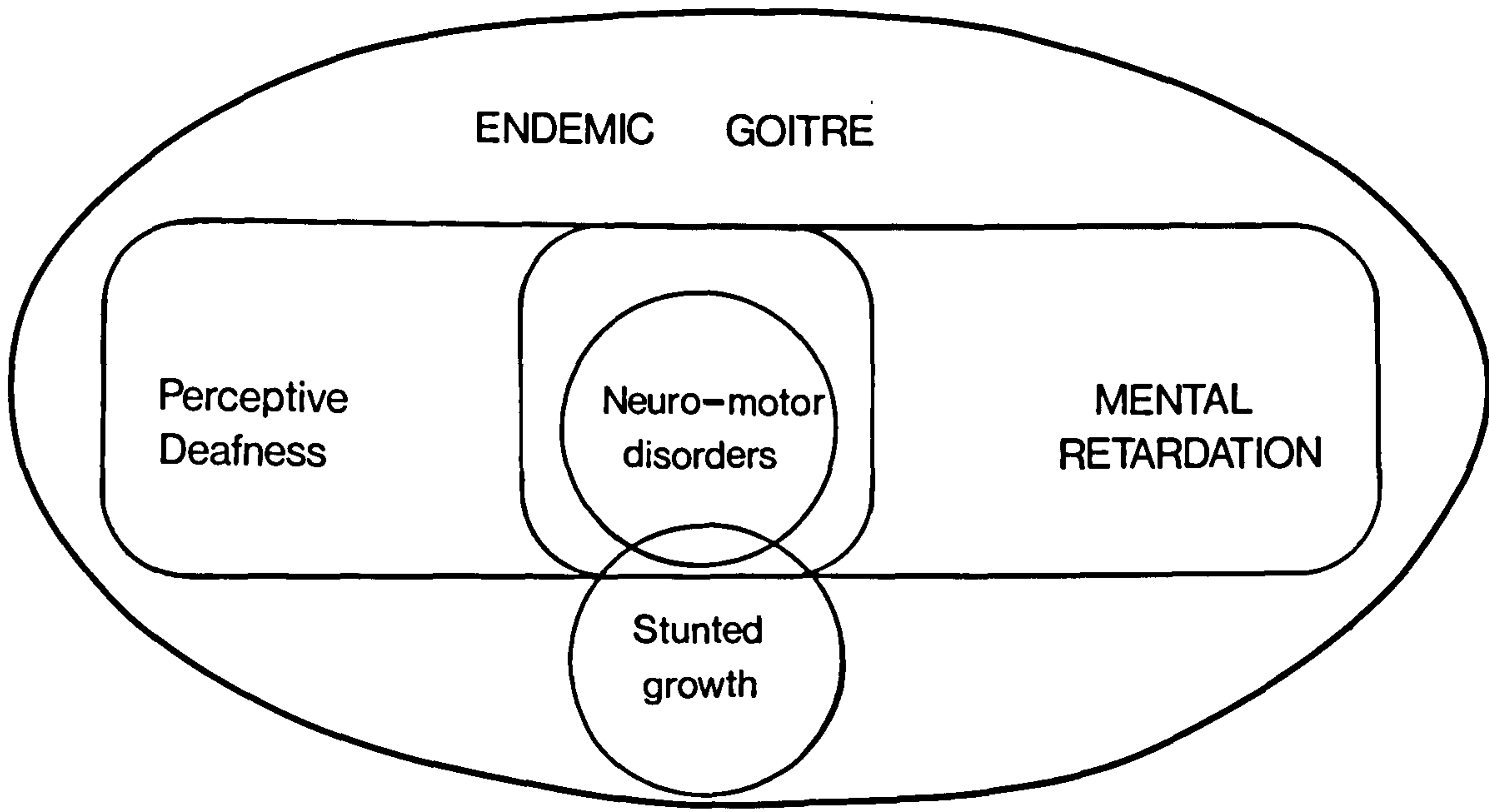


Fig. 3

Fig. 4 **Iodisation and deaf-mutism in Switzerland.**
Drawn from data of Wespi (284).

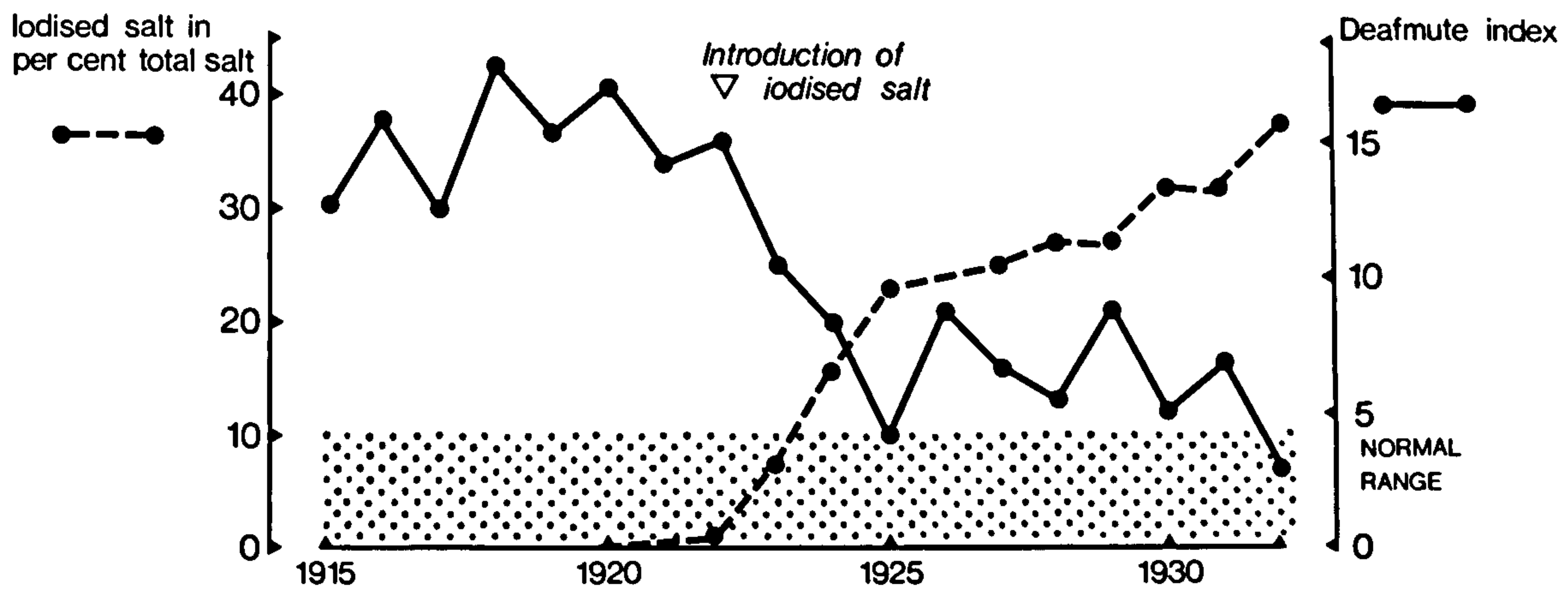
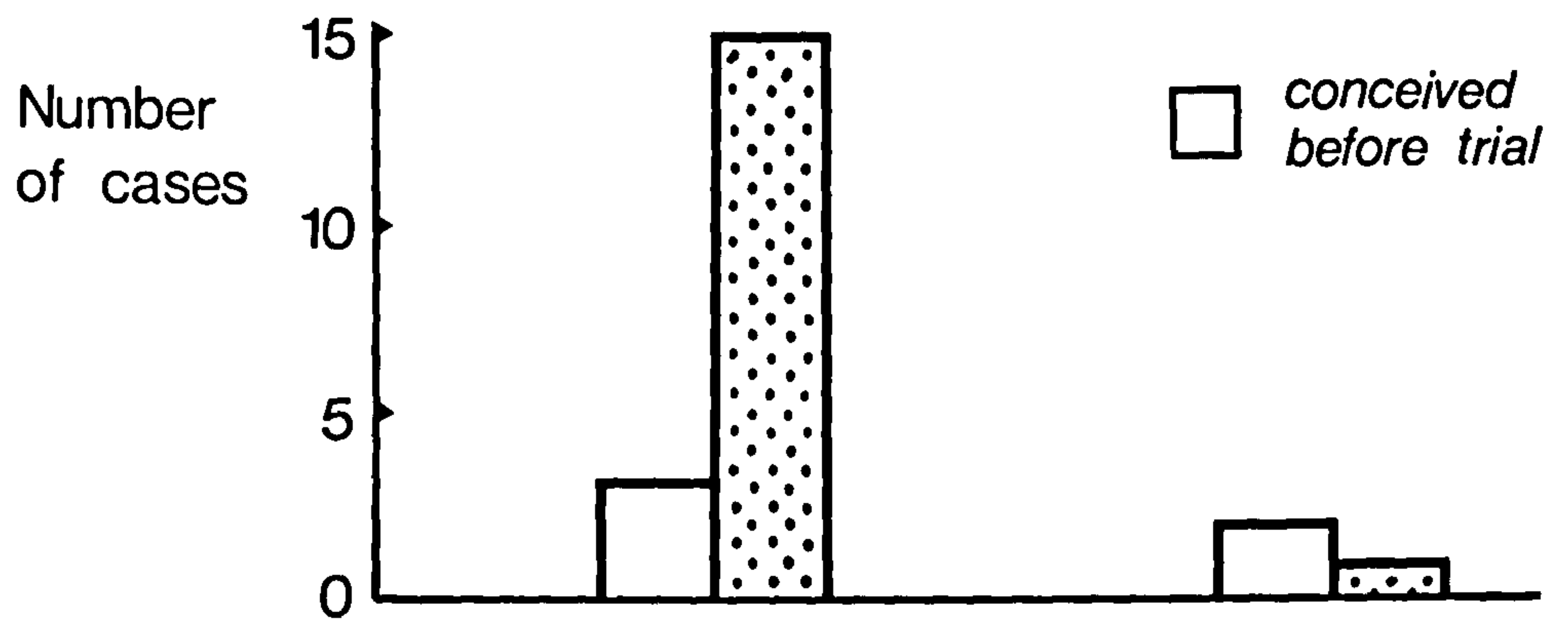


Fig. 4

Fig. 5 Prevention of endemic cretinism in the Jimi Valley.

MOTOR RETARDATION, DEAFNESS
AND SQUINT.



MOTOR RETARDATION AND
DEAFNESS ONLY.

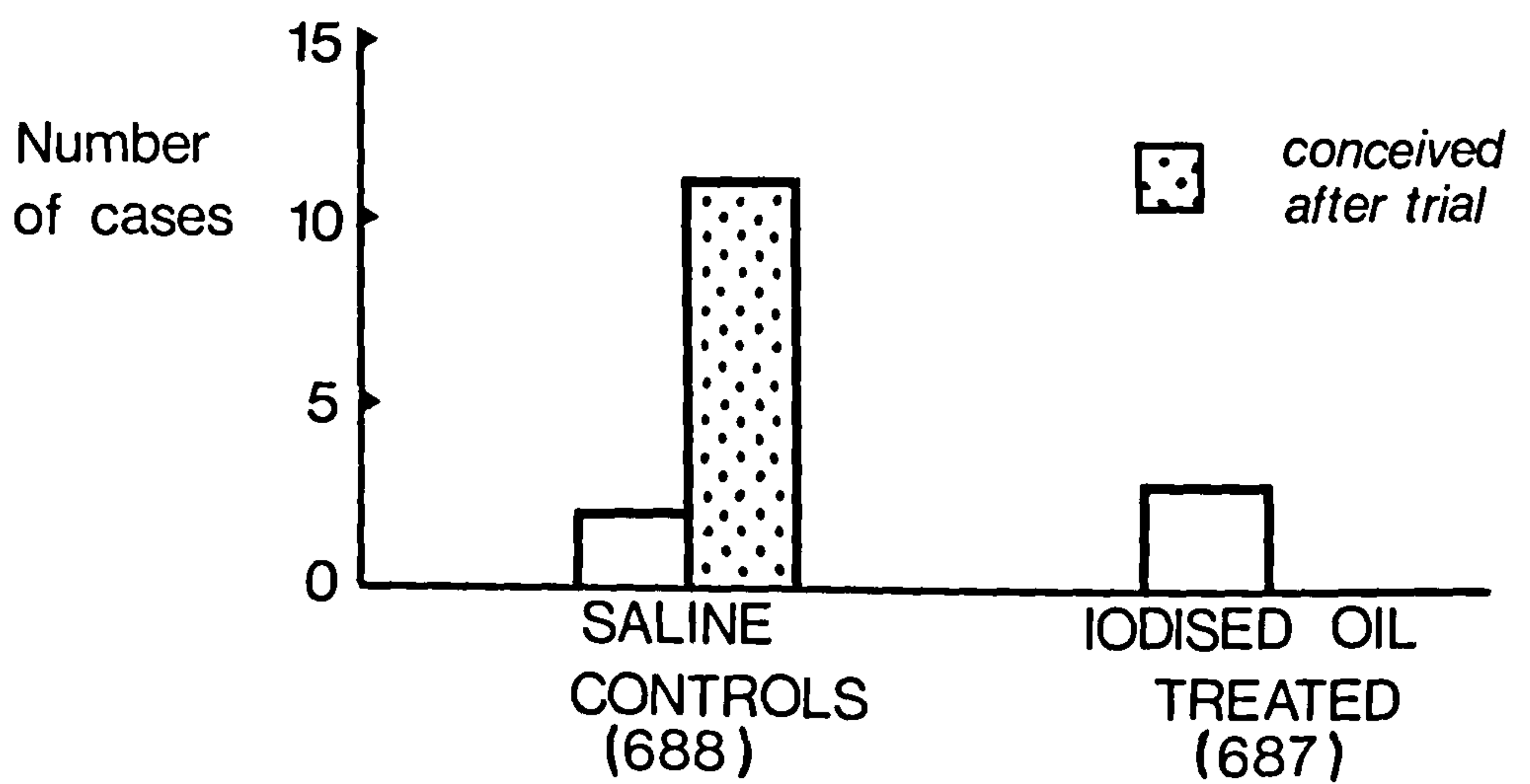


Fig. 5

Fig. 6 **Relation of serum T_4 to serum TSH in endemic goitre.**
After Chopra et al. (38).

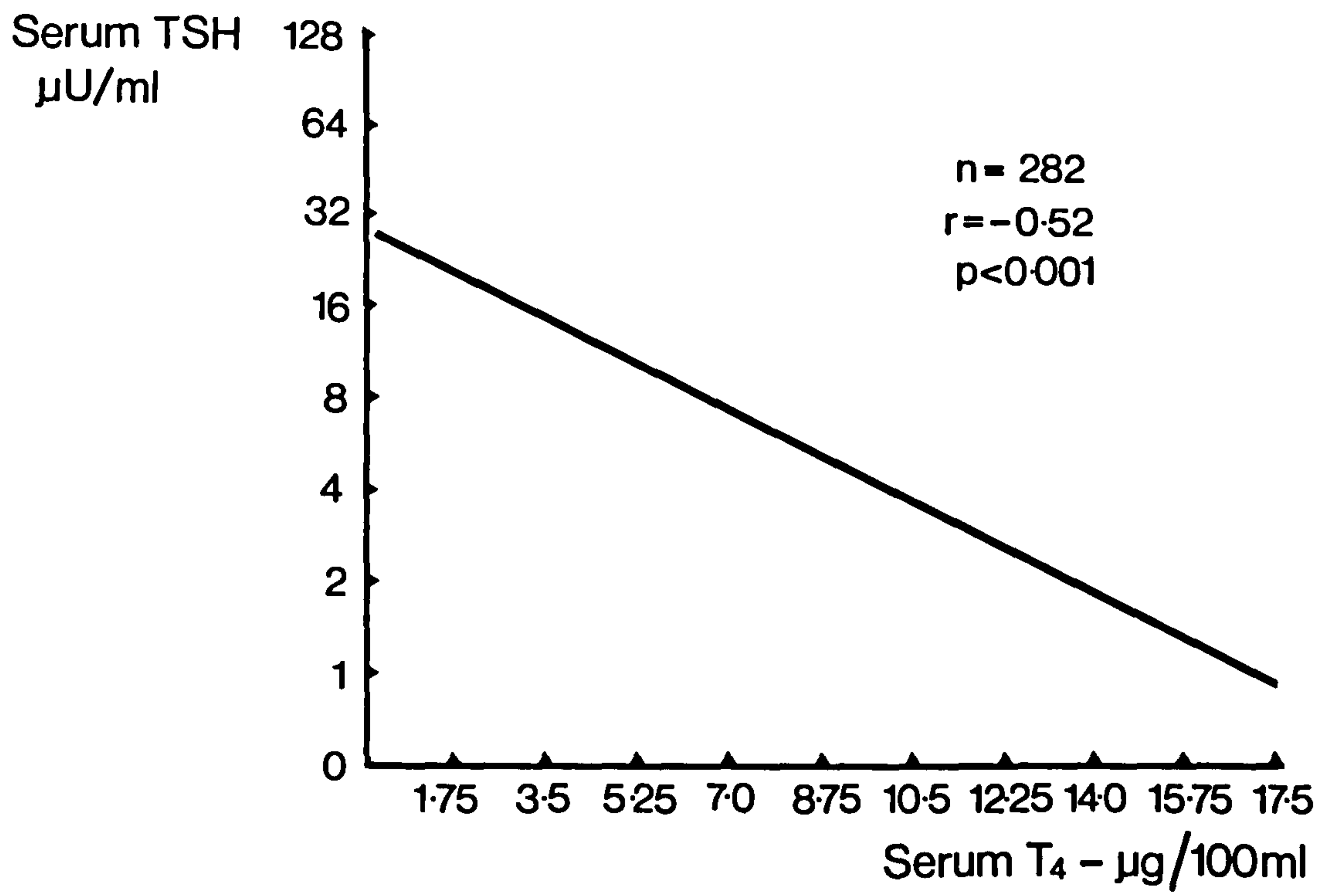


Fig. 6

Fig. 7 **Development of the HPT axis in man.**
Modified from Fisher et al. (115).

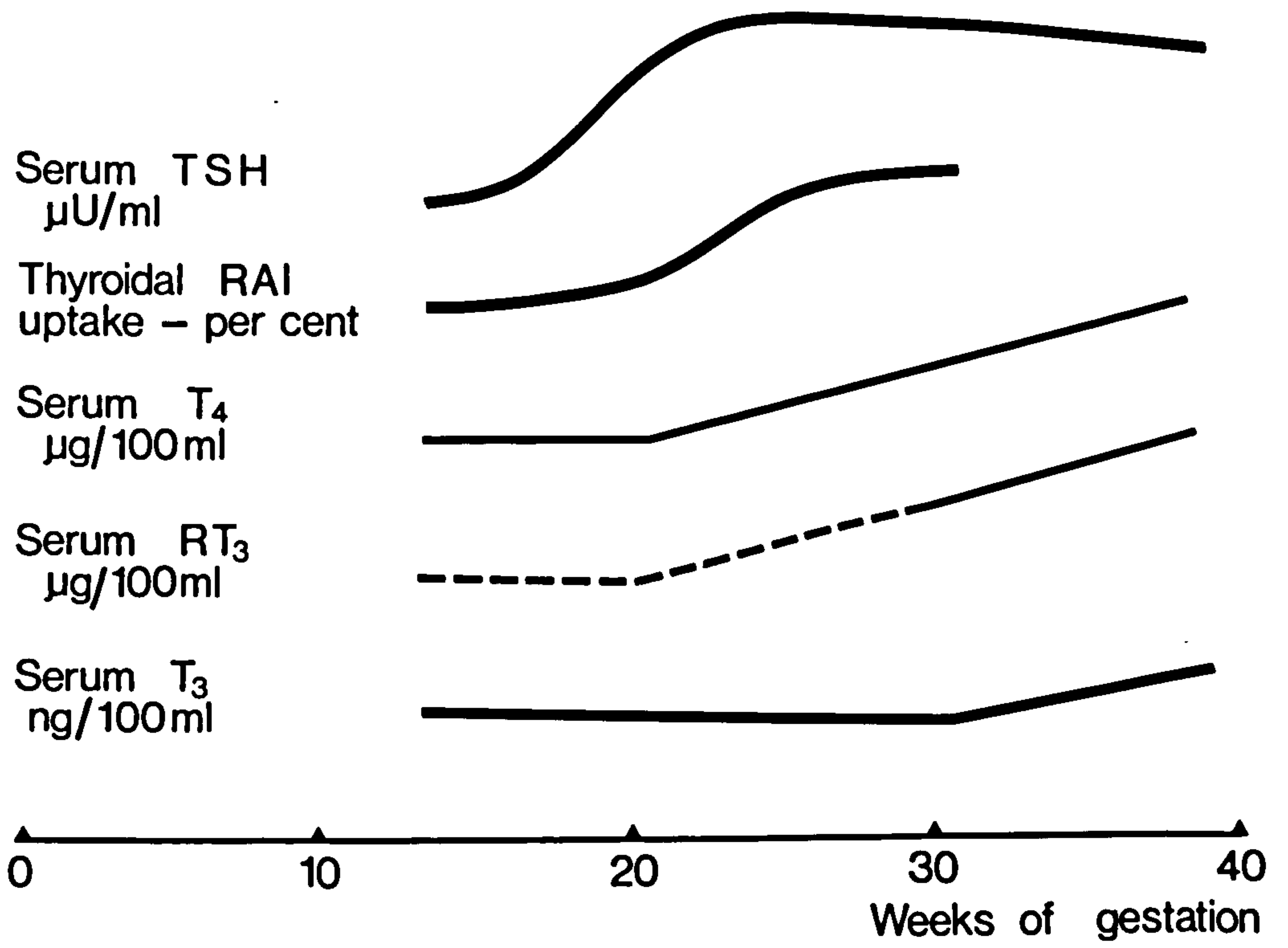


Fig. 7

Fig. 8 **Development of the HPT axis in the rat.**
Modified from Fisher et al. (115).

