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Direct and correlated responses to selection for plasma thyroxine levels in mice

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SUMMARY

Selection was carried out in mice for concentration of thyroxine hormone (T4) in plasma of males at 11 weeks of age over seven generations. Selection was practised for high level in two replicate lines and for low level in two replicate lines, and there was an unselected control. There was a response in both directions, and the divergence of 12·4 ng/ml observed in generation seven was equivalent to about 20% of the base population mean or nearly one phenotypic standard deviation. The realised heritability was 9%.

Plasma thyroxine level had a repeatability of 0·54 when two measurements were made 24 h apart. The responses made at 11 weeks in males were also evident in both males and females at 5 weeks. Plasma tri-iodo thyronine (T3) concentrations showed a correlated response almost as large, relative to the mean level, as that in T4.

Positive correlated responses were observed in total weights of the litter at 12 days, and in individual weights at 3, 6 and 9 weeks, the responses in the early weights being greater relative to their mean. The results suggest that the correlated weight changes were due to genetic responses in maternal characteristics, probably milk production, rather than individual growth.

INTRODUCTION

Knowledge of genetic covariation between the activity of endocrine systems and other traits is relevant to understanding how such systems relate to fitness and to assessing whether measures of the activity of such systems are useful selection criteria in animal improvement programmes. The effects of single genes and the differences among inbred lines have been analysed (Shire, 1976), but such variation

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may be atypical of that in outbred populations, and covariation between endocrine activity and other traits among inbreds may have arisen by chance. Endocrine characteristics have also been studied as correlated responses to selection for other traits, but again covariation may have arisen by chance. Direct studies of genetic variation by selection for the concentration of hormones in the plasma of mammals have not been reported.

Current interest in the possible use of measures of the activity of the thyroid system as a predictor of milk yield in cattle prompted this study of variation in the concentration of thyroxine in the peripheral plasma of mice and its association with mammary activity. Measures of thyroxine may aid genetic selection for milk production because thyroid hormones have a biological role in lactation (Cowie, 1961) and it is expressed in both sexes. The possible potential is demonstrated by the association between one such measure, thyroxine degradation rate, and milk production in cattle (Joakimsen, Steenberg, Lien & Theodorsen, 1971). Genetic variation in the thyroid system has been demonstrated in mice by comparisons among existing populations (e.g. Barny & Kennaway, 1937; Chai, Amin & Reineke, 1957; Synenki, Eisen, Matrone & Robison, 1972; Stewart, Batty & Harkiss, 1978) and by direct selection for iodine uptake by the gland itself (Chai, 1970).

In this paper we report an experiment in mice in which selection was practised for plasma thyroxine level and maternal and growth performance were recorded to detect any correlated changes.

MATERIALS AND METHODS

Base population, selected lines and traits recorded

Mice from the fourteenth generation of a randomly bred line (*QCX*) which had been founded by intercrossing two of the six unselected lines described by Falconer (1973) were used to form the base population, generation O, of this experiment. The *QCX* line was maintained initially by 10 and subsequently by 25 pair matings per generation. One hundred and twenty two single pair matings were made and 112 litters resulted. Plasma thyroxine (T4) levels in the sires of each of these litters were estimated and litters ranked accordingly. The top ranking 20 litters were split into two approximately equal groups, to form generation 1 of the two replicate lines, H1 and H2, selected for high thyroxine concentration. Similarly the bottom ranking 20 litters were split to form two lines, L1 and L2, selected for low thyroxine concentrations. The middle ranking 24 litters became the unselected control line (*C*) which was reproduced in the next generation by taking either a male or female from alternate litters.

In subsequent generations each line was maintained as a closed population. In each selected line 32 pair matings were made through generation 5, and 20 pairs in generation 6. On the basis of the sire's thyroxine level the highest (in *H*) or lowest (in *L*) ranking litters were taken, sufficient to provide the 32 males and females required for the next generation but without other restriction. The number of

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litters selected ranged from 6 to 11, typically 9 (or 5 or 6 to provide 20 pairs in generation 6). The control line was maintained with 12 pair matings up to generation 4, increasing to 18 and 20 matings in generations 5 and 6; as far as possible each mating was represented equally in the following generation. Within all lines mating was at random, except that full sib matings were avoided.