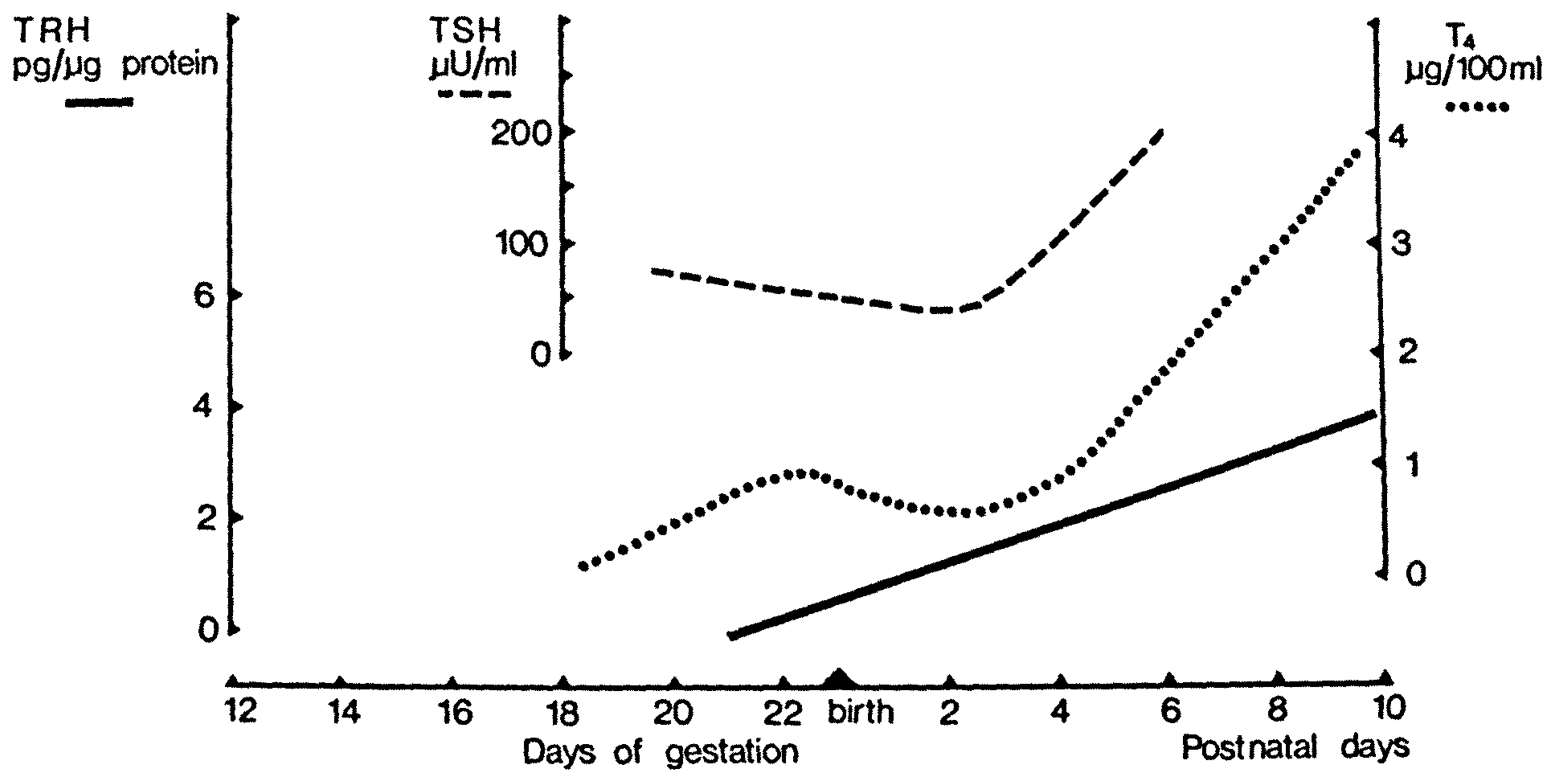


Fig. 8

Fig. 9 **Effect of LID on 4 hour RAIU.**

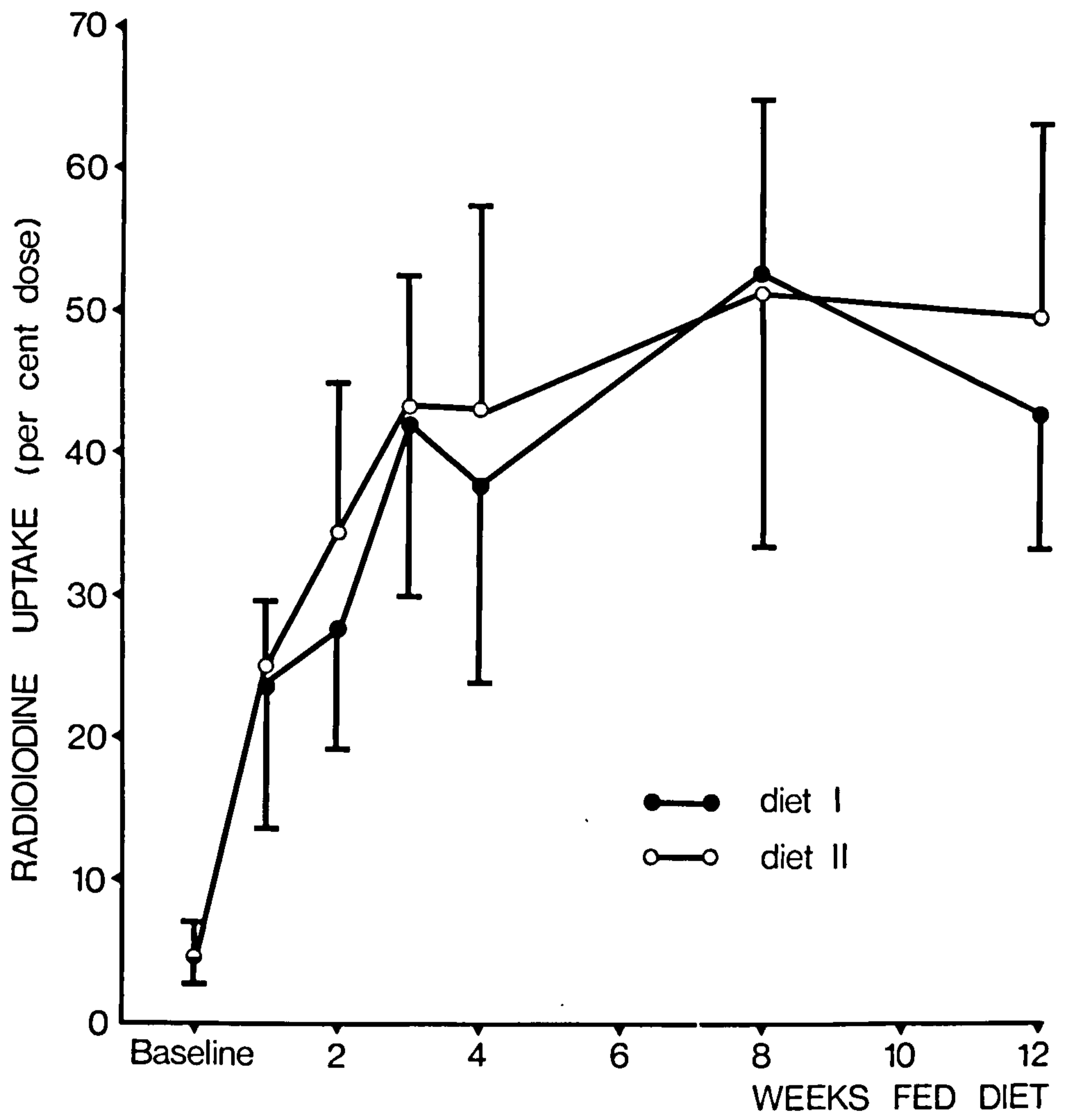


Fig. 9

Fig. 10 **Effect of LID on relative thyroid weight.**

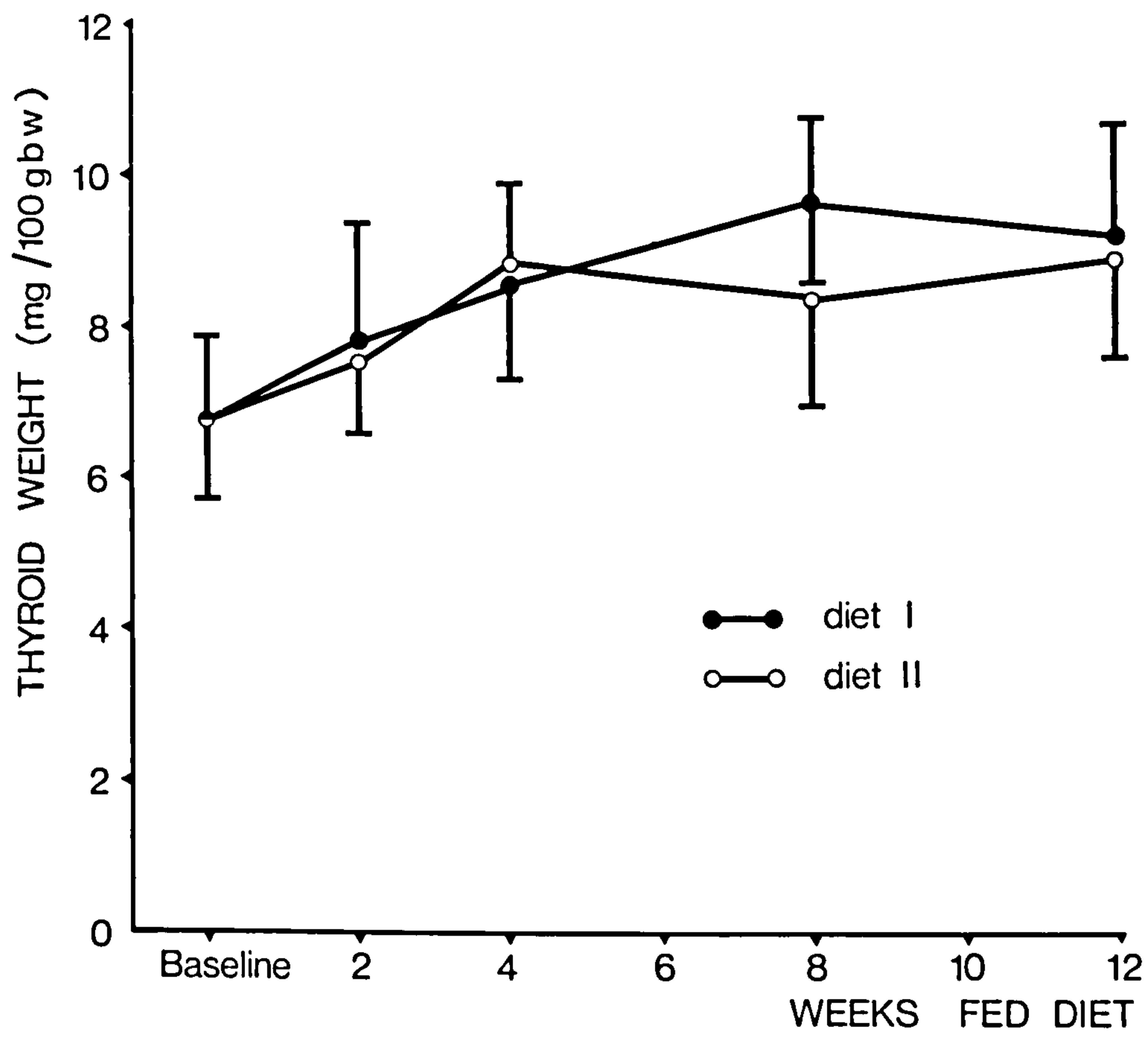


Fig. 10

Fig. 11 Effect of LID on serum T_4 concentration.

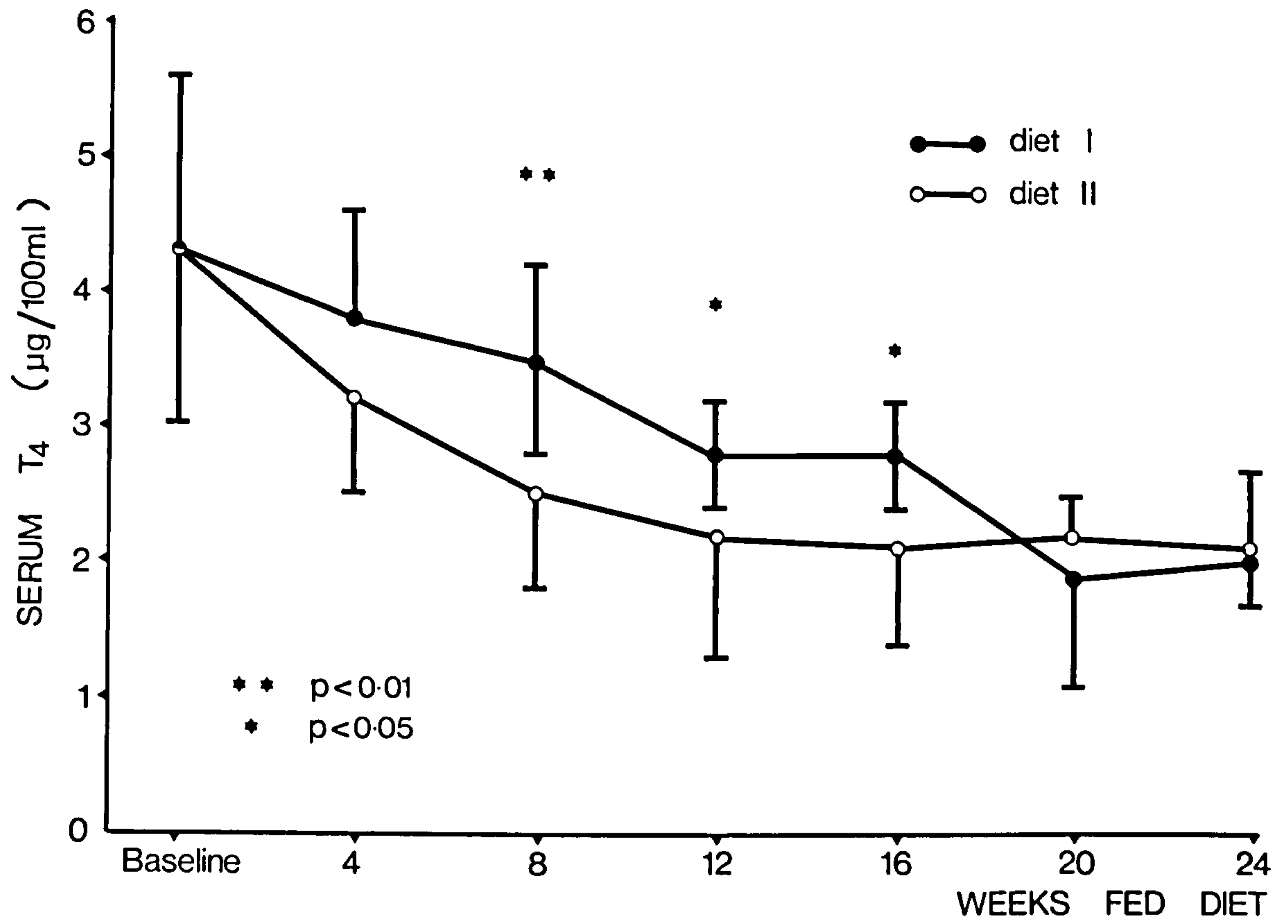


Fig. 11

Fig. 12 **Comparison of effects of diet I and diet II on
serum T₄ concentration.**

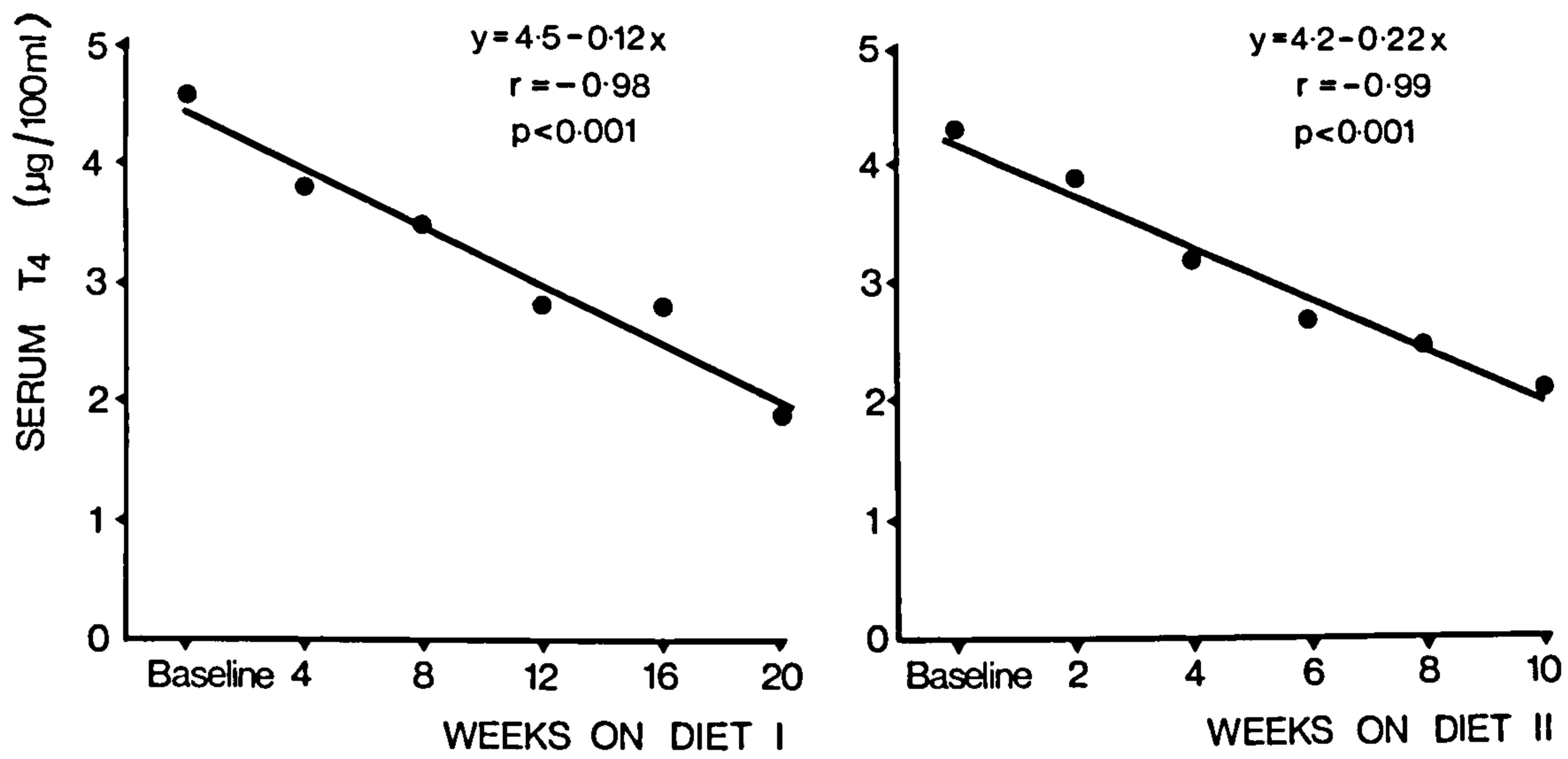


Fig. 12

Fig. 13 **Effect of LID on serum T₃ concentration.**



Fig. 13

Fig. 14 **Varying degrees of iodine deficiency.**

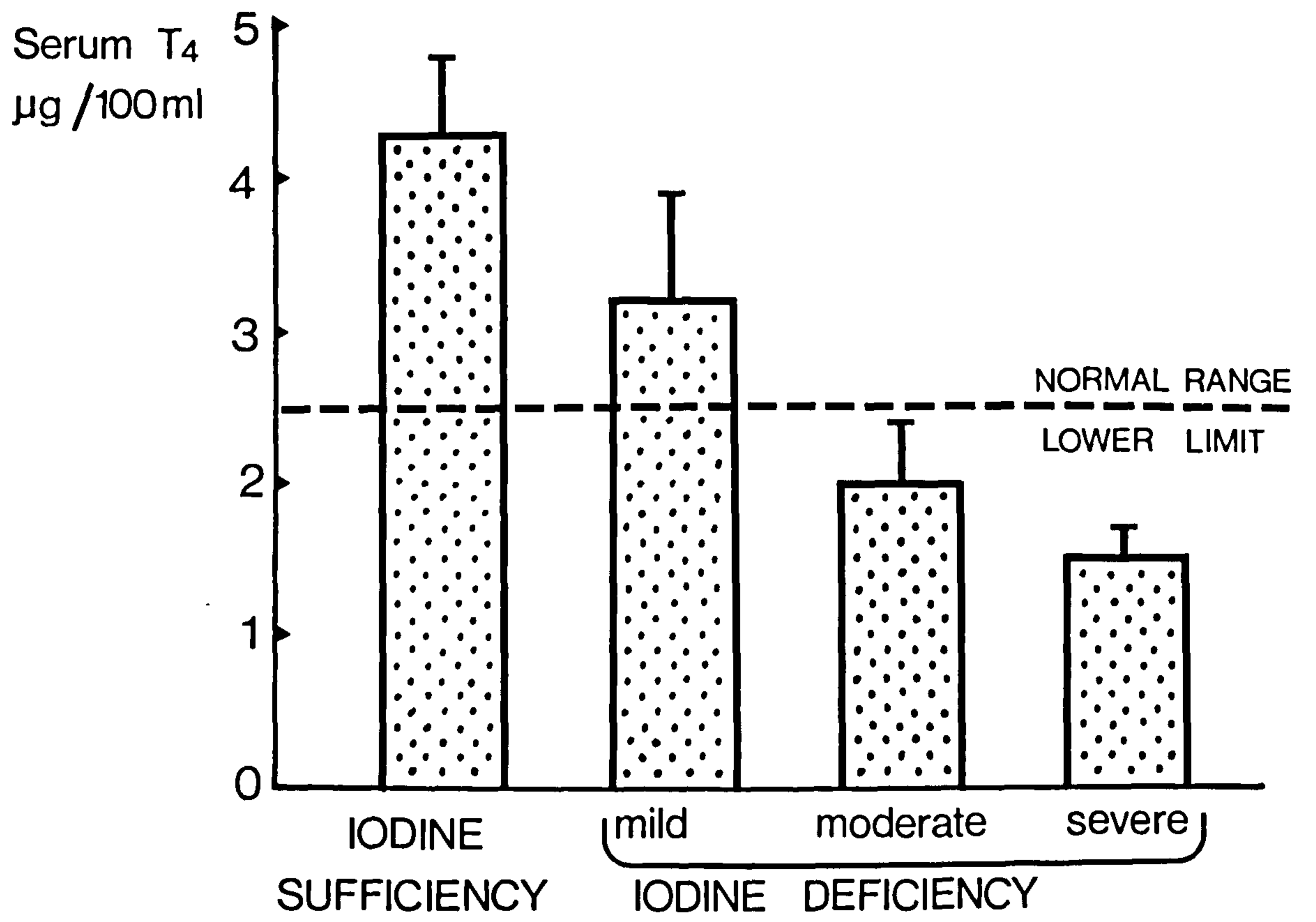


Fig. 14

Fig. 15 **Postnatal brain development in the rat.**
Drawn from data of Donaldson and Hatai (86).

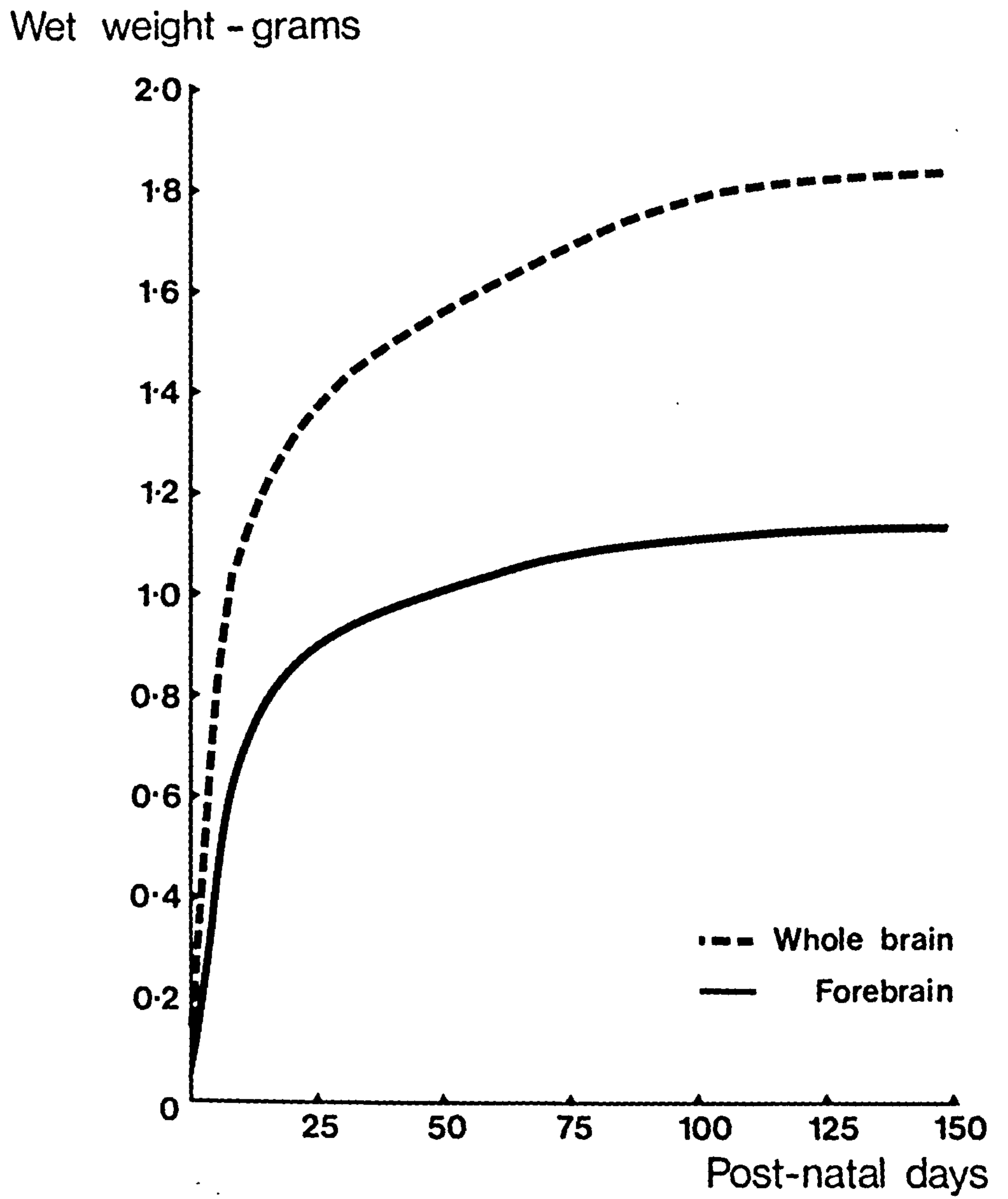


Fig. 15

Fig. 16 **Quantitative changes in DNA and protein during
brain growth in the rat. After Winick and Noble
(289).**

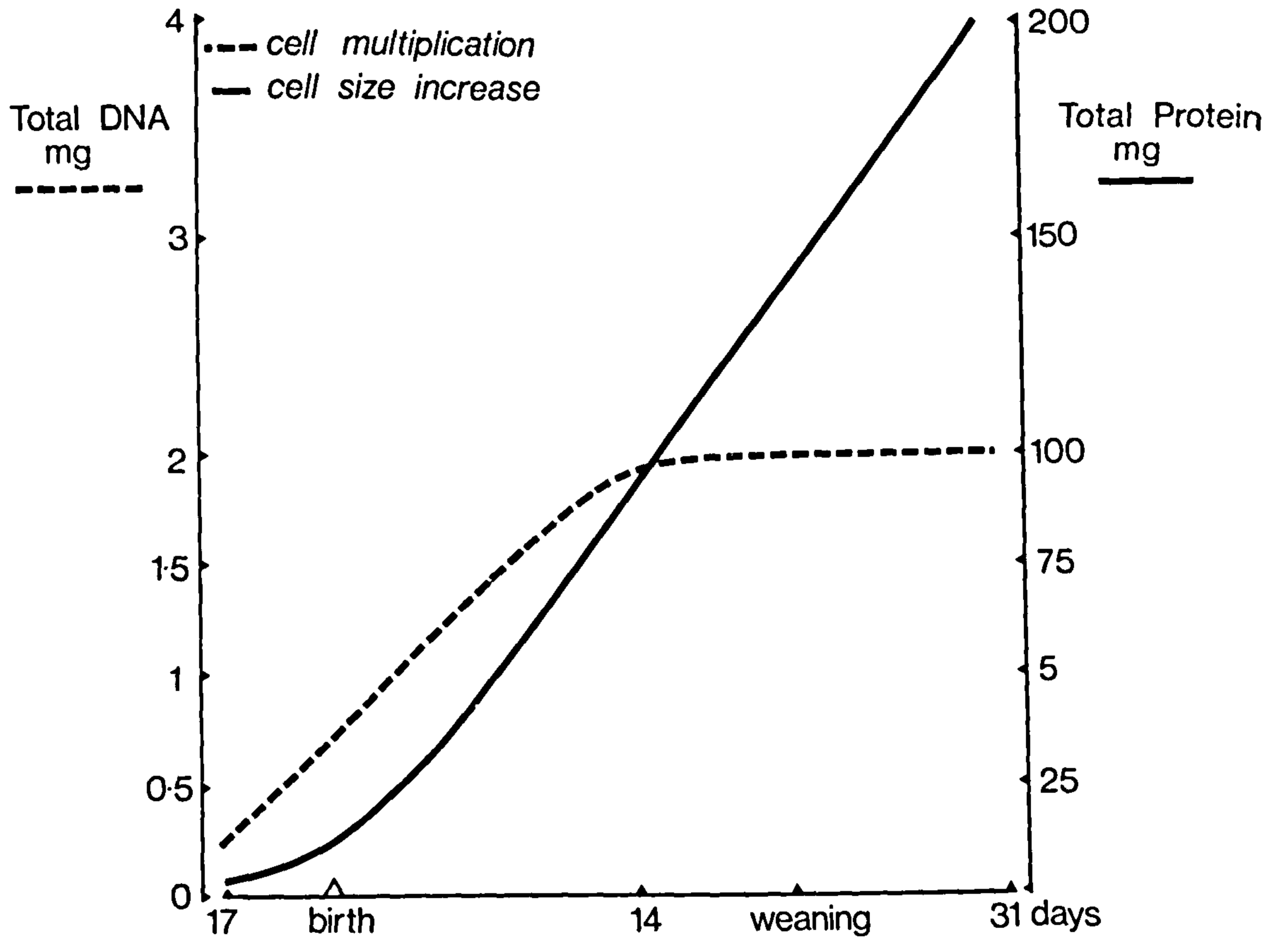


Fig. 16

Fig. 17 **Quantitative changes in DNA during forebrain growth in man. After Dobbing and Sands (79).**

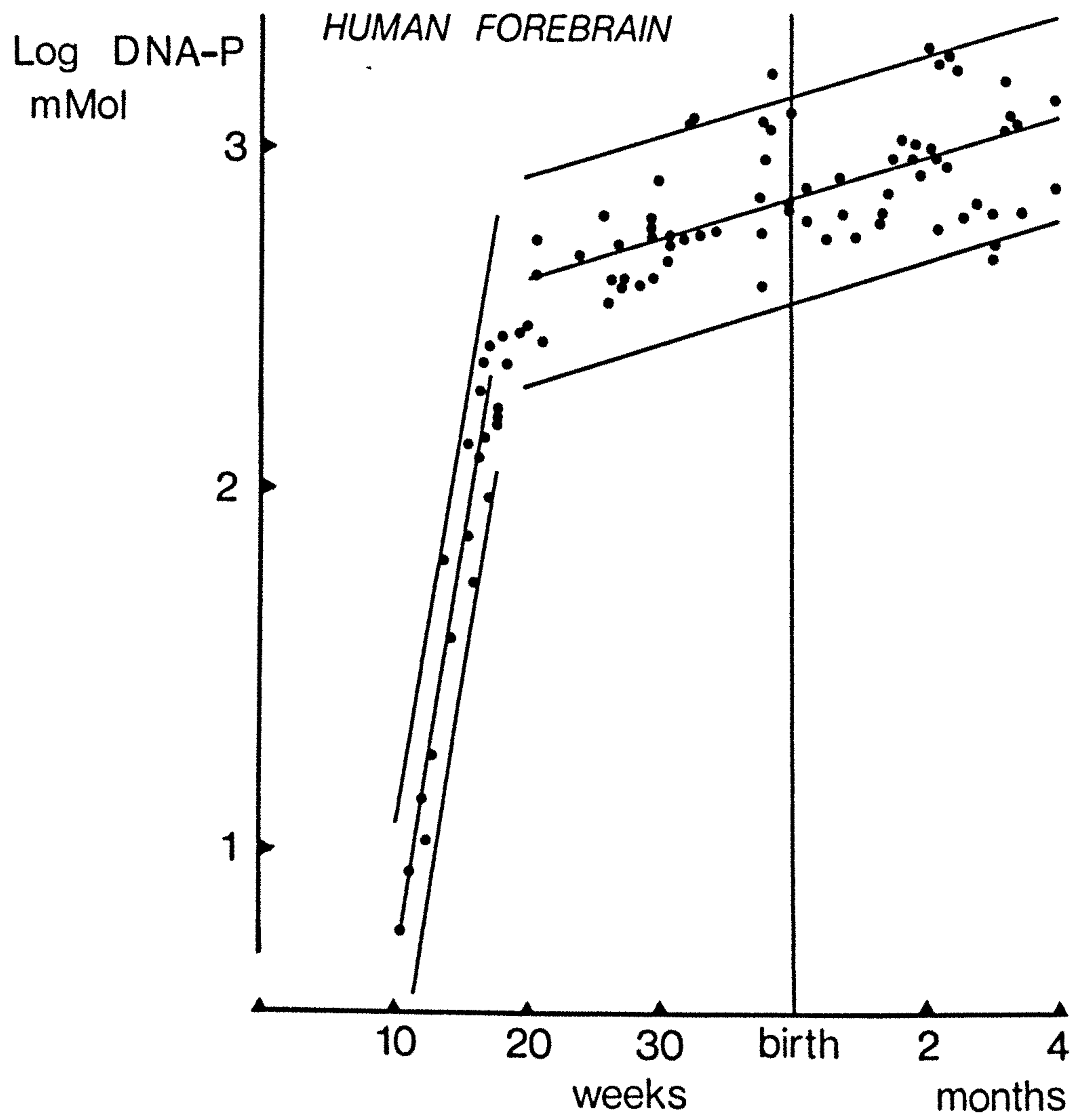
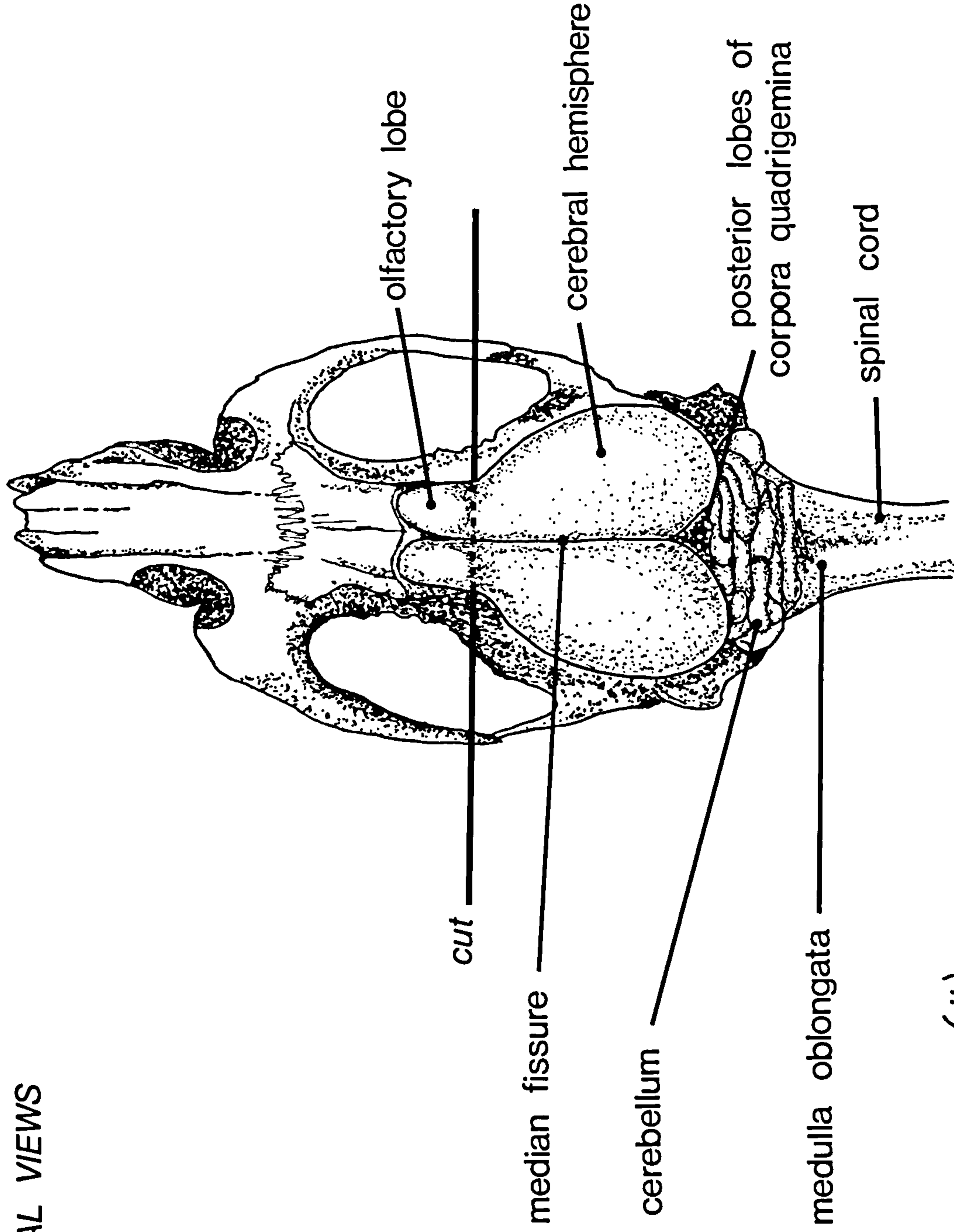
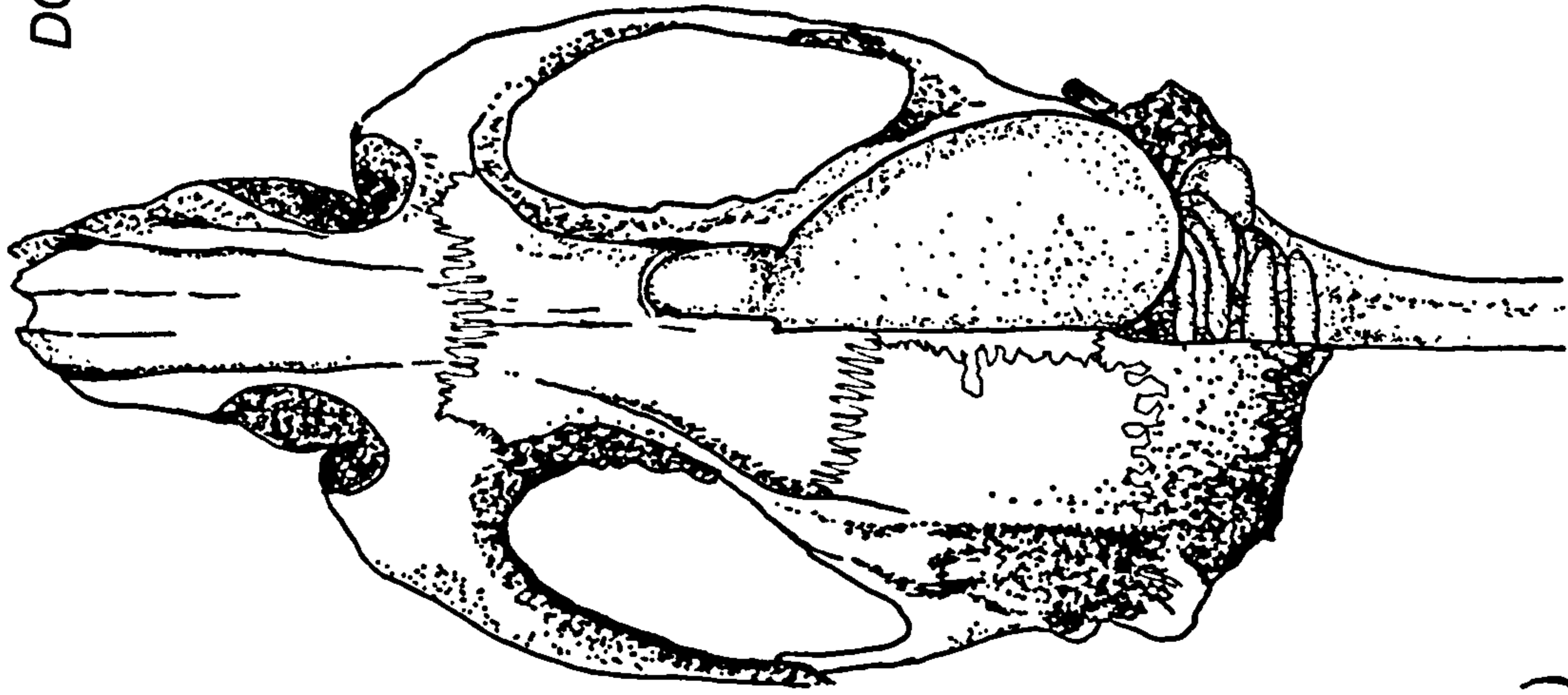


Fig. 17

Fig. 18 **Method of dissection of rat forebrain.**
Steps (i) and (ii).

DISSECTION OF RAT FOREBRAIN

DORSAL VIEWS



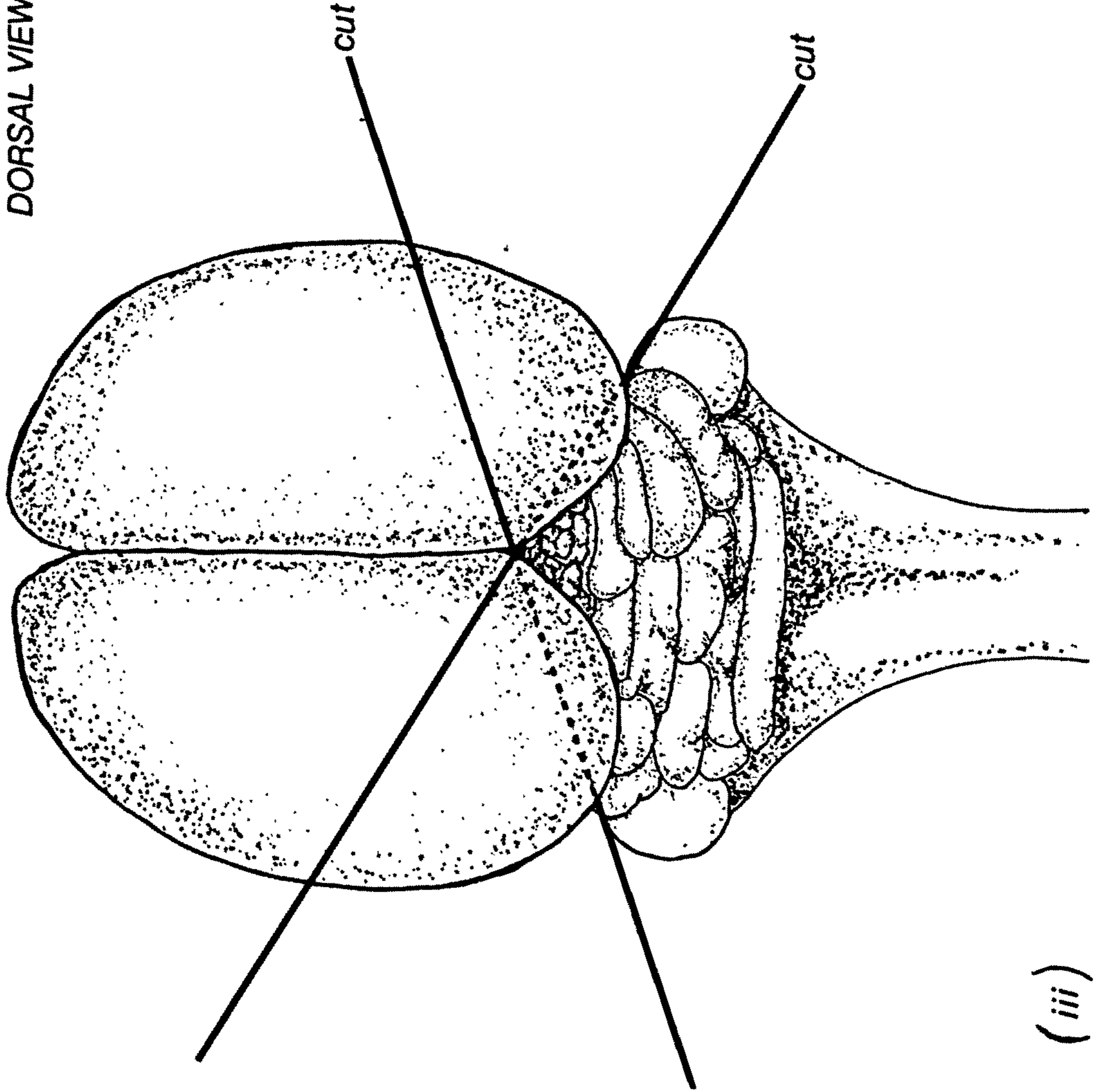
(i)

(ii)

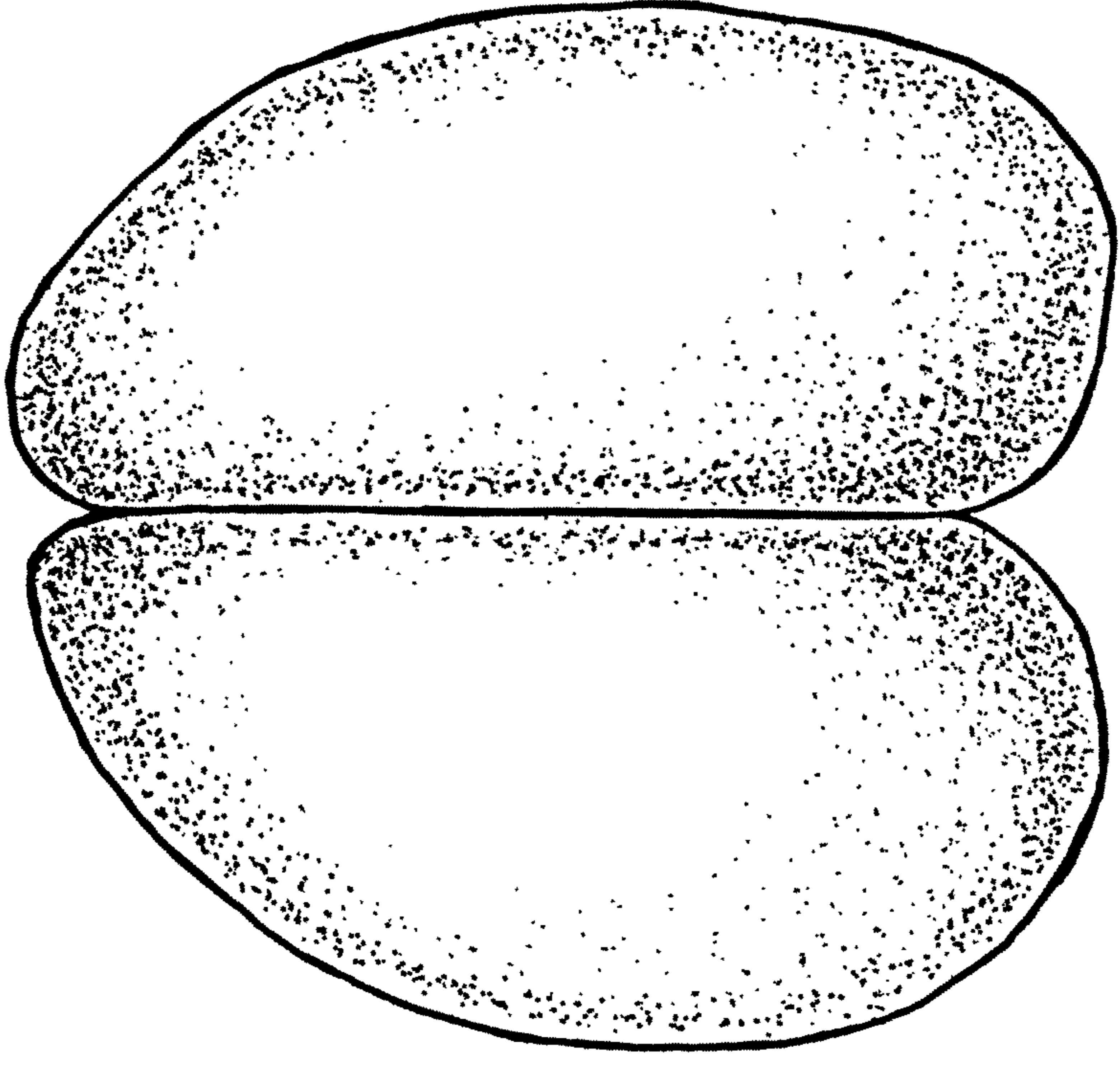
Fig. 18 Method of dissection of rat forebrain.
Steps (iii) and (iv).