Males and females were paired at about 9 weeks of age. Two weeks later males were removed and blood samples taken by cardiac puncture after exposing the heart under terminal ether anaesthesia. The age range of males was then 74–80 days. In generations 0–4 a single blood sample was taken for assay and used as the selection criterion. In generations 5 and 6 an additional sample was taken from the tail of each mouse 24 h before cardiac bleeding; hormone levels for selection were then based on the mean of the two estimates obtained.

Litters were standardized to eight young within 24 h of birth to minimize the effects of the size of the litter in the growth of young. Litters with less than eight were augmented with mice from other litters born on the same day, but the fostered young were not considered for selection. The weights of the whole litter were recorded 5 and 12 days after birth, and the mother's weight on the day of parturition and 12 days post partum. Mice were weaned at three weeks of age. They were weighed individually at 3, 6 and 9 weeks of age except in generation 7.

The concentrations in plasma of tri-iodo-thyronine (T3), the other major thyroid hormone, were estimated from the blood samples of males each generation except the second. In generations 5 and 6, plasma thyroxine was also measured in a sample of mice of each sex from each line at 5 weeks of age. The estimates were based on two blood samples taken 24 h apart from each mouse. In generation 7 body weights and gonadal fat were weighed in a sample of mice of each sex in each line at 12 weeks of age.

Assay methods

Plasma hormone content was determined using a modification of the solid phase radioimmunoassay technique of Seth, Rutherford & Mackenzie (1975) for thyroxine and of Seth, Toft & Irvine (1976) for tri-iodo-thyronine. The sensitivity (or minimum detectable concentration defined as zero standard plus two standard deviations) for T4 was in the range 3·3–17·3 ng/ml with a mean of 7·8 ng/ml and for T3 in the range 0·252–0·562 ng/ml with a mean of 0·473 ng/ml. The ovine anti-T4 and -T3 sera were kindly donated by Dr J. S. Seth and Dr J. S. Ratcliffe respectively. The former was used at a final dilution of 1:6000, the latter 1:12,000. The anti-T4 serum cross reacts with T3 2·4% relative to T4 and the anti-T3 serum with T4 0·3% relative to T3, weight for weight.

In each assay a sample from a pool of bovine plasma was included in duplicate at concentrations of 25, 50 and 100% to give six potency estimates in each assay from which within and between assay variance components were estimated. For T4 there were 7 assays, the mean potency/sample was 33·8 ng/ml and the coefficients of variation were 4·5% within assays and 6·8% between assays. The

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corresponding values for T3 were 5 assays with a mean potency per sample of 0·963 ng/ml and coefficients of variation of 7·2 and 11·1 % within and between assays respectively.

RESULTS

Direct response to selection of plasma thyroxine level

Mean levels of plasma thyroxine each generation are shown in Figure 1. The fluctuations among generations were similar in each line, indicating environmental effects common to all lines. Results are therefore expressed either as deviations