DISSECTION OF RAT FOREBRAIN

DORSAL VIEWS



(iii)



(iv)

Fig. 19 Biochemical analysis of rat forebrain.

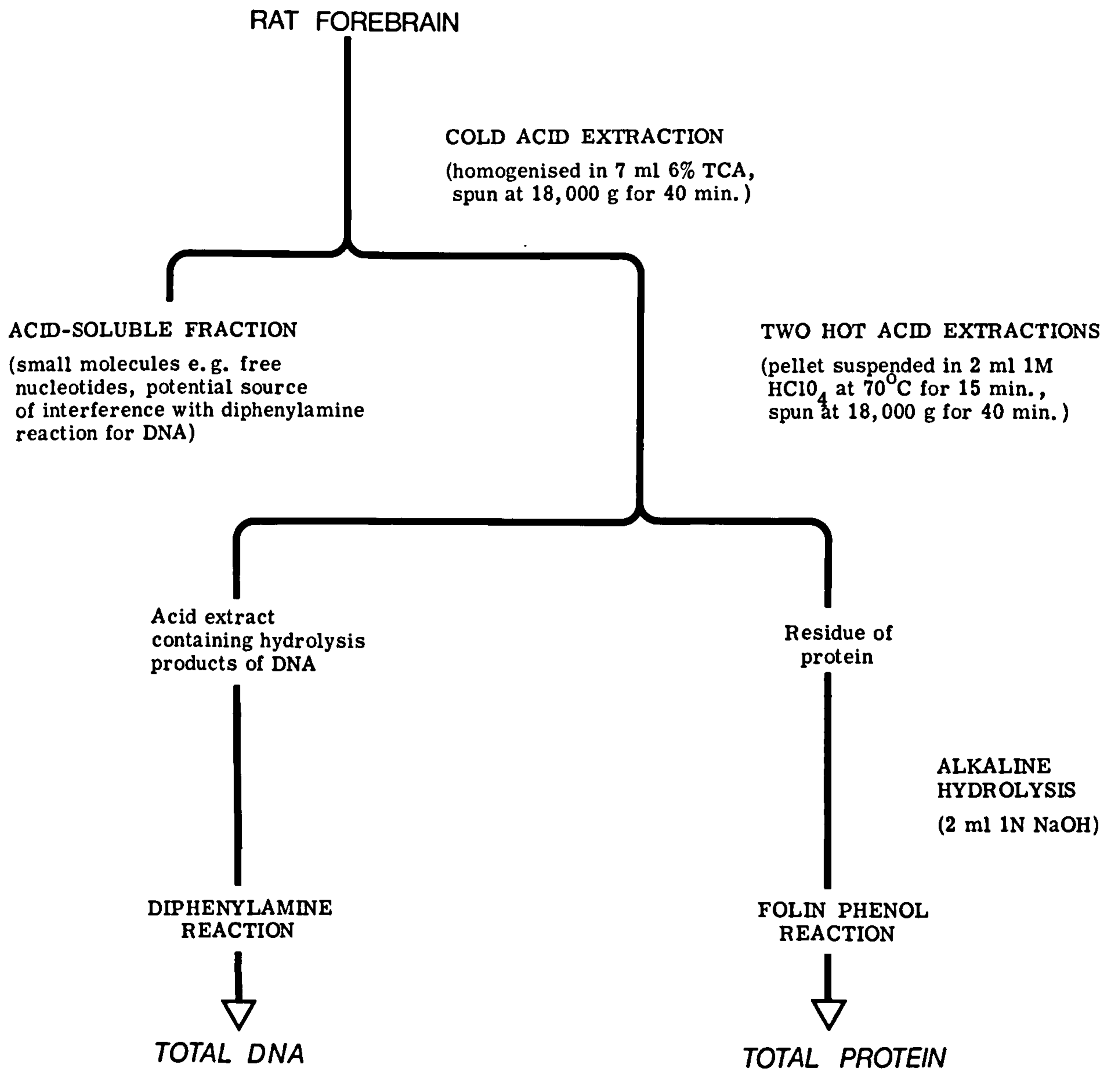


Fig. 19

Fig. 20 **Typical standard curve for DNA assay.**

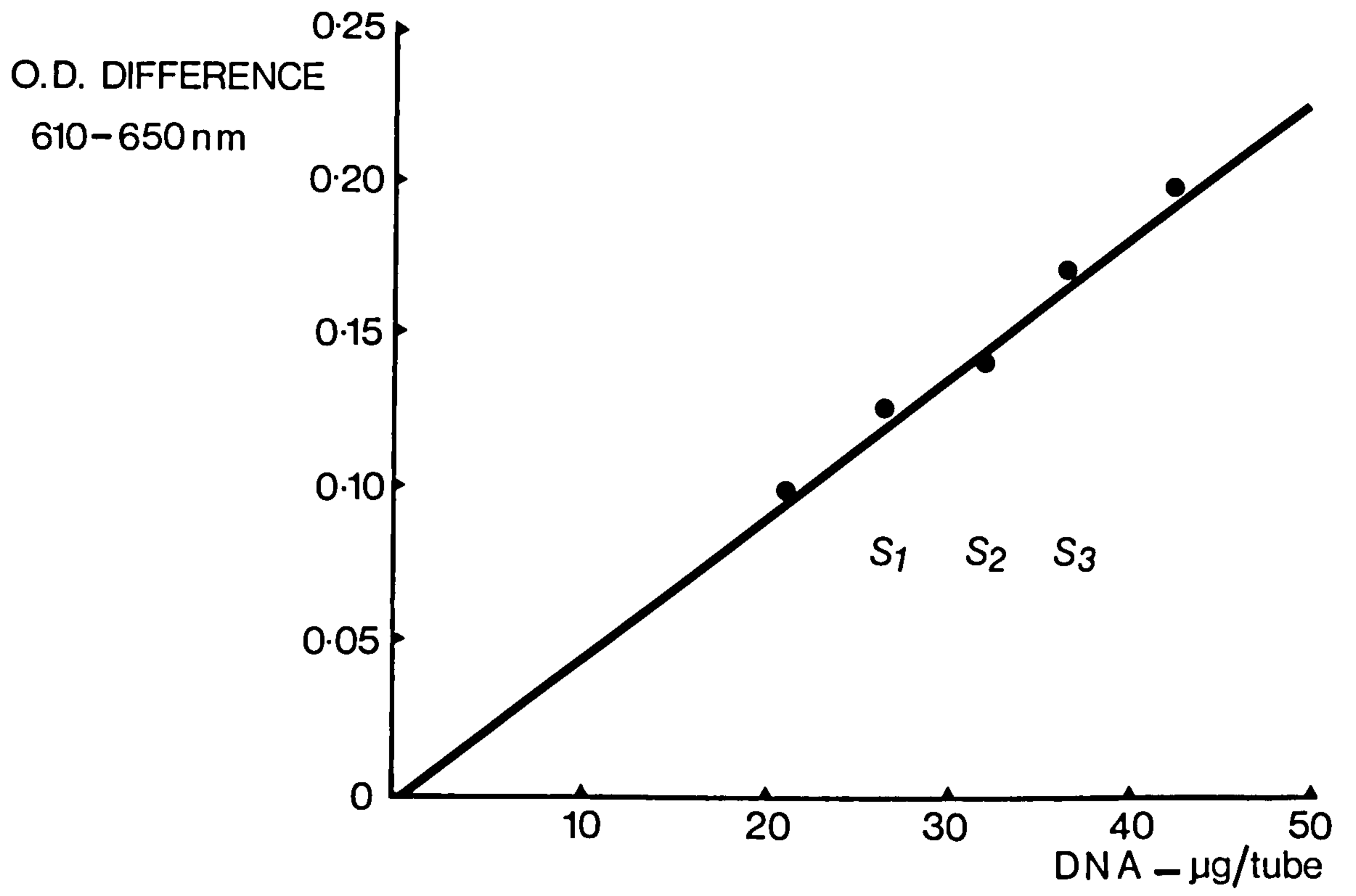


Fig. 20

Fig. 21 **Typical standard curve for protein assay.**

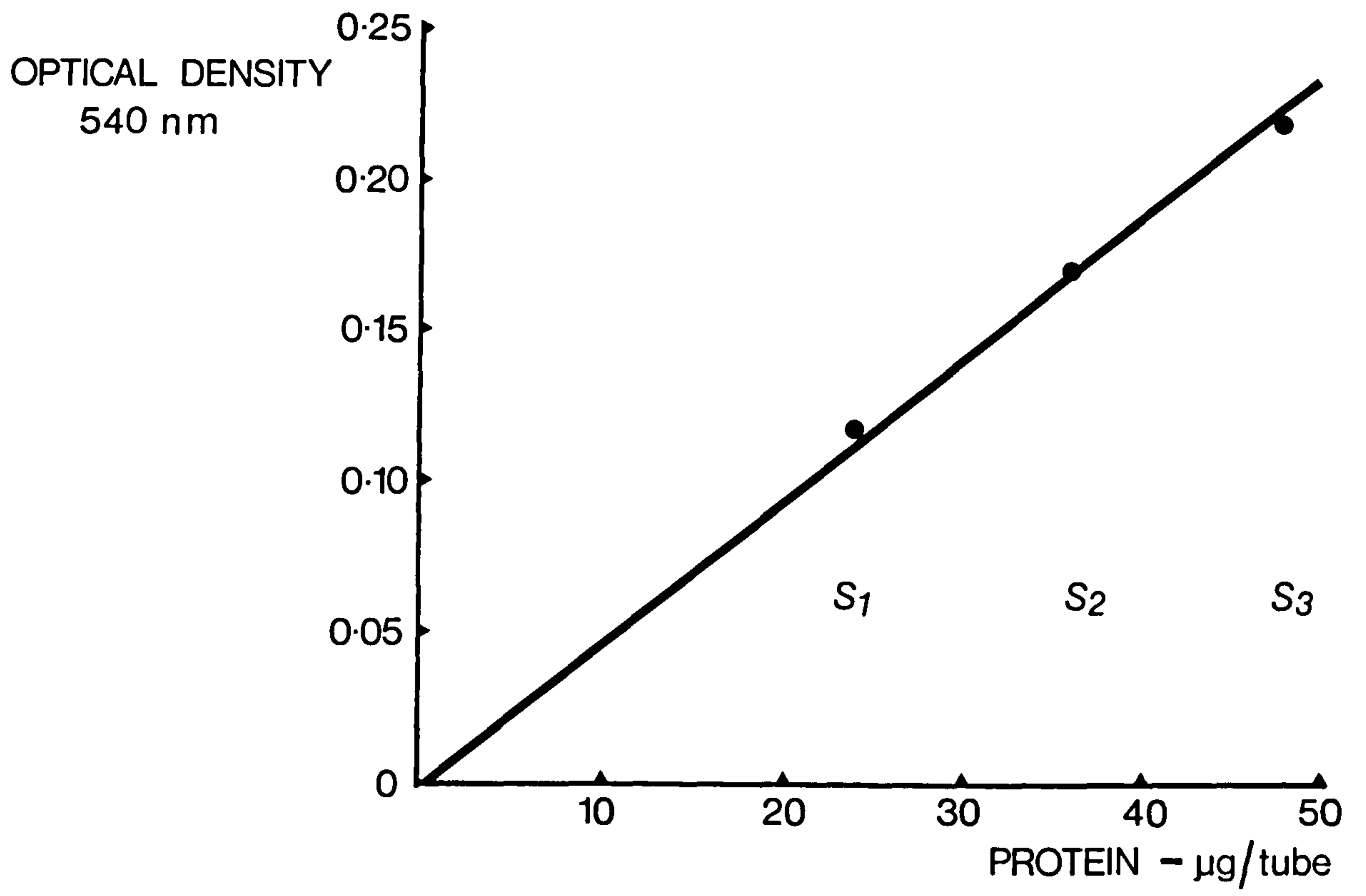


Fig. 21

Fig. 22 **Quantitative changes in DNA and protein during postnatal forebrain growth.**

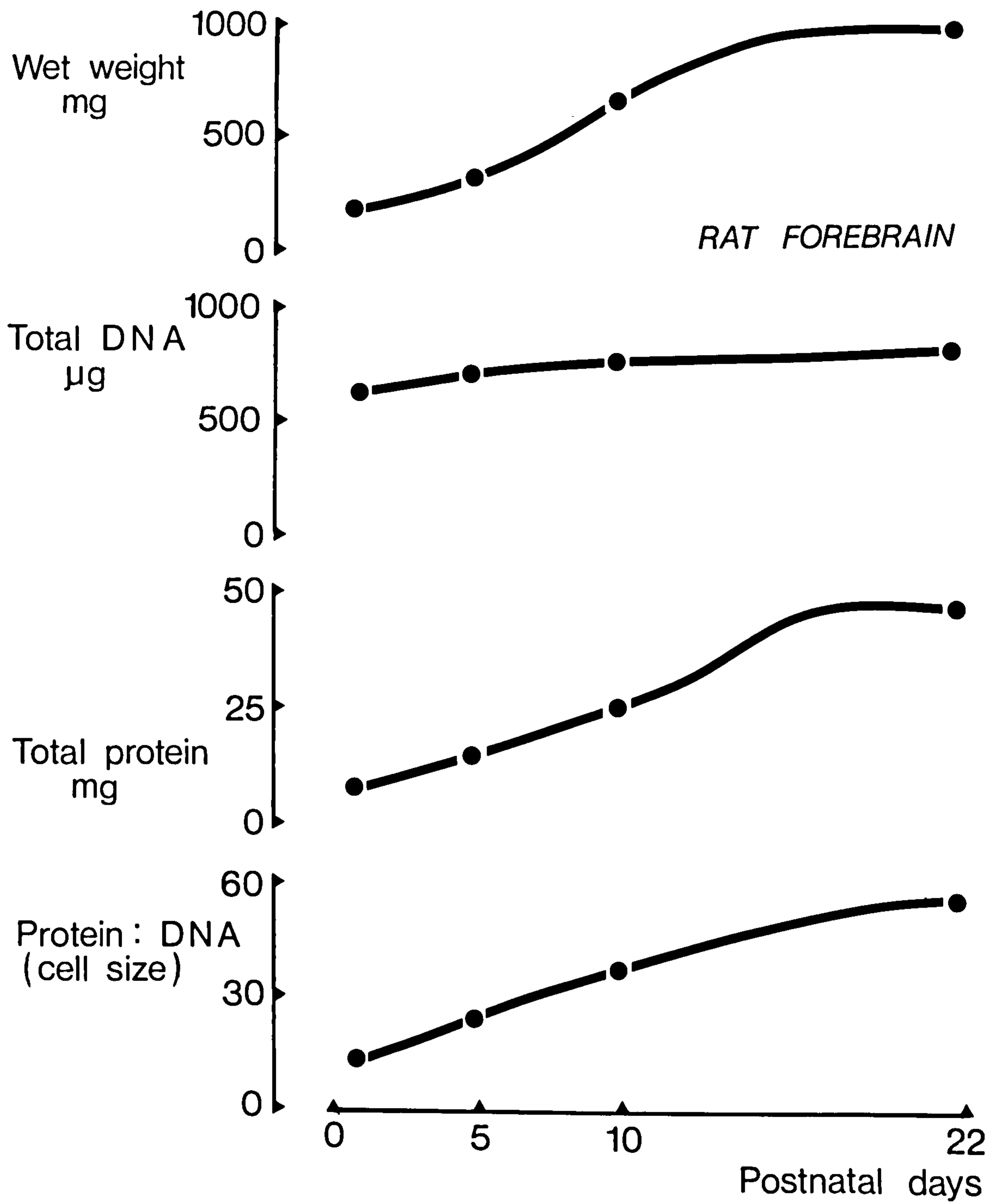


Fig. 22

Fig. 23 Design of experiments 1-4.

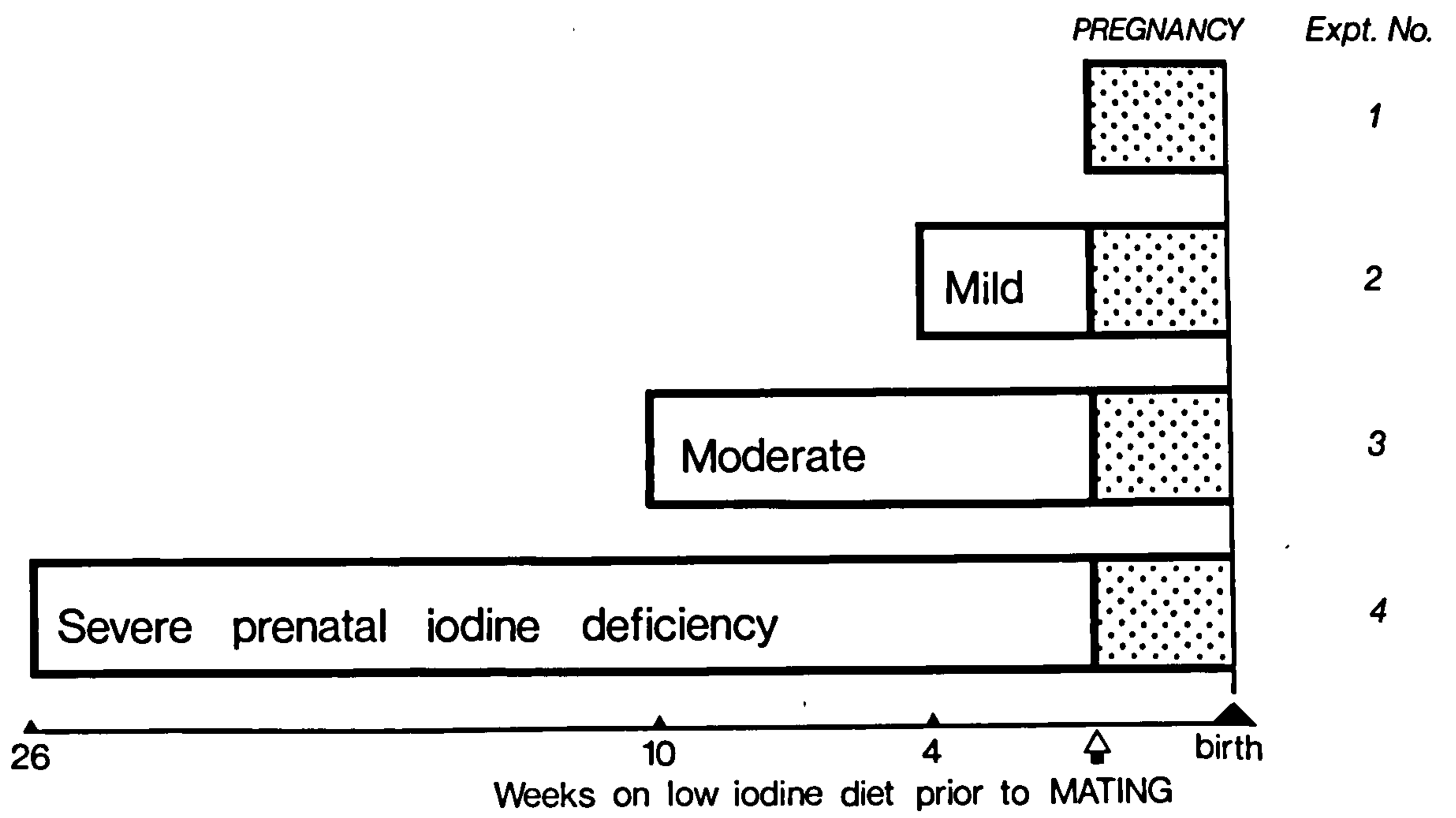


Fig. 23

Fig. 24 Growth of rats on LID for 4 weeks.

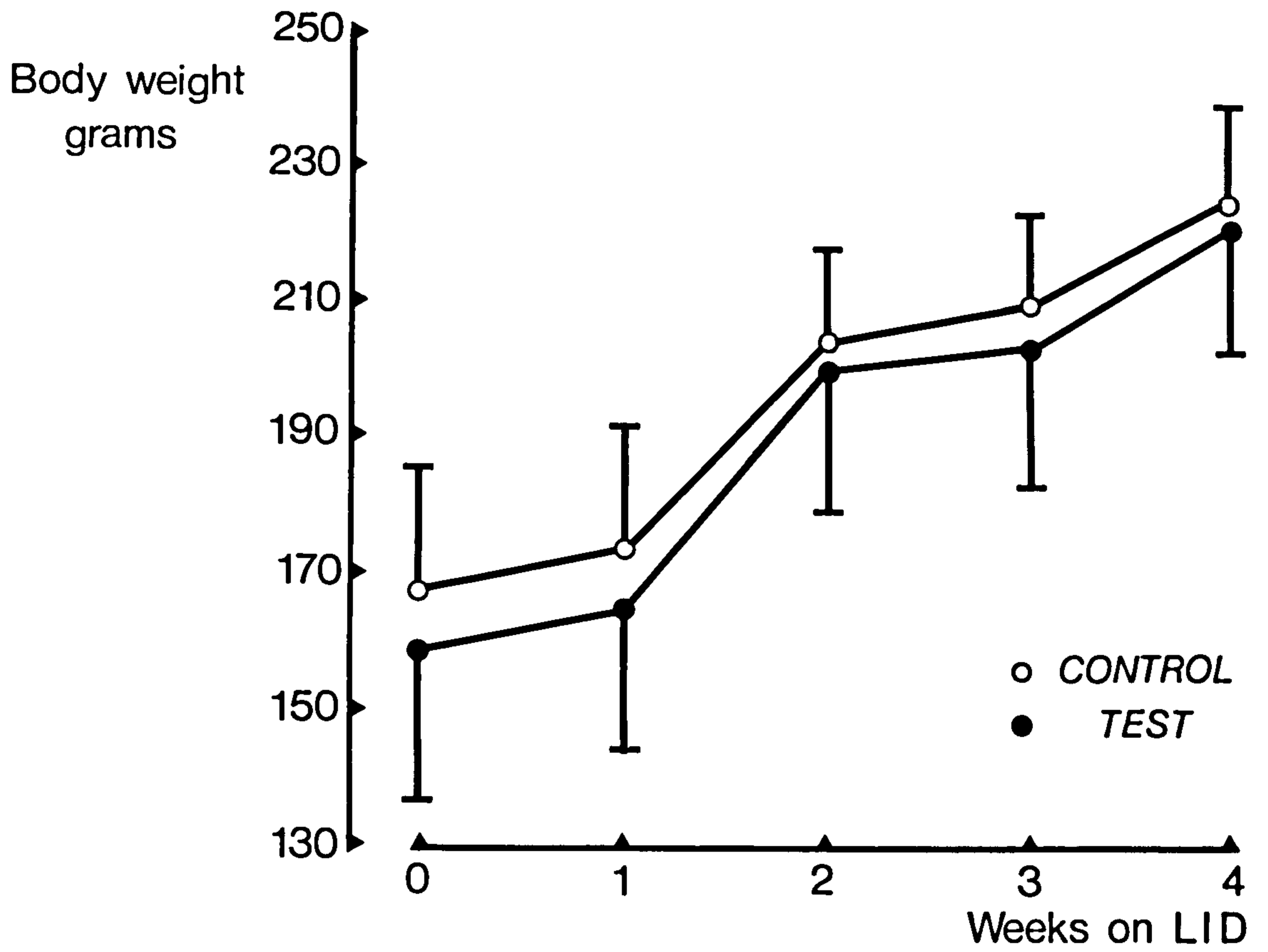
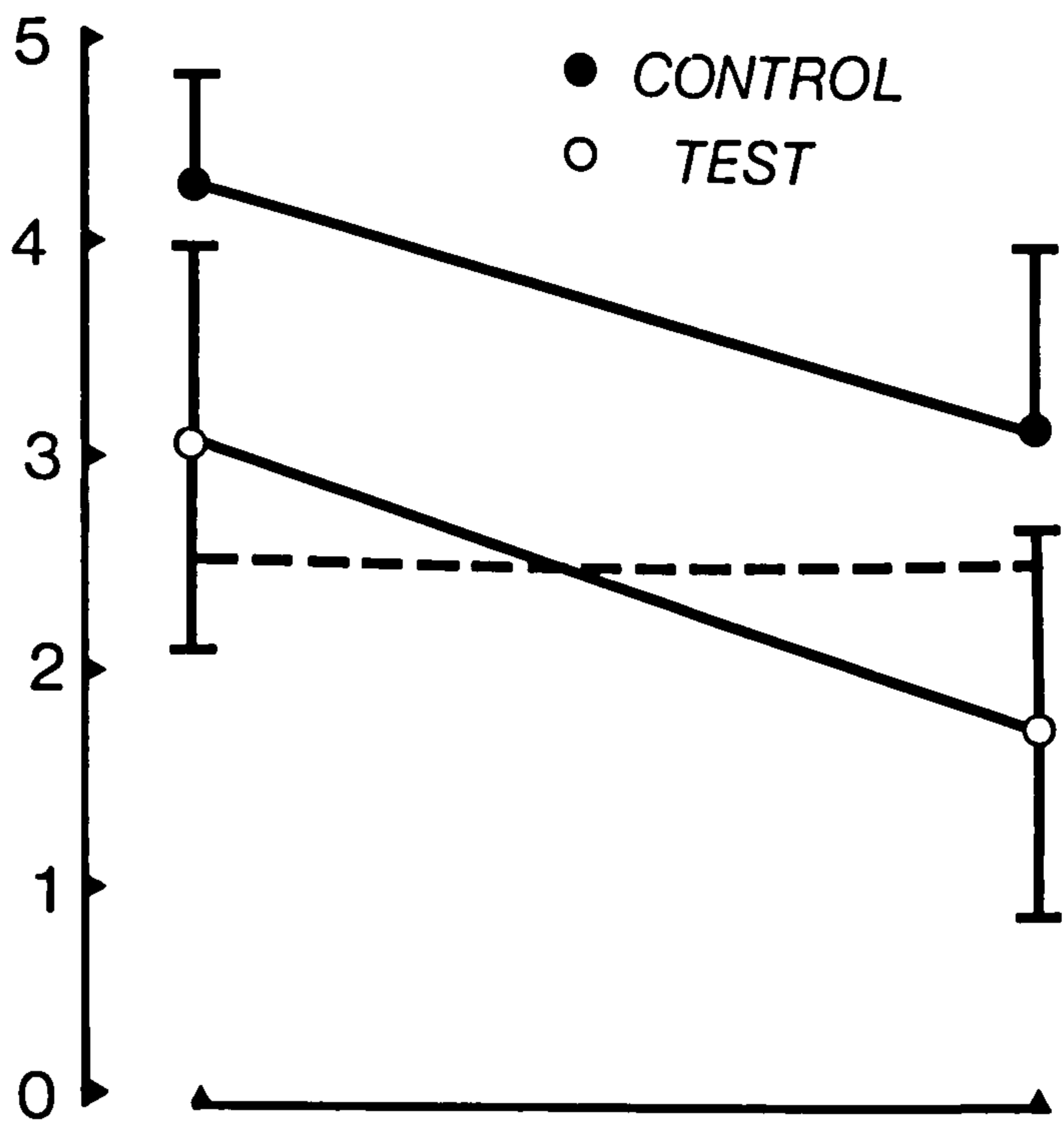


Fig. 24

Fig. 25 Changes in serum T_4 and T_3 concentrations of
animals mated after 4 weeks on LID.

Serum T₄
μg/100ml



Serum T₃
ng/100ml

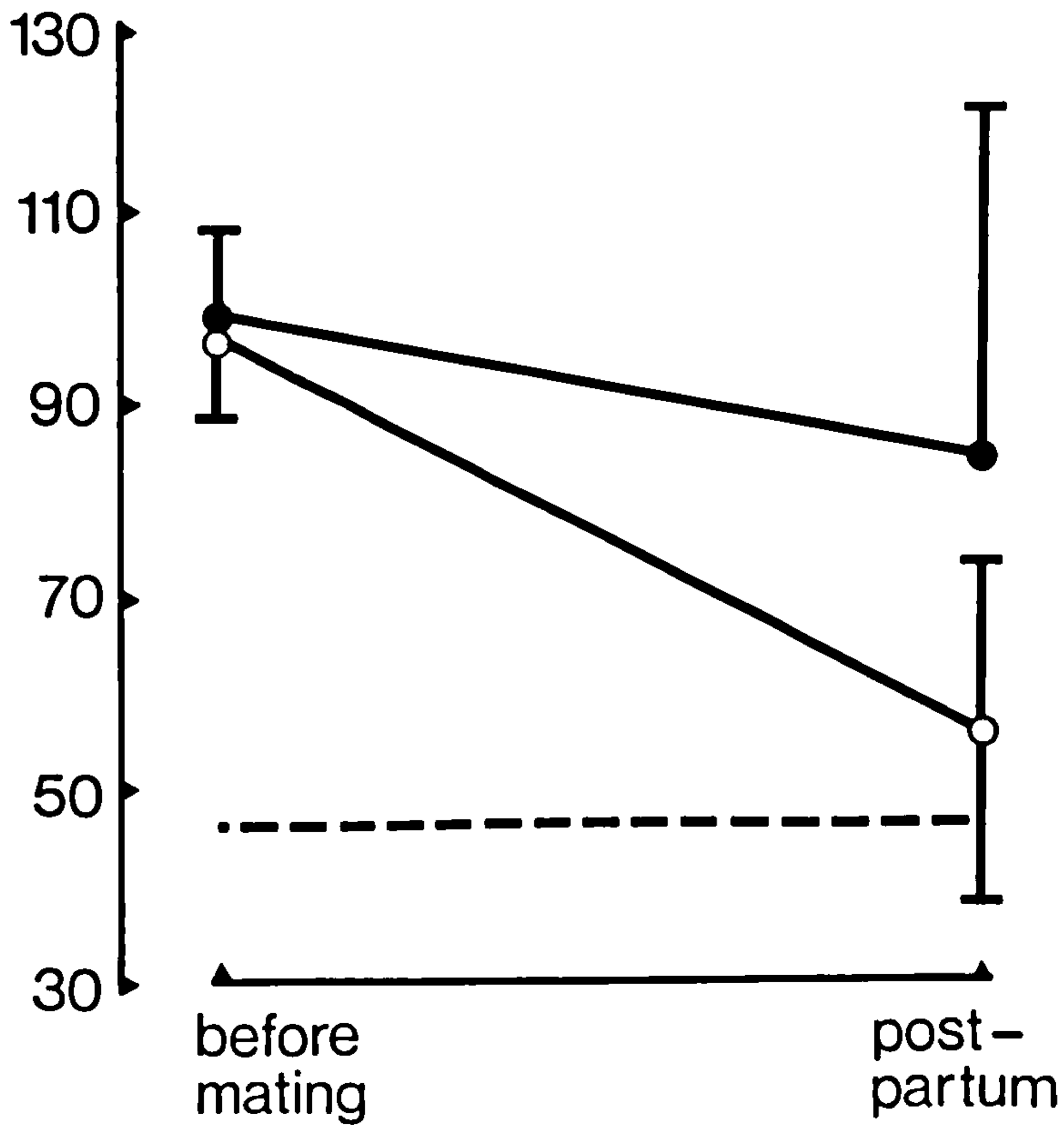


Fig. 25

Fig. 26 Comparison of serum T_4 concentrations in test and control animals after 8 weeks on LID. Broken line denotes the lower limit of the normal range. The means ± 1 S.D. are shown for the animals selected for mating after 10 weeks.

Serum T₄
μg/100ml

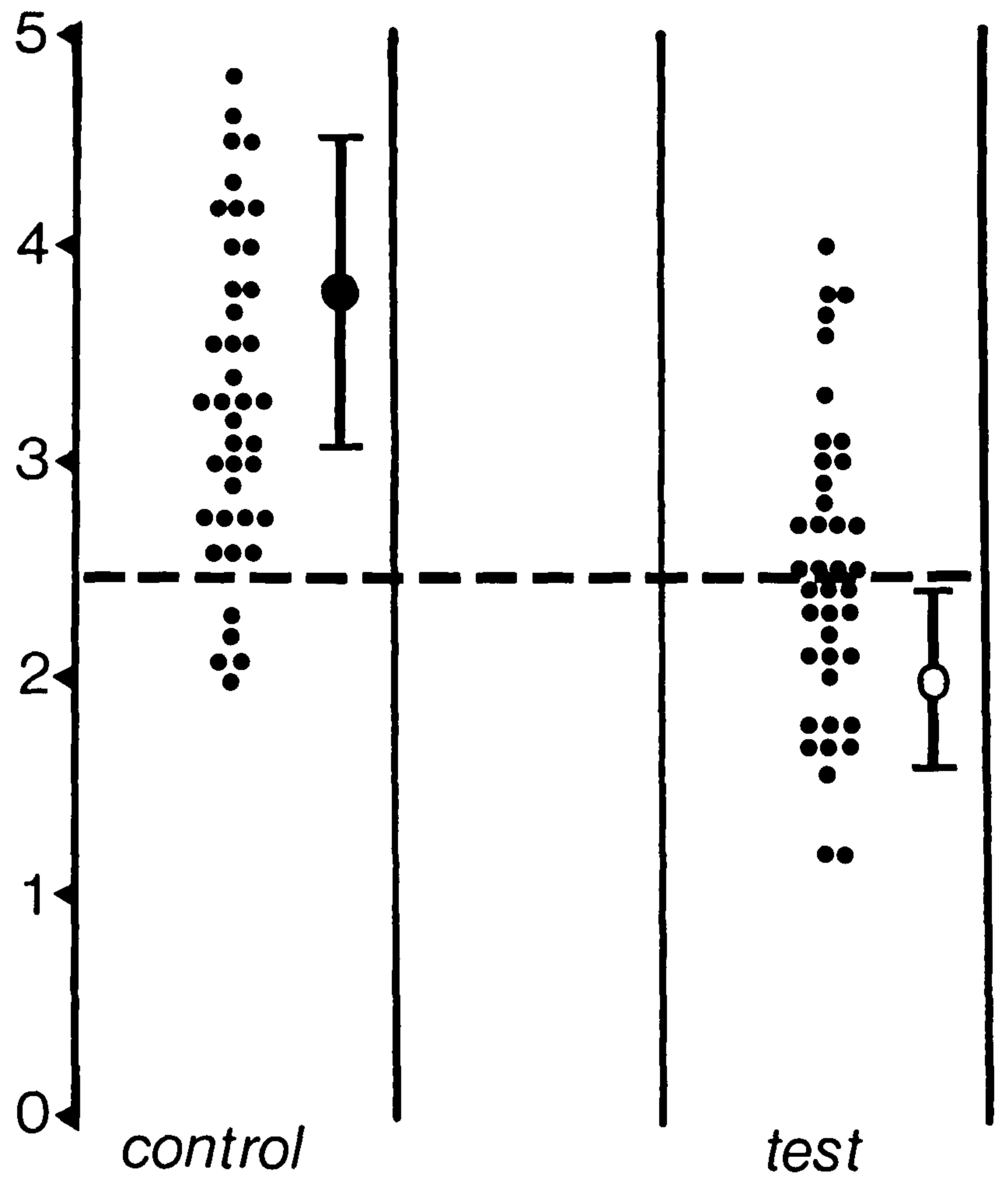


Fig. 26

Fig. 27 Changes in serum T_4 and T_3 concentrations of
animals mated after 10 weeks on LID.

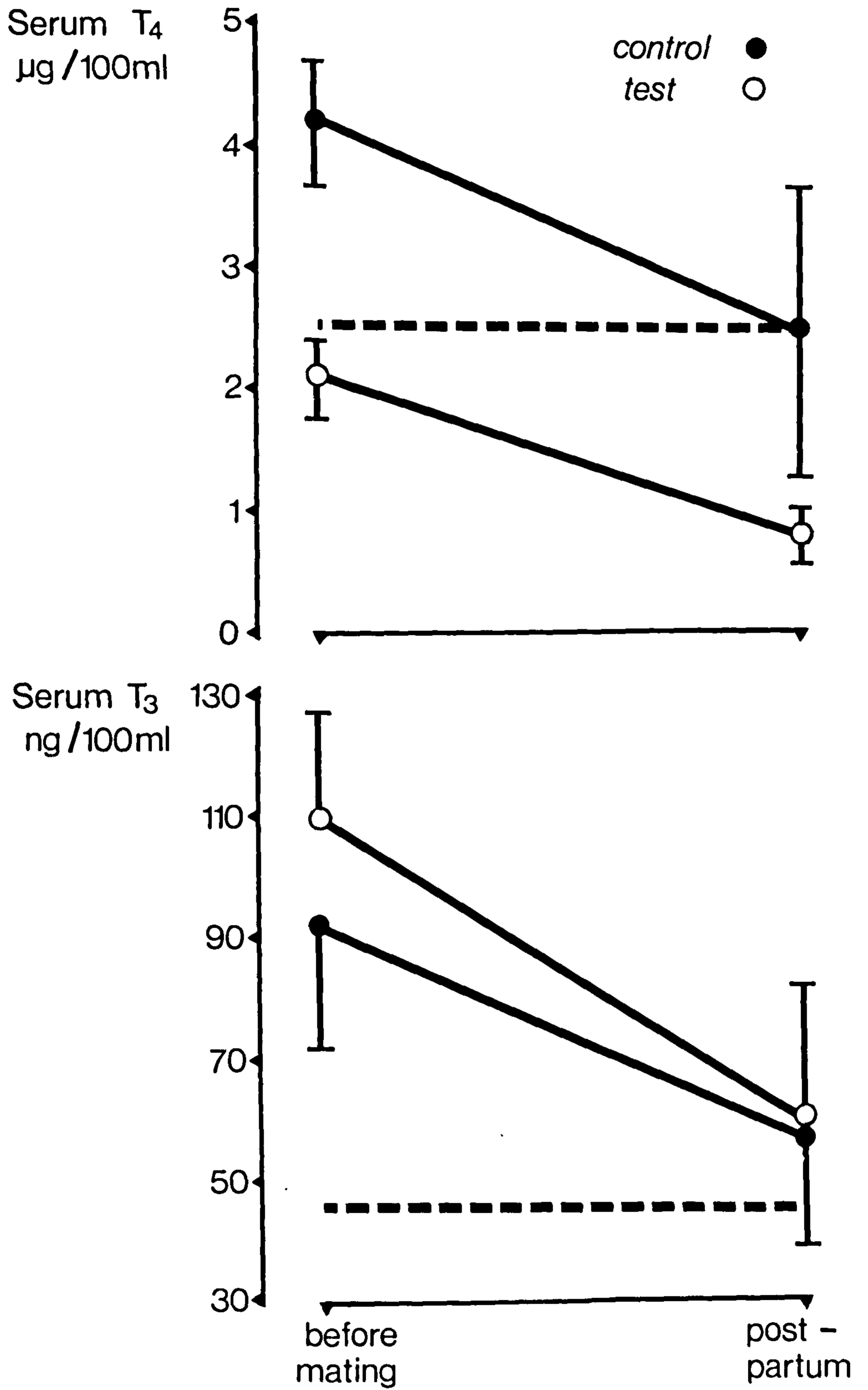


Fig. 27

Fig. 28 Changes in serum T_4 and T_3 concentrations of animals mated after 6 months on LID.

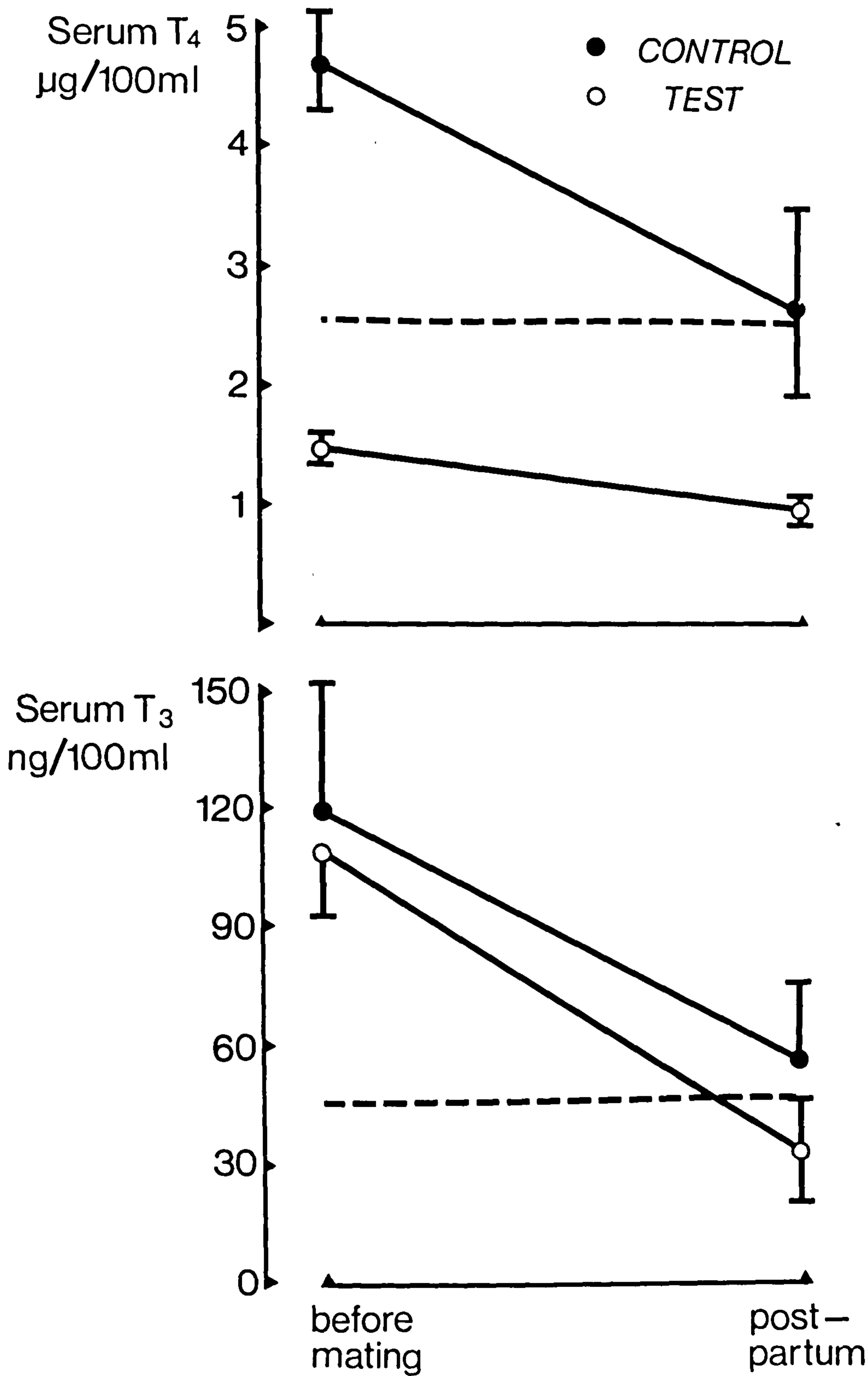


Fig. 28

Fig. 29 **Comparison of growth rate in test and control
pups during first 3 postnatal weeks.**

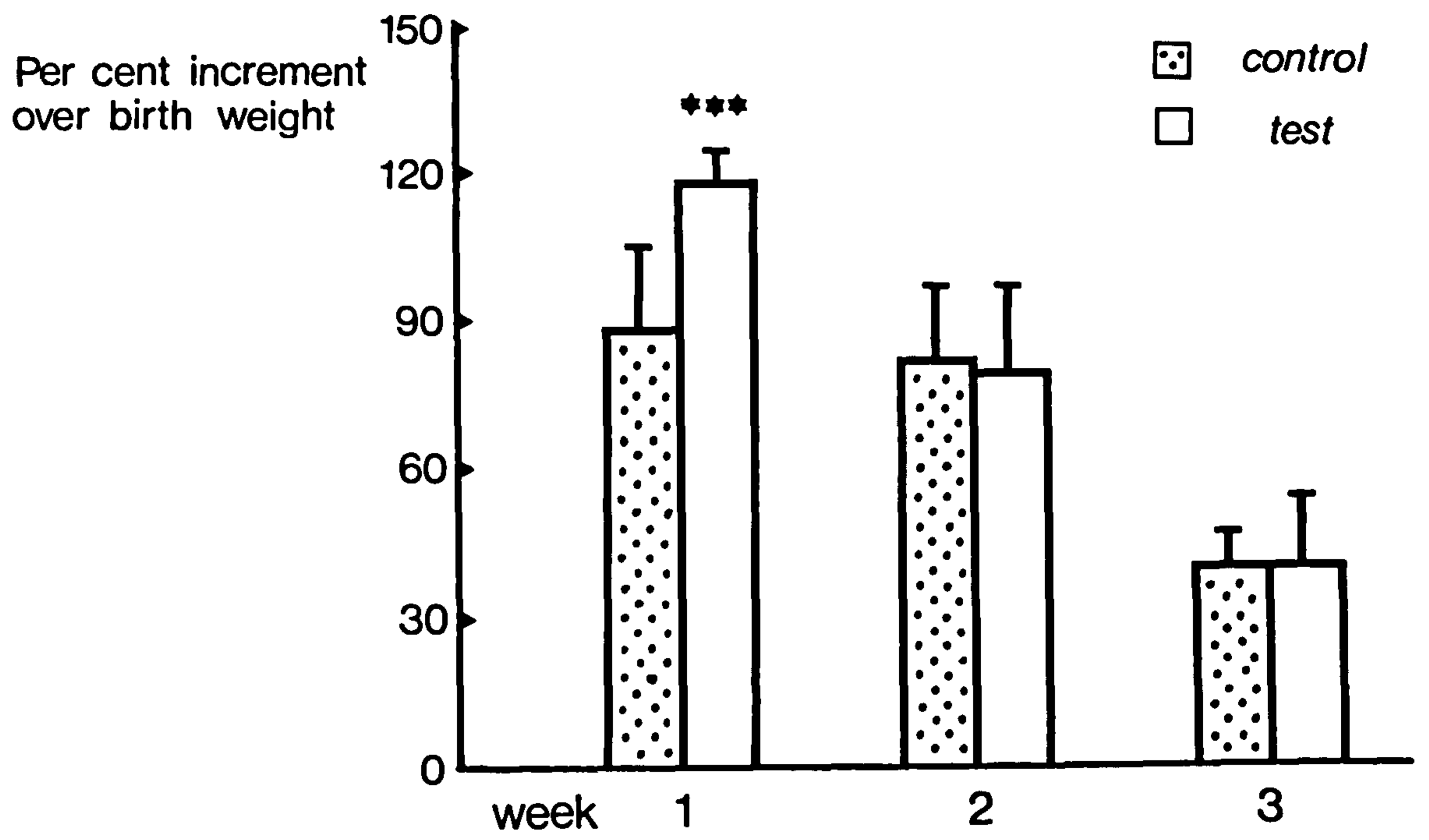


Fig. 29

Fig. 30 **Changes in serum T_4 and T_3 concentrations during pregnancy and lactation in Experiment 5.**