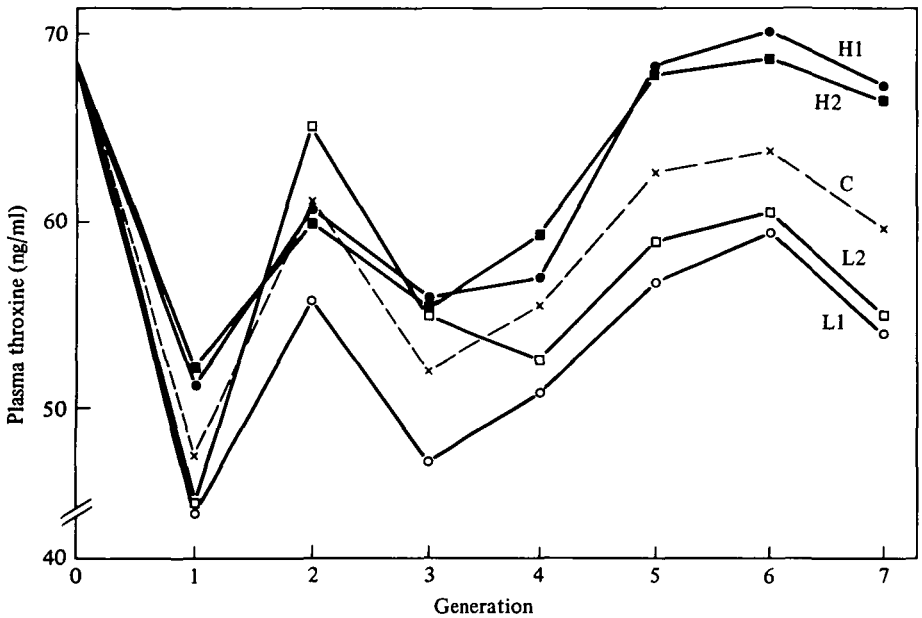

Fig. 1. Mean plasma thyroxine level of each line in each generation: H1, H2 replicates selected for high thyroxine level, L1, L2 replicates selected for low thyroxine level and C, unselected control.

of selected lines from controls or as divergence between high and low lines. The two high replicates behaved similarly to each other, as did the two low replicates, so most results are summarised as the mean of high ($\bar{H}$) or low ($\bar{L}$) lines.

Deviations of thyroxine level of $\bar{H}$ and $\bar{L}$ from control are plotted against cumulative selection differential, also averaged over replicates, in Figure 2. The response was initially erratic, but subsequently a clear divergence was maintained between H and L, reaching 12·4 ng/ml at generation 7. Realized heritabilities were computed from the regression coefficients of response, both as a deviation from control ($\bar{H}$–C or $\bar{L}$–C) and as divergence ($\bar{H}$–$\bar{L}$), on cumulative selection differential. In each case the regression was forced through the origin, realized heritabilities were taken as twice the regression coefficients because selection was on only one

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sex, approximate standard errors were computed following Hill (1977) to account for genetic drift and the values and their standard errors given in Table 1. The responses and heritabilities for both directions of selection taken separately were close to twice their calculated standard errors. The latter are larger than would appear from Figure 2 because the mean of the two selected lines is computed as the deviation from a single control. The heritability computed from the $\bar{H}$–$\bar{L}$

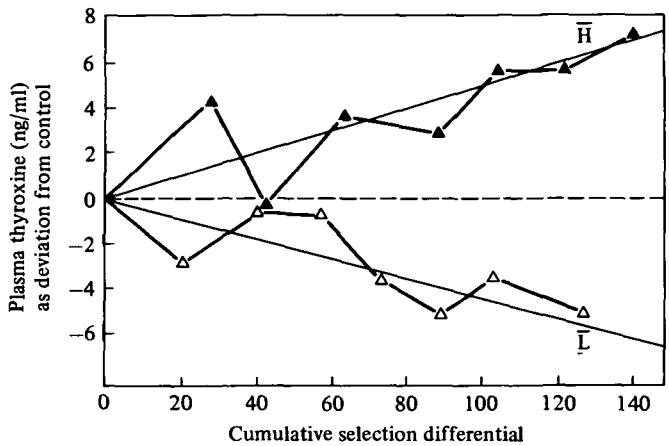

Fig. 2. Response in plasma thyroxine level of mean of high ($\bar{H}$) and low ($\bar{L}$) lines, expressed as a deviation from the unselected control line, plotted against cumulative selection differential.

Table 1. *The realized heritability of the concentration of thyroxine estimated from the mean deviation from the control (C) of lines selected for high ($\bar{H}$) and low ($\bar{L}$) concentration and from the difference between the high and low lines*

	Realized heritability (%) ± S.E.
High–Control ($\bar{H}$–$\bar{C}$)	9·6 ± 5·0
Low–Control ($\bar{L}$–$\bar{C}$)	8·6 ± 5·5
High–Low ($\bar{H}$–$\bar{L}$)	9·2 ± 2·4

divergence was highly significantly different from zero. There was no evidence of asymmetry of response to the opposite directions of selection.

Correlated responses to selection

Thyroxine at 5 weeks in males and females. The concentration of thyroxine in samples collected at five weeks of age in mice of generations 5 and 6 are given in Table 2. There was a response in the concentration of the thyroxine at this age which was equal in both sexes; in that selection was not based on the concentration at this age, this may be regarded as a correlated response. Analysis indicated that there was no interaction between line and sex.