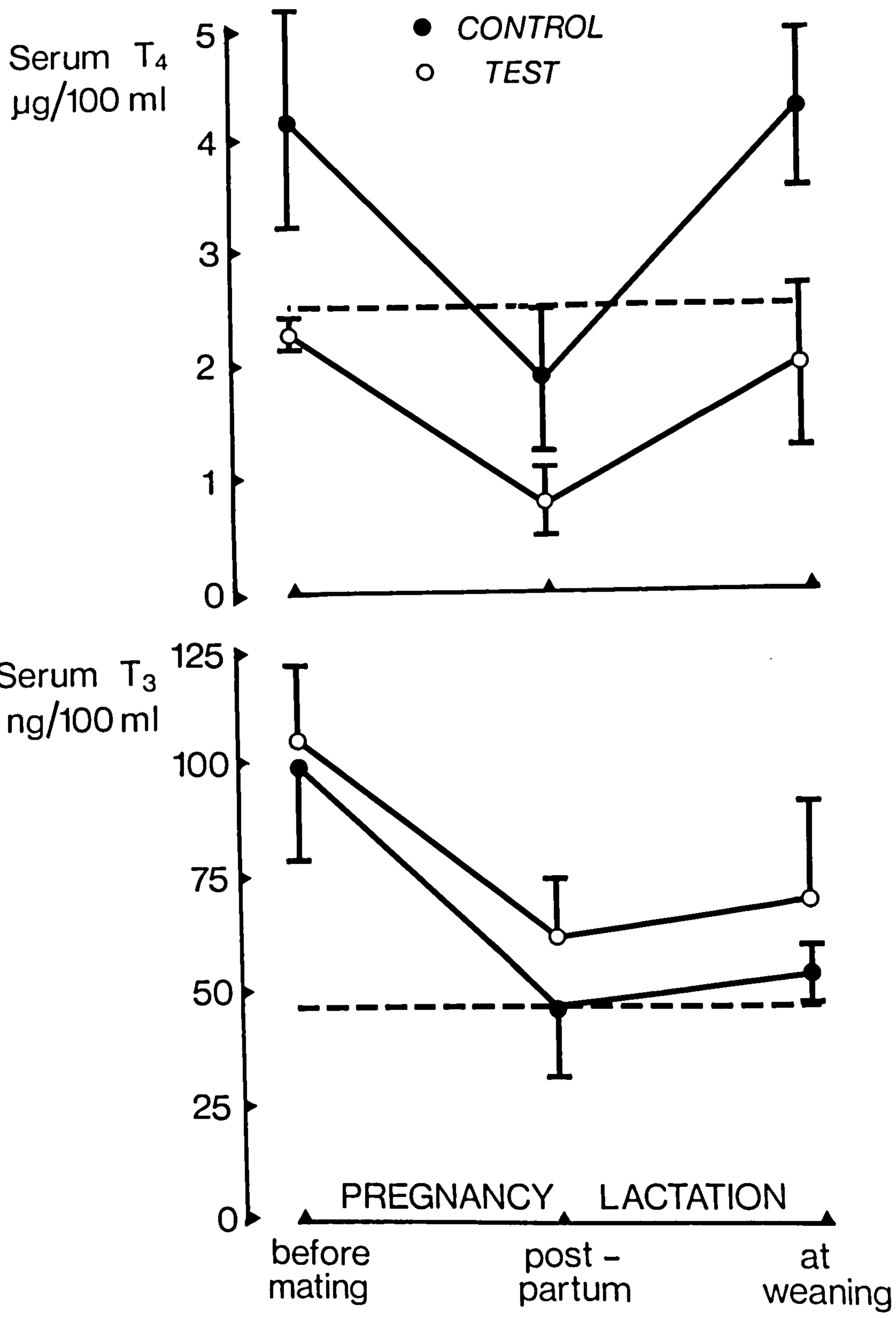


Fig. 30

Fig. 31 **Changes in thyroid hormone concentrations during pregnancy in Experiments 2, 3 and 4.**

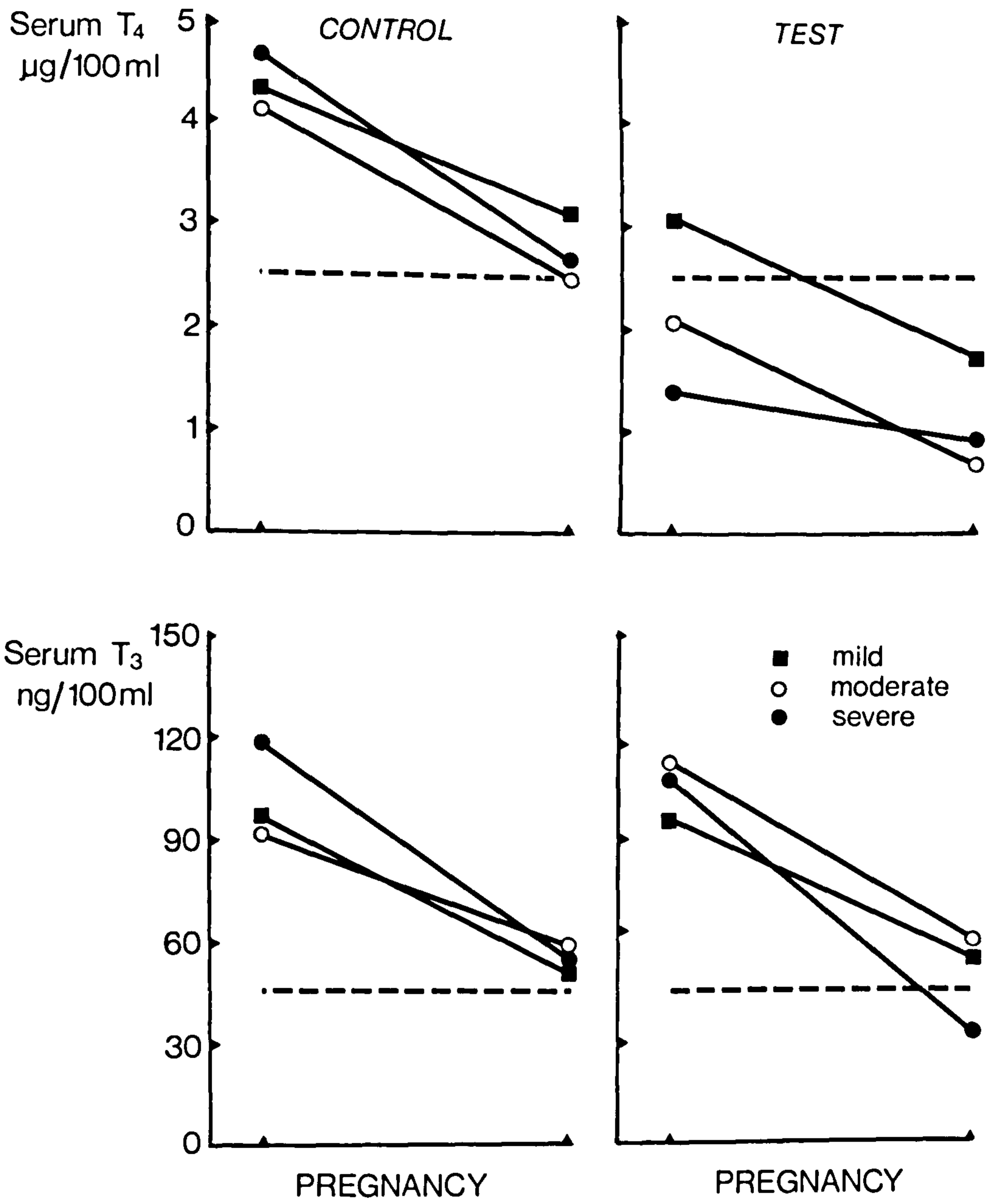


Fig. 31

Fig. 32 Changes in serum T_4 concentration due to pregnancy in Experiment 6.

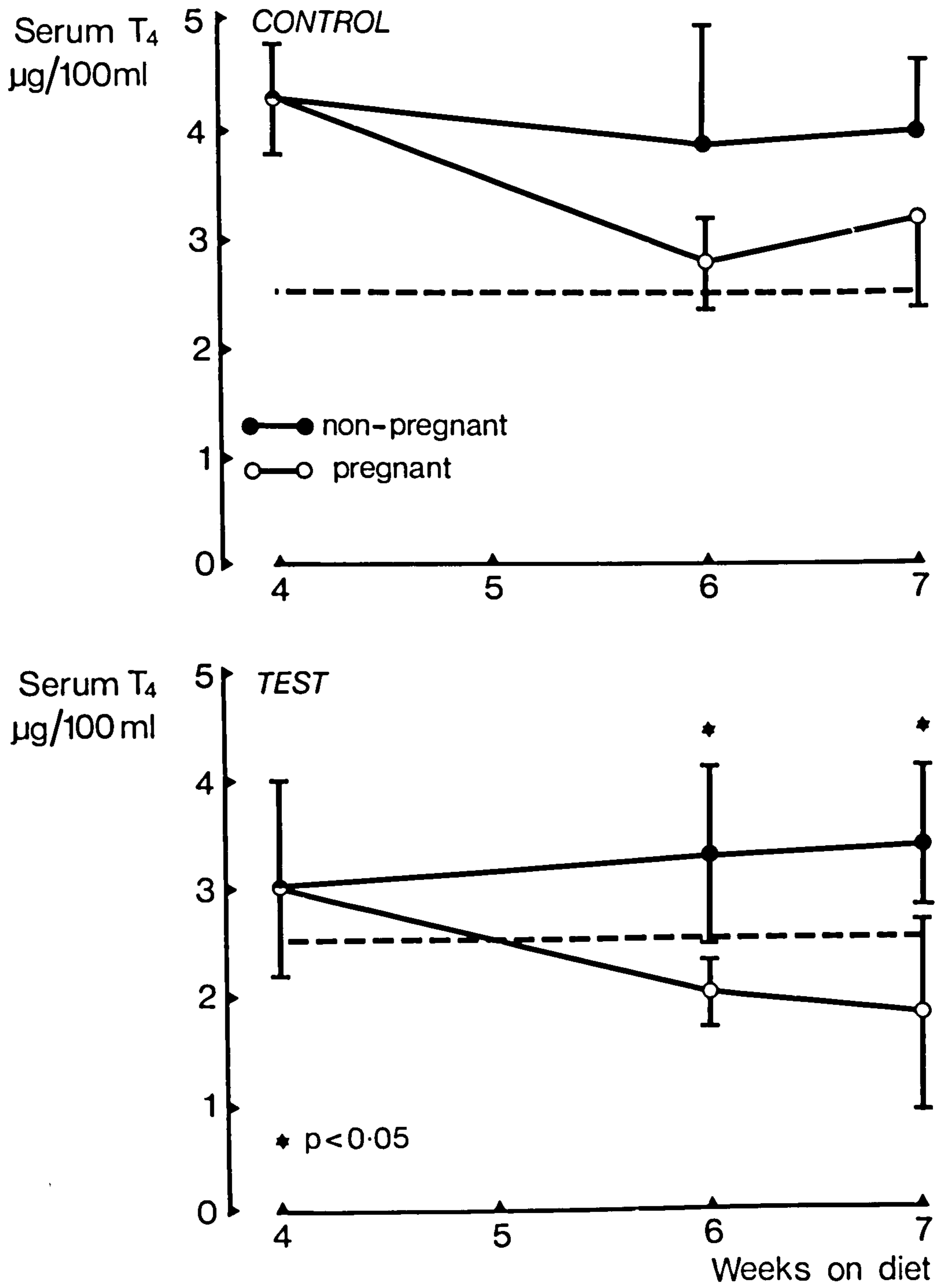


Fig. 32

Fig. 33 **Changes in serum T_3 concentration due to pregnancy in Experiment 6.**

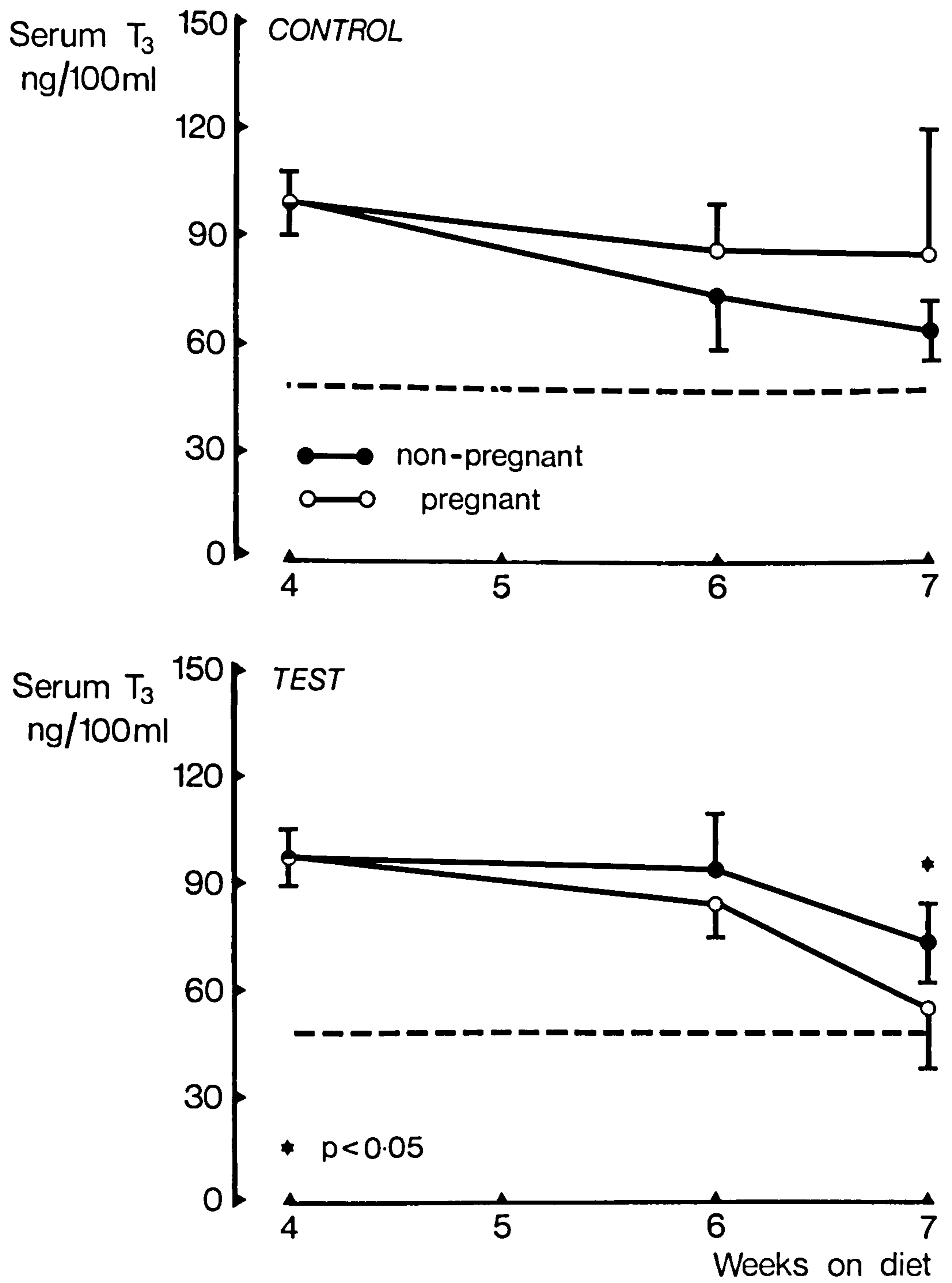


Fig. 33

Fig. 34 **Effect of mild iodine deficiency on serum T_4 and T_3 changes during pregnancy.**

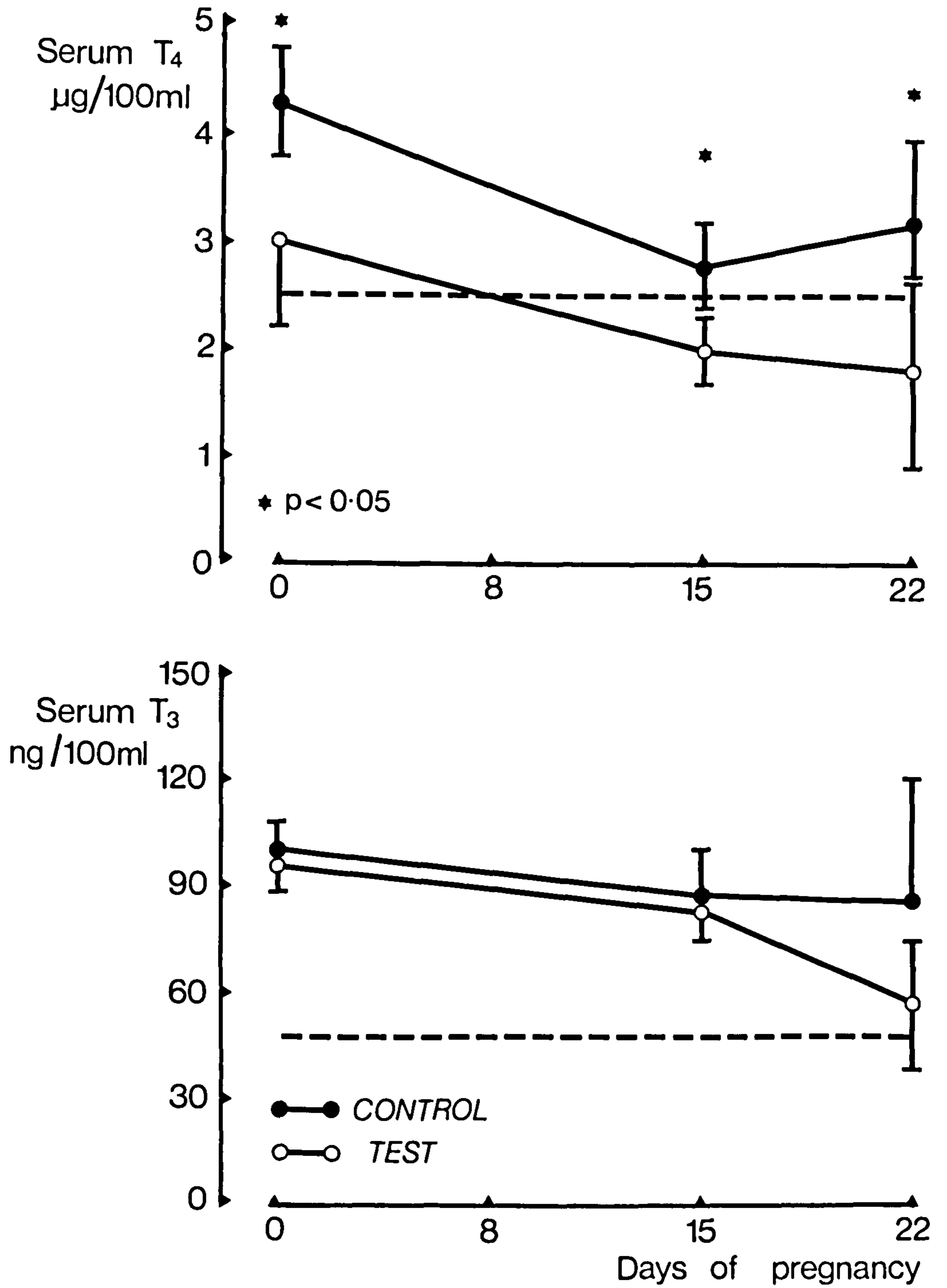


Fig. 34

Fig. 35 **Changes in serum T_4 and T_3 concentrations in mildly iodine deficient mothers during the last seven days of gestation.**

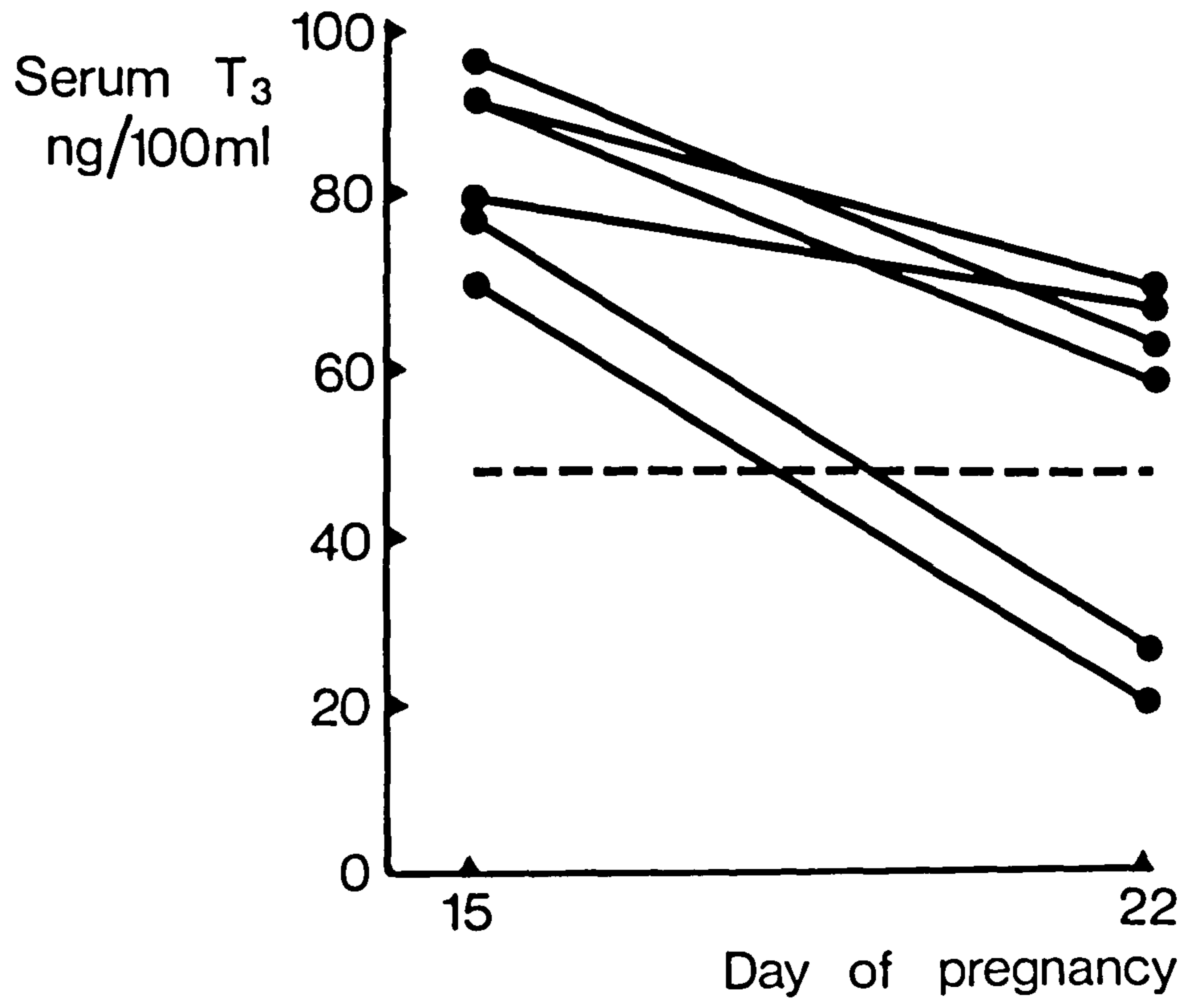
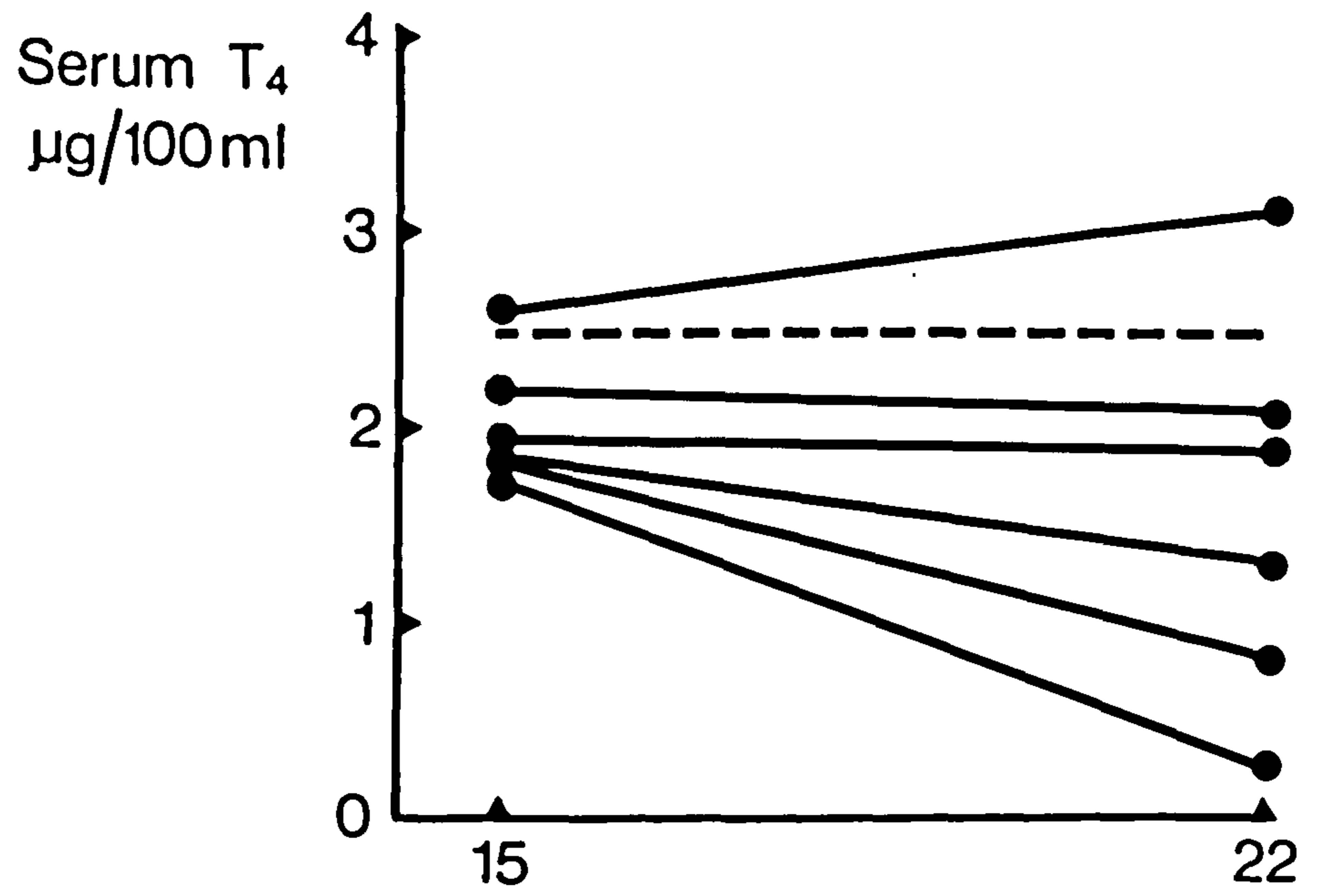


Fig. 35

Fig. 36 **Changes in serum T₄ concentration during pregnancy and lactation in Experiment 7.**

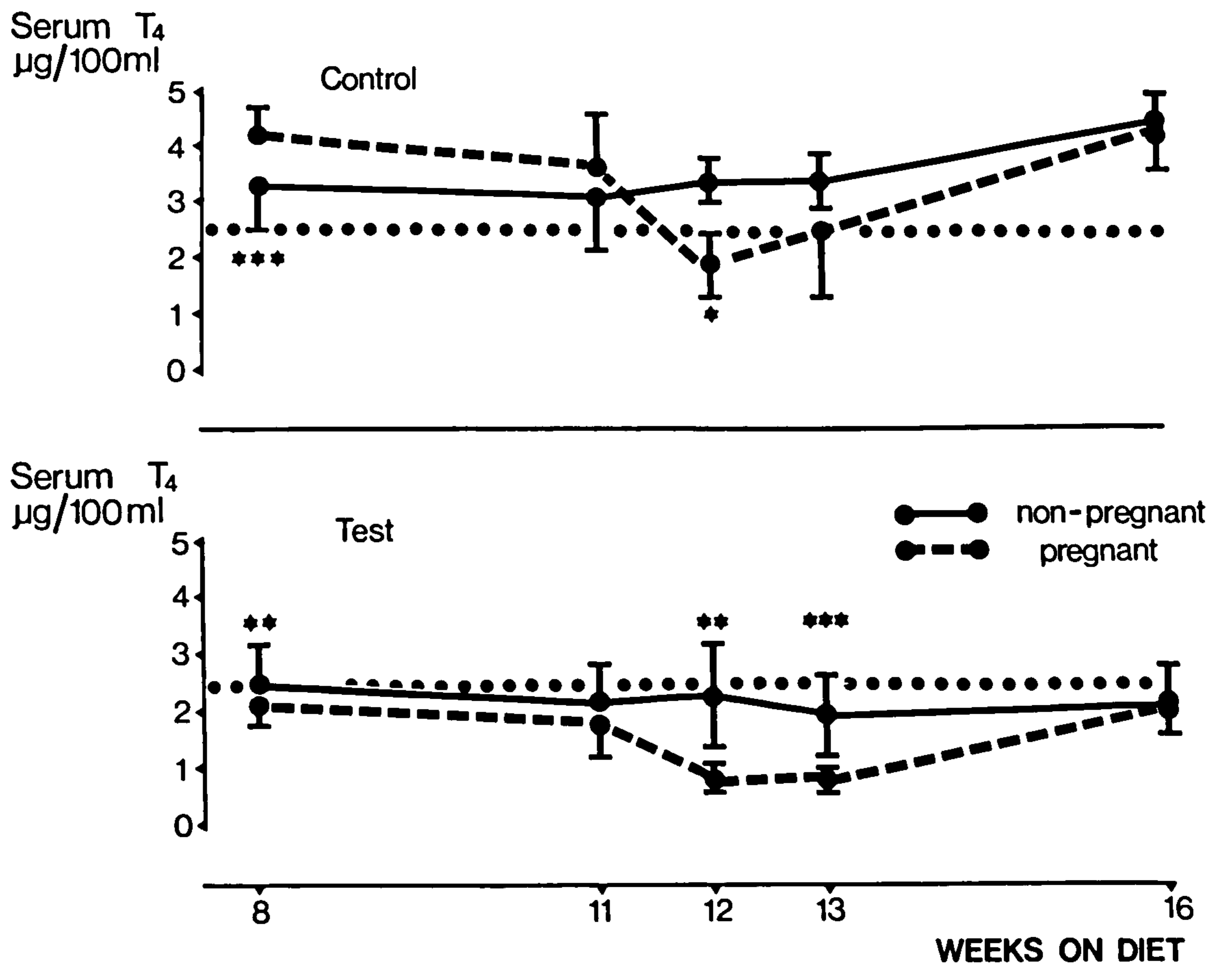


Fig. 36

Fig. 37 **Changes in serum T_3 concentration during pregnancy and lactation in Experiment 7.**

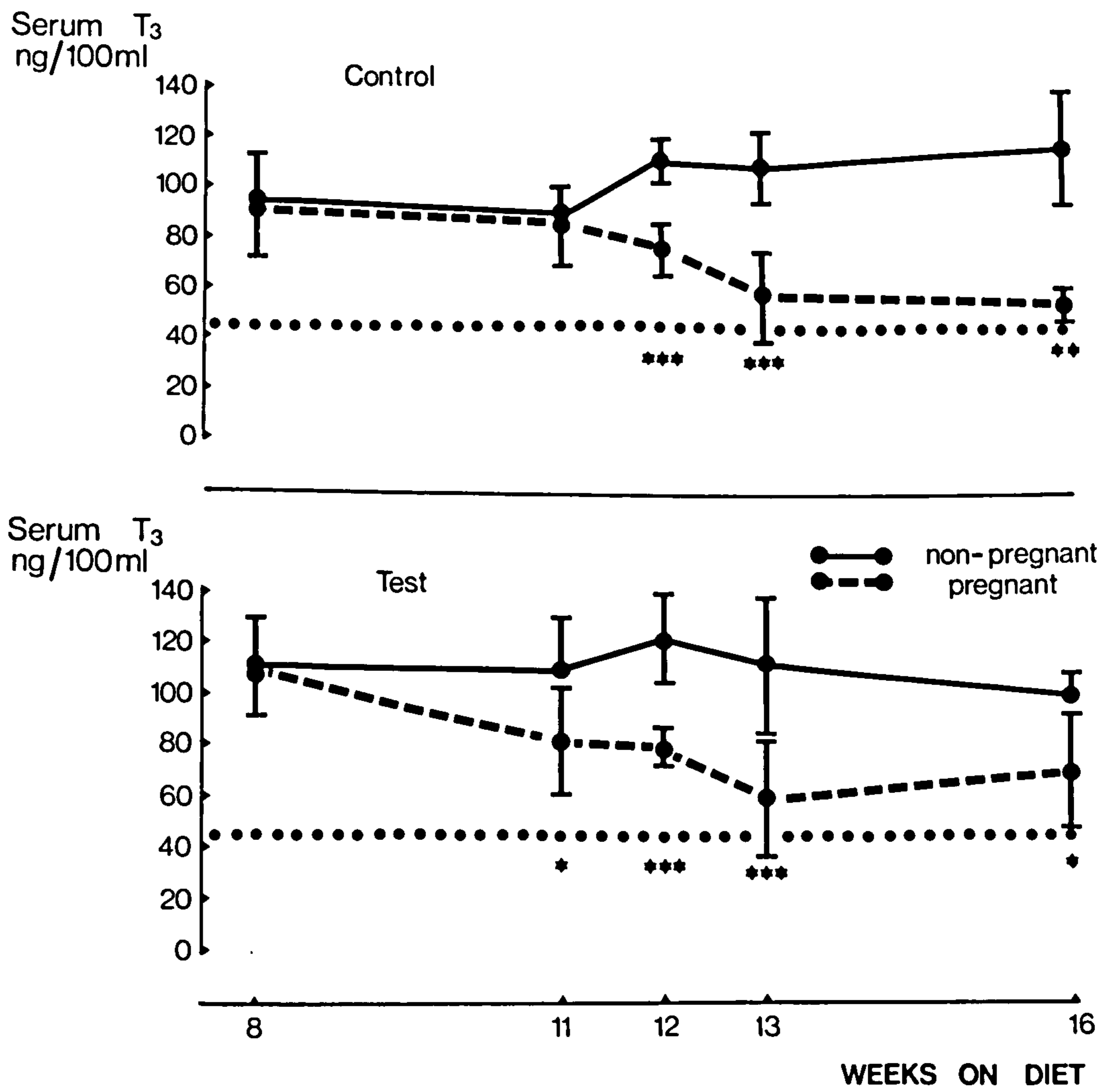


Fig. 37

Fig. 38 Effect of moderate iodine deficiency on serum T_4 ,
 T_3 and T_3/T_4 ratio during pregnancy and lactation.

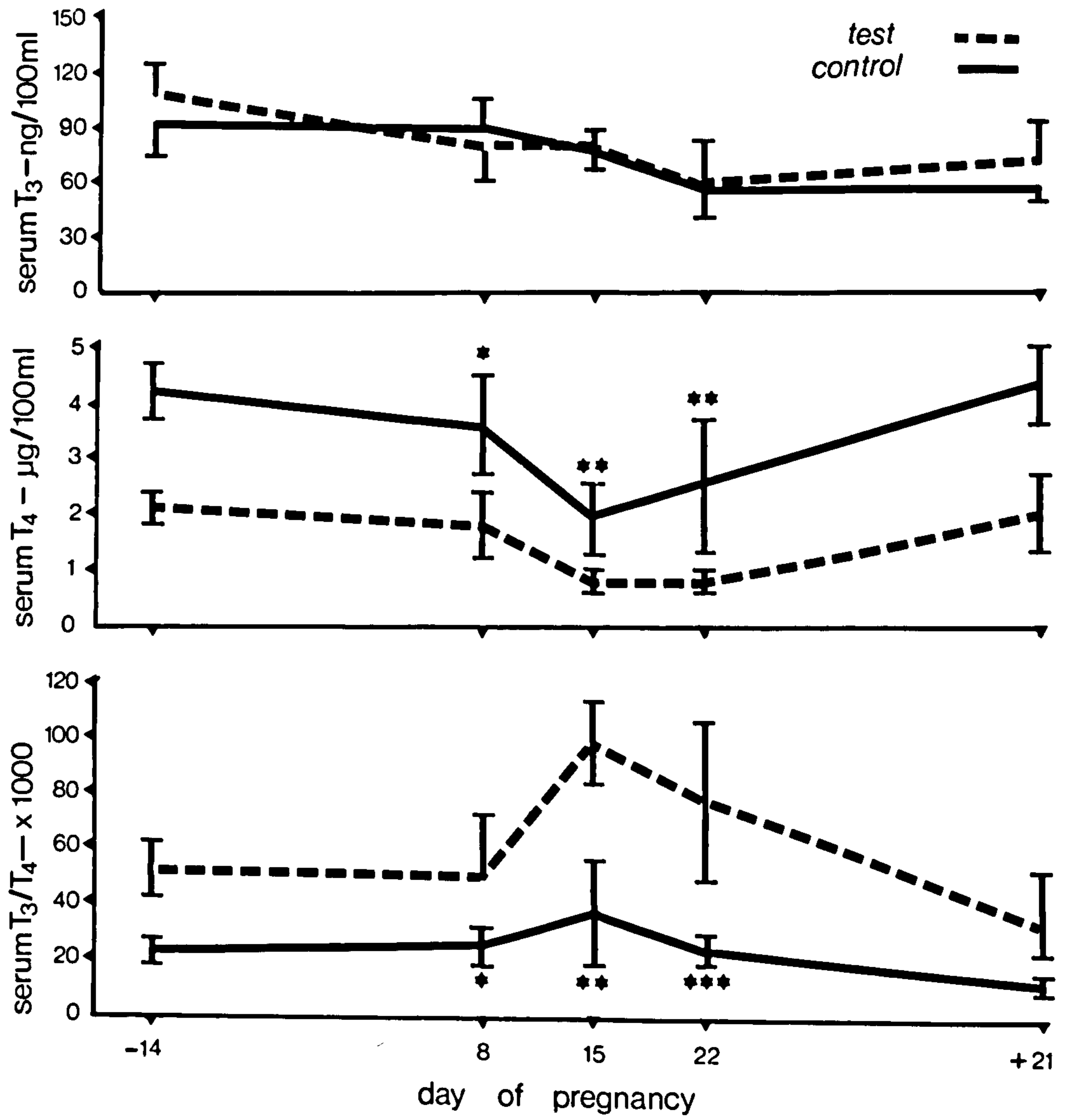


Fig. 38

Table 1

Effect of diet I for periods up to 4 weeks on relative
thyroid weight and radioactive iodine uptake

Weeks on diet	Number of animals	RTW (mg/100 gbw)	RAIU (% injected dose)
Baseline	24	6.80 \pm 1.11	4.88 \pm 2.16
1	20	8.46 \pm 1.59***	23.39 \pm 10.21***
2	15	7.78 \pm 1.61	27.72 \pm 13.99***
3	15	8.78 \pm 2.08**	42.58 \pm 13.51***
4	18	8.55 \pm 1.20***	37.98 \pm 14.44***

Statistical comparison with baseline

p value: * \langle 0.05; ** \langle 0.01; *** \langle 0.001

Table 2

Effect of diet I for periods up to 4 weeks on
serum thyroxine and triiodothyronine levels

Weeks on diet	Number of animals	Serum T ₄ ($\mu\text{g}/100\text{ ml}$)	Serum T ₃ ($\text{ng}/100\text{ ml}$)
Baseline	18	4.3 \pm 1.3	105 \pm 39
1	6	3.9 \pm 0.4	99 \pm 19
2	6	3.5 \pm 0.6	100 \pm 9
3	6	4.4 \pm 1.5	103 \pm 20
4	15	3.1 \pm 1.0**	99 \pm 16

p value: * <0.05 ; ** <0.01 ; *** <0.001

Otherwise non-significant

Table 3

Effect of diet I for periods up to 24 weeks on relative
thyroid weight and radioactive iodine uptake

Weeks on diet	Number of animals	RTW (mg/100 gbw)	RAIU (% injected dose)
Baseline	20	6.58 \pm 0.86	1.19 \pm 0.79
4	10	9.36 \pm 1.18***	36.32 \pm 21.97***
8	6	9.61 \pm 1.31***	52.96 \pm 12.38***
12	12	9.08 \pm 1.53***	42.63 \pm 9.33***
16	6	8.57 \pm 1.00***	64.81 \pm 8.24***
20	6	11.18 \pm 2.80***	68.01 \pm 10.20***
24	6	10.02 \pm 1.05***	66.11 \pm 6.50***

Table 4

Effect of diet I for periods up to 24 weeks on
serum thyroxine and triiodothyronine levels

Weeks on diet	Number of animals	Serum T ₄ ($\mu\text{g}/100\text{ ml}$)	Serum T ₃ ($\text{ng}/100\text{ ml}$)
Baseline	44	4.6 \pm 0.7	99 \pm 19
4	12	3.8 \pm 0.8**	95 \pm 26
8	7	3.5 \pm 0.7***	98 \pm 28
12	6	2.8 \pm 0.4***	92 \pm 11
16	6	2.8 \pm 0.4***	109 \pm 21
20	6	1.9 \pm 0.8***	113 \pm 22
24	6	2.0 \pm 0.3***	94 \pm 18

Table 5

Effect of diet II for periods up to 4 weeks on relative thyroid weight and radioactive iodine uptake

Weeks on diet	Number of animals	RTW (mg/100 gbw)	RAIU (% injected dose)
Baseline	20	6.80 \pm 1.11	4.88 \pm 2.16
1	12	7.61 \pm 1.29	24.77 \pm 5.22***
2	12	7.64 \pm 0.98*	34.81 \pm 10.26***
3	12	10.30 \pm 1.44***	43.50 \pm 8.77***
4	17	8.78 \pm 1.08***	43.72 \pm 13.61***

Table 6

Effect of diet II for periods up to 4 weeks on
serum thyroxine and triiodothyronine levels

Weeks on diet	Number of animals	Serum T ₄ ($\mu\text{g}/100\text{ ml}$)	Serum T ₃ ($\text{ng}/100\text{ ml}$)
Baseline	18	4.3 \pm 1.3	105 \pm 39
1	12	3.5 \pm 0.6*	116 \pm 39
2	12	3.9 \pm 1.0	105 \pm 48
3	12	3.9 \pm 1.4	110 \pm 24
4	12	3.2 \pm 0.7**	104 \pm 17

Table 7

Effect of diet II for periods up to 12 weeks on relative thyroid weight and radioactive iodine uptake

Weeks on diet	Number of animals	RTW (mg/100 gbw)	RAIU (% injected dose)
Baseline	24	6.80 \pm 1.11	4.88 \pm 2.16
2	12	7.64 \pm 0.98*	34.81 \pm 10.26***
4	17	8.78 \pm 1.08***	43.72 \pm 13.61***
6	6	7.64 \pm 0.99	42.96 \pm 12.69***
8	6	8.27 \pm 1.55*	52.07 \pm 20.94***
12	6	8.80 \pm 1.28**	50.15 \pm 13.60***

Table 8

Effect of diet II for periods up to 24 weeks on
serum thyroxine and triiodothyronine levels

Weeks on diet	Number of animals	Serum T ₄ ($\mu\text{g}/100\text{ ml}$)	Serum T ₃ (ng/100 ml)
Baseline	18	4.3 \pm 1.3	105 \pm 39
2	12	3.9 \pm 1.0	105 \pm 48
4	12	3.2 \pm 0.7*	104 \pm 17
6	6	2.7 \pm 0.3***	105 \pm 14
8	6	2.5 \pm 0.7***	101 \pm 15
10	6	2.1 \pm 0.1***	101 \pm 24
12	8	2.2 \pm 0.6***	123 \pm 18
16	9	2.1 \pm 0.7***	100 \pm 9
20	9	2.2 \pm 0.3***	123 \pm 20
24	32	2.1 \pm 0.6***	117 \pm 23

Table 9

Comparison of effects of diets I and II on
serum thyroxine levels

Weeks on diet	Serum thyroxine*		Significance of difference
	Diet I	Diet II	
4	3.8 \pm 0.8	3.2 \pm 0.7	n. s.
8	3.5 \pm 0.7	2.5 \pm 0.7	p<0.005
12	2.8 \pm 0.4	2.2 \pm 0.6	p<0.05
16	2.8 \pm 0.4	2.1 \pm 0.7	p<0.05
20	1.9 \pm 0.8	2.2 \pm 0.3	n. s.
24	2.0 \pm 0.3	2.1 \pm 0.6	n. s.

* expressed as $\mu\text{g}/100\text{ ml}$

n. s. = non-significant (p>0.05)

Table 10

Comparison of wet weight and chemical composition
of forebrain in neonates and 22 day old weanling pups

	Neonate	day 22 pup	Increment
Forebrain weight (mg)	151	1035	+ 585%
Total DNA (μ g)	620	844	+ 36%
Total protein (mg)	7.0	47.4	+ 577%
Protein:DNA ratio	11.4	56.3	+ 279%

Values given are means of at least 12 control animals

Table 11

Effect of LID introduced at mating on neonatal body
and forebrain weights (all pups)

Male and female pups (n = 33)	Control (19)	Test (14)	Significance of difference
Body weight (g)	5.61 \pm 0.69	5.91 \pm 0.54	n. s.
Forebrain weight (mg)	150.79 \pm 11.18	162.18 \pm 6.76	p<0.005
Relative forebrain weight (mg/g)	27.07 \pm 1.95	27.58 \pm 1.82	n. s.

Values given are means \pm one S.D.

Statistical comparison using Student's t test

Table 12

Effect of LID introduced at mating on neonatal body
and forebrain weights (male pups)

Male pups (n = 20)	Control (13)	Test (7)	Significance of difference
Body weight (g)	5.58 \pm 0.60	6.28 \pm 0.43	p<0.01
Forebrain weight (mg)	149.33 \pm 7.19	166.56 \pm 4.73	p<0.001
Relative forebrain weight (mg/g)	26.96 \pm 2.04	26.59 \pm 1.30	n. s.

Table 13

Effect of LID introduced at mating on DNA and protein content
of neonatal forebrain

Male and female pups (n = 33)	Control (19)	Test (14)	Significance of difference
Total DNA (μg)	622 \pm 71	626 \pm 50	n. s.
Total protein (mg)	7.27 \pm 1.39	7.22 \pm 1.49	n. s.
Protein:DNA ratio	12.01 \pm 3.12	11.74 \pm 3.10	n. s.

Table 14

Effect of LID introduced at mating on thyroid parameters
of mothers in immediate post-partum period

	Control (2)	Test (2)	% difference
Thyroid weight (mg)	11.42	20.96	+ 83
RTW (mg/100g)	4.34	8.05	+ 85
RAIU (% dose)	4.56	33.31	+ 630

Table 15

Effect of LID introduced at mating on
serum thyroid hormone levels of post-partum mothers

	Control (2)	Test (2)	% difference
Serum T ₄ (μ g/100 ml)	3.2	2.9	-10
Serum T ₃ (ng/100 ml)	120	121	0

Table 16

Effect of LID fed to mothers from 4 weeks before mating
and throughout gestation on litter size and
perinatal mortality

	Control	Test
Number of litters ⁺	4 (5)	5 (6)
Number of pups	35 (39)	57 (58)
Average litter size	9 (8)	11 (10)
Liveborn	30	57
Stillborn	5	0
Postmature	4	1

⁺Numbers in parentheses include litters delivered by uterotomy

Table 17

Effect of LID fed to mothers from 4 weeks before mating and throughout gestation on body and forebrain weights of newborn

	Control (4)	Test (5)	% change	Significance of difference
Body weight (g)	5.76 ± 0.39	5.43 ± 0.26	-6	n. s.
Forebrain weight (mg)	156.86 ± 9.32	151.11 ± 8.11	-4	n. s.
Relative forebrain weight (mg/g)	27.40 ± 1.53	27.92 ± 1.85	+1	n. s.