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Table 2. *Plasma thyroxine levels (ng/ml) at 5 weeks of age in males and females of generations 5 and 6 (the concentration for each mouse was the mean of the concentrations measured in 2 samples collected at an interval of 24 h)*

Generation		H1	H2	C	L1	L2	$\bar{H}-\bar{L}$	Bleed 1	Bleed 2	♂	♀	♂–♀
5	*n*	38	36	32	36	28	—	170	170	84	86	—
	Level	68·3	69·2	63·6	61·6	62·2	6·9*	65·7	64·2	66·4	63·6	2·8NS
6	*n*	40	40	38	36	36	—	190	190	90	100	—
	Level	64·8	64·0	58·6	53·8	60·6	7·0*	59·7	60·9	60·7	60·0	0·7NS
Mean		66·6	66·6	61·1	57·7	61·4	7·0	62·7	62·6	63·6	61·8	1·8

NS, $P > 0{\cdot}05$; * $P < 0{\cdot}05$ (tested using within-replicate error).

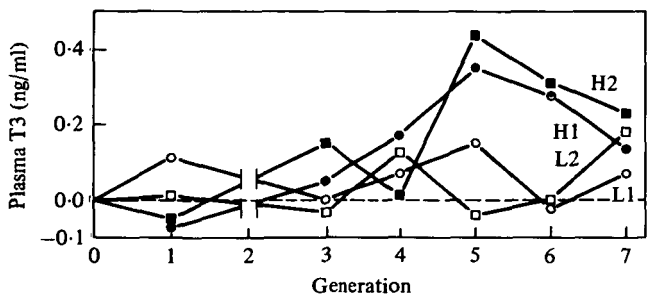

Fig. 3. Mean plasma tri-iodo-thyronine concentration in each selected line expressed as a deviation from the unselected control line.

Table 3. *Direct and correlated responses to selection in absolute units and relative to the mean (μ) and to the phenotypic* S.D. *within lines (σ) of the various traits. To compare responses over different numbers of generations, the regression (b), forced through the origin, of divergence in response ($\bar{H}-\bar{L}$) on generation for each trait was used to give the predicted total response over six generations of selection (R) as $R = 6b$*

Trait	b	R	μ	R/μ(%)	σ	R/σ
Plasma thyroxine (ng/ml)*	1·74	10·4	59·6	17·5	13·3	0·78
Plasma T3 (ng/ml)*	0·0271	0·163	1·06	15·3	0·36	0·45
Maternal wt. gain (g)	0·147	0·88	8·2	10·8	3·0	0·29
Litter gain 5–12 days (g)	0·336	2·02	17·9	11·3	4·5	0·45
Litter wt. 12 days (g)	0·659	3·96	40·3	9·8	5·6	0·71
Individual 3 wk. wt. (g)	0·185	1·11	8·6	12·8	2·3	0·47
Individual 6 wk. wt. (g)	0·167	1·00	20·0	5·0	2·2	0·46
Individual 9 wk. wt. (g)	0·081	0·48	22·5	2·1	2·1	0·23

*Regressions computed over 7 generations, but response predicted for 6 generations for comparison.

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Tri-iodo thyronine (*T3*). The concentrations in plasma of T3 are shown in Figure 3 each generation for each selected line as a deviation from the control.

To facilitate comparisons among responses, some of which were measured for different numbers of generations the responses were standardized to that expected over six generations, computed as 6 times the regression of the response on