Numbers in parentheses represent numbers of litters rather than pups.
Statistical comparison using unpaired Student's t test.

Table 18

Effect of LID fed to mothers from 4 weeks before mating and throughout gestation
on neonatal forebrain chemical composition

	Control (4, 30)	Test (5, 57)	% change	Significance of difference
Total DNA (μ g)	627 \pm 21	610 \pm 21	-3	n. s.
Total Protein (mg)	7.1 \pm 0.6	7.0 \pm 0.4	-2	n. s.
Protein:DNA (mg/mg)	11.30 \pm 0.59	11.45 \pm 0.61	+1	n. s.

First number in parentheses: number of litters

Second number: number of brains analysed

Table 19

Effect of iodine supplementation on thyroid function of animals fed LID for

4 weeks prior to mating

	Control (5)	Test (5)	% change*	Significance of difference
Relative thyroid weight (mg/100 g)	6.23 ± 0.79	8.87 ± 0.73	+42	p<0.001
4 hr RAIU (% dose)	16.58 ± 4.86	38.91 ± 15.66	+135	p<0.02
Serum T ₄ (µg/100 ml)	4.3 ± 0.5	3.1 ± 0.9	-23	p<0.05
Serum T ₃ (ng/100 ml)	99 ± 9	97 ± 8	-2	n.s.

*% change refers to alterations in test animals

Numbers in parentheses refer to individual animals

Table 20

Results of thyroid function tests performed after 7 weeks of LID on animals mated

	<u>after 4 weeks</u>			
	Control (10)	Test (10)	% change	Significance of difference
Relative thyroid weight (mg/100 g)	5.88 ± 1.47	8.83 ± 1.61	+50	p<0.01
4 hr RAIU (% dose)	13.23 ± 4.67	43.41 ± 14.02	+221	p<0.001
Serum T ₄ (µg/100 ml)	3.5 ± 0.7	2.5 ± 1.1	-29	p<0.05
Serum T ₃ (ng/100 ml)	76 ± 28	64 ± 15	-16	n.s.

Table 21

Effect of LID on body weights of animals fed ad libitum for
10 weeks prior to mating

Weeks	0	5	10
Control (40)	168 ± 17*	240 ± 25	257 ± 18
Test (40)	159 ± 21	238 ± 21	255 ± 19
Difference	n. s.	n. s.	n. s.

* Body weights are expressed in grams
Statistical comparison by unpaired t test
n. s. = non-significant ($p > 0.05$)

Table 22

Effect of iodine deprivation for 8 weeks on total serum T₃ and T₄ levels and T₃/T₄ ratio

	Serum T ₃ (ng/100 ml)	Serum T ₄ (μg/100 ml)	$\frac{\text{Serum T}_3}{\text{Serum T}_4} \times 1000$
Control (40)	95 ± 18	3.3 ± 0.8	29.53 ± 7.61
Test (40)	111 ± 19	2.5 ± 0.7	47.99 ± 18.41
p value	<0.001	<0.001	<0.001

Numbers in parentheses refer to sera analysed

Value of p calculated by standard t test

Table 23

Comparison of total serum T₃ and T₄ levels and T₃/T₄ ratio in control and test animals selected for mating

	Serum T ₃ (ng/100 ml)	Serum T ₄ (μg/100 ml)	$\frac{\text{Serum T}_3}{\text{Serum T}_4} \times 1000$
Control (20)	99 ± 18	3.8 ± 0.7	27.01 ± 6.72
Test (20)	115 ± 19	2.0 ± 0.4	58.89 ± 20.29
p value	<0.001	<0.001	<0.001

Table 24

Effect of iodine supplementation on thyroid function of infertile animals

fed LID for 13 weeks

	Control (5)	Test (5)	% change	Significance of difference
Relative thyroid weight (mg/100 g)	7.26 ± 2.17	10.39 ± 1.85	+43	p<0.02
4 hr RAIU (% dose)	3.13 ± 1.54	57.59 ± 22.76	+1740	p<0.001
Serum T ₄ (µg/100 ml)	3.4 ± 0.5	1.9 ± 0.7	-44	p<0.01
Serum T ₃ (ng/100 ml)	108 ± 14	112 ± 27	+4	n.s.

Table 25

Effect of LID fed to mothers from 10 weeks before
mating and throughout gestation on litter size and
incidence of postmaturity

	Control	Test
Number of litters	4 (5)	4 (5)
Number of pups	19 (23)	23 (30)
Average litter size	5 (5)	6 (6)
Pups born postmature	4 (17%)*	7 (23%)

*expressed as percentage of total number of pups

Table 26

Effect of LID fed to mothers from 10 weeks before mating and throughout gestation
on body and forebrain weights of newborns

	Control (4, 19)	Test (4, 23)	% change	Significance of difference
Body weight (g)	6.60 ± 0.60	5.14 ± 1.31	-22	n. s.
Forebrain weight (mg)	176.57 ± 6.17	147.73 ± 23.88	-16	p<0.05
Relative forebrain weight (mg/g)	26.90 ± 2.25	29.53 ± 4.93	+10	n. s.

Table 27

Effect of moderate iodine deficiency on body and forebrain weights of pups born

on day 22 of gestation

	Control (3, 14)	Test (3, 15)	% change	Significance of difference
Body weight (g)	6.85 ± 0.40	5.73 ± 0.70	-17	n. s.
Forebrain weight (mg)	176.87 ± 7.52	155.38 ± 22.44	-13	n. s.
Relative forebrain weight (mg/g)	25.83 ± 0.84	27.68 ± 0.76	+4	n. s.

Table 28

Effect of LID fed to mothers from 10 weeks before mating and throughout gestation
on neonatal forebrain chemical composition

	Control (4, 19)	Test (4, 23)	% change	Significance of difference
Total DNA (μ g)	581 \pm 11	562 \pm 20	-3	n. s.
Total protein (mg)	7.5 \pm 0.4	6.0 \pm 1.1	-20	p<0.05
Protein:DNA (mg/mg)	12.87 \pm 0.61	10.61 \pm 1.91	-18	n. s.

Table 29

Effect of moderate iodine deficiency on forebrain content of DNA
and protein in pups born on day 22 of gestation

	Control (3, 14)	Test (3, 15)	% change	Significance of difference
Total DNA (μ g)	582 \pm 14	569 \pm 18	-3	n. s.
Total protein (mg)	7.5 \pm 0.5	6.5 \pm 0.3	-14	p<0.05

Table 30

Effect of moderate iodine deficiency on cell size in forebrains of pups
born on day 22 of gestation

	Control (3, 14)	Test (3, 15)	% change	Significance of difference
Protein:DNA (mg/mg)	12.87 \pm 0.75	11.49 \pm 0.90	-11	n. s.
Weight:DNA (mg/ μ g)	304 \pm 6	274 \pm 38	-10	p<0.001

Table 31

Effect of LID fed for 24 weeks on serum T₄ and T₃ concentrations

	Control (30)	Test (30)	Significance of difference
Serum T ₄ (μg/100 ml)	4.1 ± 1.0	2.1 ± 0.6	p<0.001
Serum T ₃ (ng/100 ml)	114 ± 21	117 ± 23	n. s.

Table 32

Comparison of levels of serum T₄ and T₃ in animals selected for mating

	Control (10)	Test (10)	Significance of difference
Serum T ₄ (μg/100 ml)	4.7 ± 0.4	1.5 ± 0.1	p<0.001
Serum T ₃ (ng/100 ml)	119 ± 32	109 ± 16	n. s.

Table 33

Effect of LID fed for six months prior to mating and
throughout gestation on litter size and perinatal
mortality

	Control	Test
No. of litters	3	3
Average litter size	7	10
No. of pups	21	29
Born alive	9 (63%)	0 (0%)
Stillborn	11 (52%)	10 (35%)
Died in utero	1 (5%)	19 (65%)

Table 34

Effect of severe prenatal iodine deficiency on body and forebrain growth and development

	Control (3, 12)	Test (3, 29)	% change	Significance of difference
Body weight (g)	6.55 ± 0.46	6.30 ± 0.90	-4	n. s.
Forebrain weight (mg)	176.68 ± 8.23	196.60 ± 12.81	+11	n. s.
Relative forebrain weight (mg/g)	26.94 ± 0.97	31.40 ± 3.23	+16	n. s.

Table 35

Effect of severe prenatal iodine deficiency on neonatal forebrain chemical composition

	Control (3, 21)	Test (3, 29)	% change	Significance of difference
Total DNA (μ g)	548 \pm 29	580 \pm 85	+6	n. s.
Total Protein (mg)	9.21 \pm 0.23	8.02 \pm 0.39	-13	p<0.01
Protein:DNA (mg/mg)	16.85 \pm 1.25	13.83 \pm 2.19	-18	n. s.

Table 36

Effect of severe iodine deficiency on thyroid function of animals
sacrificed in the immediate post-partum period

	Control (3)	Test (3)	Significance of difference
Serum T ₄ ($\mu\text{g}/100 \text{ ml}$)	2.7 \pm 0.8	1.00 \pm 0.02	p<0.025
Serum T ₃ (ng/100 ml)	57 \pm 18	33 \pm 13	n. s.
RTW (mg/100 g)	6.69 \pm 0.44	11.41 \pm 1.26	p<0.005
RAIU (% dose)	2.70 \pm 0.60	41.63 \pm 17.14	p<0.02

Table 37

Effect of combined prenatal and postnatal iodine deficiency on body weights of pups
during the period of maternal lactation

	Control	Test	% change	Significance of difference
Day 0	6.12 ± 0.44 (24)	5.73 ± 0.38 (24)	-6	p<0.001
Day 7	11.18 ± 1.66 (19)	12.54 ± 1.04 (20)	+12	p<0.005
Day 14	20.37 ± 3.93 (19)	22.32 ± 0.99 (20)	+9	p<0.05
Day 21	28.34 ± 5.91 (19)	31.09 ± 2.91 (20)	+9	n. s.

The numbers of pups are in parentheses

Values given are means ± 1 S. D.

Table 38

Effect of combined prenatal and postnatal iodine deficiency on body and forebrain weights of
22 day old weanlings

Male and female pups (n = 39)	Control (19)	Test (20)	% change	Significance of difference
Body weight (g)	30.63 ± 6.87	32.46 ± 2.94	+5	n. s.
Forebrain weight (mg)	1031.64 ± 67.45	1009.84 ± 47.94	-3	n. s.
Relative forebrain weight (mg/g)	35.02 ± 6.44	31.27 ± 2.09	-11	p<0.025

Table 39

Effect of male or female sex on body and forebrain weights of test pups at 22 postnatal days

	Male (14)	Female (6)	% change	Significance of difference
Body weight (g)	33.36 ± 2.76	30.36 ± 2.35	-9	p<0.025
Forebrain weight (mg)	1030.20 ± 38.87	963.34 ± 30.61	-7	p<0.001
Relative forebrain weight (mg/g)	31.04 ± 2.28	31.79 ± 15.76	+2	n.s.

Table 40

Effect of combined prenatal and postnatal iodine deficiency on body and forebrain weights of

22 day old male weanlings

	Control (12)	Test (14)	% change	Significance of difference
Body weight (g)	30.34 ± 6.81	33.36 ± 2.76	+9	n. s.
Forebrain weight (mg)	1043.63 ± 56.32	1030.20 ± 38.87	-2	n. s.
Relative forebrain weight (mg/g)	35.76 ± 6.73	31.04 ± 2.28	-14	p<0.05

Table 41

Effect of combined prenatal and postnatal iodine deficiency on forebrain content of

DNA and protein in 22 day old weanlings

	Control (19)	Test (20)	% change	Significance of difference
Total DNA (μ g)	853 \pm 91	836 \pm 76	-2	n. s.
Total Protein (mg)	47.01 \pm 10.01	47.36 \pm 10.62	+1	n. s.
Protein:DNA (mg/mg)	55.27 \pm 10.06	57.32 \pm 15.08	+4	n. s.

Table 42

Effect of combined prenatal and postnatal iodine deficiency on forebrain content of
DNA and protein in 22 day old male weanlings

	Control (12)	Test (14)	% change	Significance of difference
Total DNA (μ g)	866 \pm 78	822 \pm 63	-5	n. s.
Total Protein (mg)	48.24 \pm 11.29	47.43 \pm 11.82	-2	n. s.
Protein:DNA (mg/mg)	55.68 \pm 11.38	58.21 \pm 16.37	+2	n. s.

Table 43

Effect of male or female sex on forebrain content of DNA and protein in test pups
at 22 postnatal days

	Male (14)	Female (6)	% change	Significance of difference
Total DNA (μ g)	822 \pm 63	867 \pm 99	+5	n. s.
Total Protein (mg)	47.43 \pm 11.82	47.19 \pm 8.11	-1	n. s.
Protein:DNA (mg/mg)	58.21 \pm 16.37	55.25 \pm 12.68	-6	n. s.

Table 44

Effect of LID for 16 weeks and lactation during 3 weeks on in vitro
thyroid function at 21 postnatal days

	Control (3)	Test (3)	Significance of difference
Thyroid weight (mg)	14.81 \pm 1.91	22.53 \pm 7.78	p<0.005
Relative thyroid weight (mg/100 g)	5.18 \pm 0.28	7.72 \pm 1.85	n. s.
RAIU (% dose)	1.57 \pm 1.03	24.86 \pm 9.35	p<0.001

Table 45

Effect of moderate iodine deficiency on serum thyroxine concentration before
and after successful pregnancy

	Control (3)	Test (3)	% change	Significance of difference
Before mating	4.2 ± 1.0*	2.3 ± 0.05	-45	p<0.025
Post-partum	1.9 ± 0.6	0.8 ± 0.3	-57	p<0.05
At weaning	4.3 ± 0.7	2.0 ± 0.7	-53	p<0.05

* Values expressed as µg/100 ml

Table 46

Effect of moderate iodine deficiency on serum triiodothyronine concentration
before and after successful pregnancy

	Control (3)	Test (3)	% change	Significance of difference
Before mating	101 ± 23*	106 ± 15	+5	n. s.
Post-partum	46 ± 13	62 ± 12	+35	n. s.
At weaning	54 ± 6	70 ± 22	+30	n. s.

* Values expressed as ng/100 ml

Table 47

Effects of pregnancy and lactation on serum thyroid hormone concentrations of

control mothers

	Serum T ₃ (ng/100 ml)	Serum T ₄ (µg/100 ml)	$\frac{\text{Serum T}_3}{\text{Serum T}_4} \times 1000$
Non-pregnant (5)	117 ± 24	4.6 ± 0.6	25.96 ± 6.78
21 days post-partum (3)	54 ± 6	4.3 ± 0.7	12.82 ± 3.15
p value	<0.005	n.s.	<0.01

Table 48

Effects of pregnancy and lactation on serum thyroid hormone concentrations of test mothers

	Serum T ₃ (ng/100 ml)	Serum T ₄ (μg/100 ml)	$\frac{\text{Serum T}_3}{\text{Serum T}_4} \times 1000$
Non-pregnant (9)	100 ± 9	2.1 ± 0.7	53.44 ± 18.80
21 days post-partum (3)	70 ± 22	2.0 ± 0.7	36.74 ± 15.26
p value	<0.05	n.s.	n.s.

Table 49

Effect of combined prenatal and postnatal iodine deficiency on thyroid function in the 22 day old weanling

	Control	Test	Significance
Thyroid weight (mg)	5.49 ± 2.65 (7)	7.41 ± 1.08 (9)	n. s.
Relative thyroid weight (mg/100 g)	15.88 ± 5.94 (7)	22.12 ± 1.99 (9)	p<0.02
4 hr RAIU (% dose)	1.39 ± 0.78 (10)	35.79 ± 8.95 (9)	p<0.01
Serum T ₄ (µg/100 ml)	5.0 ± 1.5 (9)	5.0 ± 0.9 (11)	n. s.
Serum T ₃ (ng/100 ml)	75 ± 35 (9)	121 ± 32 (11)	p<0.01

Table 50

Comparison of thyroid function in control weanlings and their mothers
at time of weaning

	Mothers (3)	Weanlings (9)	Significance of difference
Serum T ₄ ($\mu\text{g}/100 \text{ ml}$)	4.3 \pm 0.7	5.0 \pm 1.5	n. s.
Serum T ₃ (ng/100 ml)	54 \pm 6	75 \pm 35	n. s.
4 hr RAIU (% dose)	1.57 \pm 1.03	1.39 \pm 0.78	n. s.

Table 51

Comparison of thyroid function in test weanlings and their mothers

at time of weaning

	Mothers (3)	Weanlings (11)	Significance of difference
Serum T ₄ (μg/100 ml)	2.0 ± 0.4	5.0 ± 0.9	p<0.001
Serum T ₃ (ng/100 ml)	70 ± 22	121 ± 32	p<0.01
4 hr RAIU (% dose)	24.86 ± 1.85	35.79 ± 8.95	n.s.

Table 52

Effects of pregnancy and mild iodine deficiency on maternal serum T₄ concentrations (µg/100 ml)

	Control (10)	Test (10)	Significance of difference
Non-pregnant	3.9 ± 1.1 (5)	3.3 ± 0.8 (4)	n. s.
15-day pregnant	2.8 ± 0.4 (5)	2.0 ± 0.3 (6)	p<0.005
p value	n. s.	<0.02	
Non-pregnant	4.0 ± 0.7 (5)	3.4 ± 0.7 (4)	p<0.025
<6 hr post-partum	3.2 ± 0.8 (5)	1.8 ± 0.9 (6)	p<0.025
p value	n. s.	<0.02	

Numbers in parentheses refer to sera analysed

Table 53

Effects of pregnancy and mild iodine deficiency on maternal serum T₃ concentrations (ng/100 ml)

	Control (10)	Test (10)	Significance of difference
Non-pregnant	75 ± 18 (5)	93 ± 16 (4)	n. s.
15-day pregnant	87 ± 13 (5)	84 ± 10 (6)	n. s.
p value	n. s.	n. s.	
Non-pregnant	65 ± 8 (5)	73 ± 11 (4)	n. s.
<6 hr post-partum	85 ± 36 (5)	56 ± 18 (6)	n. s.
p value	n. s.	<0.025	

Table 54

Effect of pregnancy on serum T₃, T₄ and T₃/T₄ ratio in control animals fed LID with iodine supplements for 10 weeks prior to mating

	Serum T ₃ (ng/100 ml)	Serum T ₄ (μg/100 ml)	$\frac{\text{Serum T}_3}{\text{Serum T}_4} \times 1000$
Non-pregnant	90 ± 11 (4)	3.1 ± 1.0 (4)	30.18 ± 7.92 (4)
8-day pregnant	87 ± 18 (3)	3.6 ± 0.9 (3)	25.01 ± 6.77 (3)
p value	n.s.	n.s.	n.s.
Non-pregnant	111 ± 9 (4)	3.4 ± 0.4 (4)	34.78 ± 6.36 (9)
15-day pregnant	76 ± 10 (5)	1.9 ± 0.6 (5)	37.20 ± 18.79 (5)
p value	<0.001	<0.005	n.s.
Non-pregnant	108 ± 14 (5)	3.4 ± 0.5 (5)	31.27 ± 3.97 (5)
<6 hr post-partum	57 ± 18 (8)	2.5 ± 1.2 (8)	24.17 ± 4.76 (8)
p value	<0.001	n.s.	<0.02

Table 55

Effect of pregnancy on serum T_3 , T_4 and T_3/T_4 ratio in test animals fed

LID for 10 weeks prior to mating

	Serum T_3 (ng/100 ml)	Serum T_4 (μ g/100 ml)	$\frac{\text{Serum } T_3}{\text{Serum } T_4} \times 1000$
Non-pregnant	110 \pm 21 (5)	2.2 \pm 0.6 (5)	42.66 \pm 12.74 (5)
8-day pregnant	81 \pm 21 (6)	1.8 \pm 0.6 (6)	49.64 \pm 22.30 (6)
p value	<0.05	n.s.	n.s.
Non-pregnant	123 \pm 18 (8)	2.3 \pm 0.9 (8)	43.54 \pm 15.19 (8)
15-day pregnant	79 \pm 8 (3)	0.8 \pm 0.2 (3)	97.92 \pm 14.89 (3)
p value	<0.001	<0.005	<0.001
Non-pregnant	112 \pm 27 (8)	1.9 \pm 0.7 (8)	48.75 \pm 16.83 (8)
<6 hr post-partum	59 \pm 23 (9)	0.8 \pm 0.2 (9)	77.31 \pm 28.18 (9)
p value	<0.001	<0.001	<0.025

Table 56

Effect of moderately severe iodine deficiency on changes in maternal serum T₄ during pregnancy and lactation

	Control	Test	Significance
Before mating	4.2 ± 0.5 (8)	2.1 ± 0.3 (9)	p<0.001
day 8	3.6 ± 0.9 (3)	1.8 ± 0.6 (6)	p<0.02
day 15	1.9 ± 0.6 (5)	0.8 ± 0.2 (3)	p<0.01
day 22	2.5 ± 1.2 (8)	0.8 ± 0.2 (9)	p<0.005
At weaning	4.3 ± 0.7 (3)	2.0 ± 0.7 (3)	p<0.02

Sera analysed represented by numbers in parentheses

Statistical comparison by unpaired t test

Table 57

Effect of moderately severe iodine deficiency on changes in
maternal serum T₃ during pregnancy and lactation

	Control	Test	Significance
Before mating	92 ± 20 (8)	110 ± 18 (9)	n. s.
day 8	87 ± 18 (3)	81 ± 21 (6)	n. s.
day 15	76 ± 10 (5)	79 ± 8 (3)	n. s.
day 22	57 ± 18 (8)	59 ± 23 (9)	n. s.
At weaning	54 ± 6 (3)	70 ± 22 (3)	n. s.

Table 58

Effect of moderately severe iodine deficiency on changes in maternal serum
 T_3/T_4 ratio (x 1000) during pregnancy and lactation

	Control	Test	Significance
Before mating	22.07 ± 4.60 (8)	52.43 ± 10.26 (9)	p<0.001
day 8	25.01 ± 6.77 (3)	44.64 ± 22.30 (6)	p<0.05
day 15	37.20 ± 18.79 (6)	97.92 ± 14.89 (3)	p<0.005
day 22	24.17 ± 4.76 (8)	77.31 ± 28.18 (9)	p<0.001
At weaning	12.82 ± 3.15 (3)	36.74 ± 11.26 (3)	p<0.05

Table 59

Changes in maternal serum T₄ concentrations during the second week of pregnancy

	day 8 of gestation	day 15 of gestation	% change	Significance of difference
Control	3.6 ± 0.9 (3)	1.9 ± 0.6 (5)	-47	p<0.001
Test	1.8 ± 0.6 (6)	0.8 ± 0.2 (3)	-56	p<0.01

Values expressed as µg/100 ml

Table 60

Changes in maternal serum T₃ concentrations during the last seven days of pregnancy

	day 15 of gestation	<6 hr post-partum	% change	Significance of difference
Control	76 ± 10 (5)	57 ± 18 (8)	-25	p<0.05
Test	79 ± 8 (3)	59 ± 23 (9)	-25	p<0.05

Values expressed as ng/100 ml

Table 61

Changes in maternal serum T₄ concentrations during the period of lactation

	day 22 of gestation	postnatal day 21	% change	Significance of difference
Control	2.5 ± 1.2 (8)	4.3 ± 0.7 (3)	+72	p<0.02
Test	0.8 ± 0.2 (9)	2.0 ± 0.4 (3)	+150	p<0.001

Values expressed as µg/100 ml