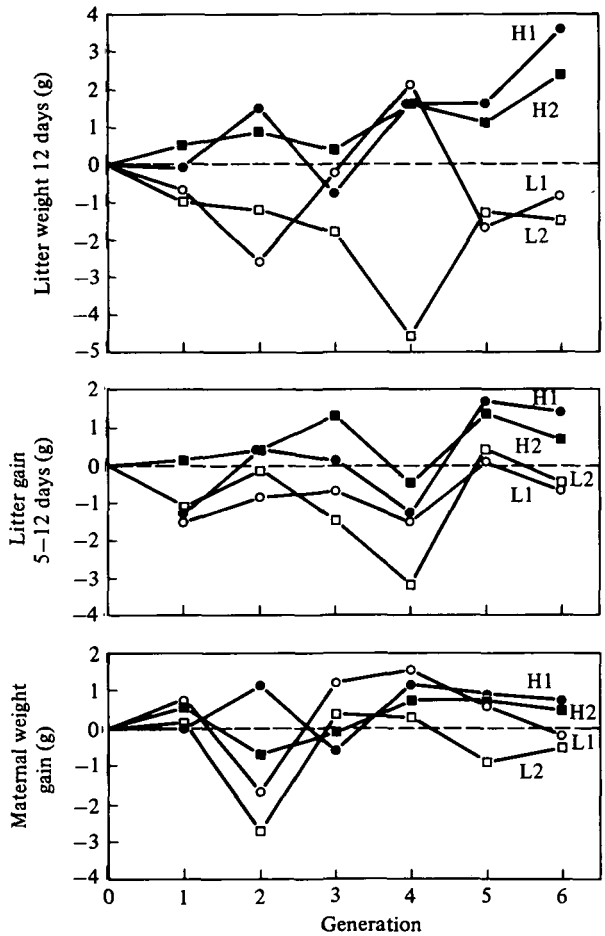

Fig. 4. Litter weight at 12 days, litter weight gain from 5–12 days and maternal weight gain from parturition to 12 days post partum of each line expressed as a deviation from the unselected control line.

generation number and these are given in Table 3. In addition to absolute comparisons the responses are also expressed as multiples of the mean and of the phenotypic standard deviation of the traits so that relative comparisons would also be made. Relative to their standard deviations the response in T3 was approximately one half of that in the T4 selected but both responses were similar relative to their means.

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Maternal and litter weights. Traits which were examined as indicators of maternal performance were weight of the litter at 12 days, standardized to eight mice, weight gain of the litter from 5 to 12 days, and weight gain of the dam from parturition to 12 days post partum. Approximately 10% of litters lost one or two young before 12 days, so weights from such litters with n survivors were scaled by 8/n. Means of each trait for each selected line and generation are expressed as a deviation from

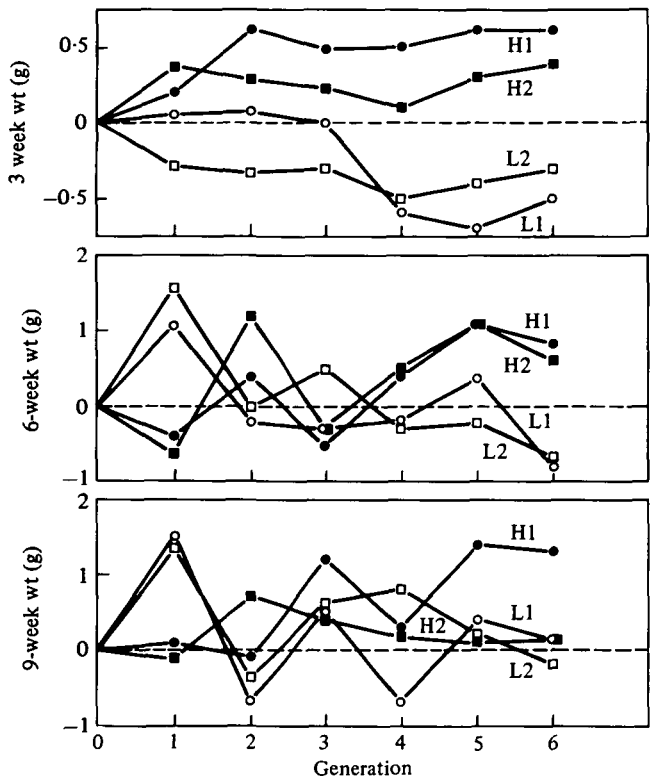

Fig. 5. Individual body weight at 3 weeks, 6 weeks and 9 weeks of each line expressed as a deviation from the unselected control line.

the control in Figure 4; because these are regarded as maternal traits, the generation number is that of the dam.

The regressions and relative responses are given in Table 3. An appreciable divergence (between high and low lines) in litter growth from 5–12 days and rather more in 12 day litter weight occurred (relative to their standard deviations this was 70% of the direct response). The changes in maternal weight gain were relatively smaller.

Individual weights. Mean weights of individual mice at 3, 6 and 9 weeks for each selected line as a divergence from control are shown in Figure 5, and regressions of divergence on generation number in Table 3. The increased weight at 12 days in lines selected for higher rather than low thyroxine levels persists to 3 weeks and

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beyond; but the tendency is for the divergence to be constant in absolute terms and thus become a smaller proportion of the mean weight at increasing ages.

Gonadal fat. The amounts of gonadal fat as a proportion of body weight of 12 week old animals of generation 7 are given in Table 4. The high lines were fatter relative to body weight, more so in females than in males.

Table 4. *Body weights and gonadal fat relative to body weight of 12 week old mice at generation 7 (10 mice/sex/line)*

	♂, ♀ mean					$\bar{H}$–$\bar{L}$		
	H1	H2	C	L1	L2	♂	♀	♂, ♀ mean
Body wt. (g)	27·7	25·1	25·3	25·4	25·3	0·3 NS	1·7*	1·0 NS
Gonadal fat/ body wt. (mg/g)	17·7	17·3	14·5	12·0	14·4	2·7*	5·8***	4·3***

NS, $P > 0{\cdot}05$; *, $P < 0{\cdot}05$; *** $P < 0{\cdot}001$ (Tested using within-replicate error).

Intra-class correlation and repeatability of thyroxine

The intra-class correlation of full sib family members (t_{FS}) of thyroxine level was estimated in generations 1–5, and estimates were pooled as they were homogeneous. The pooled estimate of t_{FS} was $0{\cdot}15 \pm 0{\cdot}04$. The value of $2t_{FS} = 0{\cdot}30$ is roughly three times the realized heritability estimate for thyroxine level, suggesting there are substantial maternal (and perhaps non-additive genetic) effects common to family members.

Data from generations 5 and 6 when two thyroxine measures were made on each mouse were used to estimate repeatability, as were data on another sample of mice from these two generations which were sampled twice at 5 weeks of age. Sexes ages and generations were pooled since estimates were homogeneous, to give an overall repeatability estimated by product moment correlation within lines of $0{\cdot}54 \pm 0{\cdot}03$.

DISCUSSION

Selection for the concentration of thyroxine hormone in the blood plasma of males led to changes in the concentration of the hormone in young animals of both sexes, proving there is genetic variation for the trait. The correlated change in growth prior to weaning and maternal weight changes during early lactation suggest that the altered thyroxine concentration may have affected milk production.

The difference in the concentration of thyroxine between the two high and the two low lines after five generations of selection was 8·7 ng/ml (estimated from regression, Table 3), about 15% of the overall mean, or two genetic standard deviations. Although not a direct comparison, Chai (1970) reported very little response to selection for the rate of uptake of iodine (^{131}I) by the thyroid gland during the first five generations. Subsequently, the rate of response increased in

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the high line so that after 11 generations the heritability was 0·49 for the high line but essentially nought for the low. The change here was in both directions. The relative response (15% of the mean) may also be compared to the variation in concentration of total thyroxine reported by Stewart *et al.* (1978) among inbred lines where the range was approximately 50% of the mean. The absolute levels in the assays used in the two studies are however quite different, Stewart et al. (1978) report variation about a mean of 5 μg/ml compared with the present variation about a mean of 60 ng/ml.

The principal source of variation in the concentration of thyroxine was, however, environmental not genetic. All lines fluctuated in a marked and similar way from generation to generation (Figure 1). Under natural conditions thyroid activity is known to have a seasonal trend largely related to variations in the ambient temperature (see review by Werner & Nauman, 1968); although the present results did not indicate a systematic seasonal effect. The fluctuations were unlikely to be related to ambient temperature, which was maintained constant, but possibly to changes in other components of the environment such as the quality of feed or a subclinical disease status; thyroid activity is known to be influenced by nutritional factors (Eayrs & Williams, 1966).

The repeatability of the concentration of the thyroxine was 54% although the two samples were taken only 1 day apart. With this repeatability, the variance of the mean of two observatons would be expected to be 77% of that of a single observation, and so the heritability of the concentration estimated from the mean of two observations would be about 12% rather than 9% for a single sample. With mice and with present assay techniques it would not be feasible to obtain more than two estimates of the concentration, but with large domestic animals this restriction would not be present, and multiple sampling procedures could be used.

Correlated Traits

The possibility that other traits might show a correlated response to the selection was of particular interest. In particular, the observation that there was no interaction between the response and the sex of the mice indicated that the same genes caused variation in both sexes. Any association between thyroxine and a female sex limited trait such as lactation could therefore be detected equally well in males as in females.

The genetic regressions (e.g. b_{A21}) of other traits (e.g. 2) on plasma thyroxine level (1) can be estimated from the ratios (b_2/b_1) of the regression coefficients of response on generation number given in Table 3. Genetic correlations (e.g. r_{A12}) can be estimated as (b_2/b_1) (σ_{A1}/σ_{A2}) but not solely from our data because the genetic variances (σ^2_{A2}) of the correlated traits are needed. To give an indication of the magnitude of the genetic correlations, estimates of heritability (h^2_2) from the literature were taken and used with the phenotypic variances of Table 3 to estimate σ_{A2} as $h_2\,\sigma_{p2}$. The heritability of thyroxine level was taken as 0·09 from our study, and hence from Table 3, $\sigma_{A1} = 3{\cdot}99$.

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Trait	h_2^2	σ_{A2}	b_2/b_1	r_A
12 day litter weight (Eisen *et al.* 1970)	0·11	1·86	0·379	0·81
3 week individual weight (Frahm & Brown, 1975)	0·17	0·95	0·106	0·45
6 week individual weight (Falconer, 1973)	0·37	1·34	0·096	0·29

These correlation estimates include, however, both direct and maternal genetic effects.

Although it was not possible to make observations of the production directly, the results suggest milk production is associated with thyroxine concentration. In particular, the growth rate of pups to 12 days of age differed by 10% after six generations. Hanrahan & Eisen (1970*a*) found that day 12 post partum corresponds to the time of peak lactation in mice, and the litter weights at this age is generally used as an index of lactation performance (Falconer, 1947; Hanrahan & Eisen, 1970*b*). The phenotypic correlation of 12 day litter weight with milk production (assuming the latter to be the only source of maternal effect on a litter weight at 12 days) is estimated to be 0·67 (Nagai & Sarkar, 1977) and the genetic correlation to be 0·45 (Hanrahan & Eisen, 1970*b*). Furthermore, cross-fostering studies (Cox, Legates & Cockerham, 1959; El-Oksh, Sutherland & Williams, 1967; Nagai, 1971) have revealed that a considerable proportion (70%) of the variation in 12 day litter weight is due to maternal environment.

An alternative explanation of the results presented would be that altered thyroxine had changed growth directly. Mice selected for high or low thyroid activity expressed a simultaneous increase or decrease in the rates of growth and maturation (Chai, 1970). Synenki, Eisen, Matrone & Robison (1972) reported a positive correlated response in thyroid activity of mice selected for 6 week body weight. This has recently been confirmed (Eisen, E. J. personal communication) using estimates of plasma thyroxine concentrations. The present divergence in 6 week weight was however less (7%) and in 9 week weight much less (3%) than that of litter weight at 12 days and of 3 week weaning weight (10%). The differences at later ages may therefore have been a carry over effect of differences in preweaning environment. Differences in preweaning body weight in mice may be brought through differences in maternal environment particularly that of lactation performance (Bateman, 1954), and the influence of the maternal environment on body weight prevails even at later ages, though to a lesser extent (Legates, 1972). The much higher genetic correlations estimated between the concentration of thyroxine and 12 day litter weight than with 6 week weight supports the view that growth increased via increased milk production.

The significance of the higher amount of gonadal fat in relation to the body weight in the high thyroxine line is not clear. One possible reason, however, is a difference in the degree of maturity between lines. Gonadal depot fat forms an increasing proportion of the total fat as the animal matures (Clarke, 1969). Since the mice from the two lines in the present study were of the same weight at the age of measurement, the 'low' thyroxine mice perhaps were less mature. Chai (1970) observed that the lines selected for low thyroid activity were comparatively

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slower in development as evidenced from the delay in opening of the eyes, appearance of the nipples and the opening of the vagina.

The results of this experiment and those of some studies of cattle (e.g. Joakimsen et al. 1971) support the hypothesis that thyroxine or other measures of the activity of the thyroid system that are not sex limited might be used as a predictive criterion of milk production. Other cattle studies however show that single samples of plasma taken from bulls under normal husbandry are unlikely to be an adequate base for such measures (Osmond, Carr, Hinks, Land & Hill, 1981).

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