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Enhanced Growth and Immune Development in Dwarf Chickens Treated with Mammalian Growth Hormone and Thyroxine[1] (41806)

JAMES A. MARSH,* WILLIAM C. GAUSE,* SANDY SANDHU,† AND COLIN G. SCANES†

*Department of Poultry and Avian Sciences, Cornell University, Ithaca, New York 14853, and †Department of Animal Sciences, Cook College, Rutgers the State University, New Brunswick, New Jersey 08903

Abstract. The effects of growth hormone and/or thyroxine treatments on antibody production, primary lymphoid organ development, and general body growth were examined in two dwarf strains (sex-linked dwarf—SLD, and autosomal dwarf—ADW) and in a normal-growing strain (K) of White Leghorn chickens. One-day-old male chicks were assigned to experimental groups and were treated either with thyroxine (T4) feed supplements or daily mammalian growth hormone (GH) injections or a combination of these treatments (T4/GH). Within the SLD strain, GH treatments resulted in a significant enhancement ($P < 0.005$) of humoral immune responsiveness and bursal growth while T4 treatments significantly ($P < 0.05$) stimulated thymic growth. Overall growth in the SLD was also stimulated by T4 treatments. GH and/or T4 treatments had no specific effects on primary lymphoid organ growth in the ADW strain but either treatment separately resulted in a significant ($P < 0.05$) increase in overall body size. None of the treatments significantly ($P > 0.05$) affected any of these parameters in the K-strain controls. Supplementation with T4 significantly elevated serum T4 levels within all strains. There were, however, no significant differences in the serum levels of T4 between strains within any of the treatment groups. Serum triiodothyronine (T3) levels were significantly lower in all treatment groups of the SLD as compared to the K-strain control. ADW serum T3 levels were significantly lower than the K-strain only in the T4-treated group. No differences ($P > 0.05$) were found between the dwarf and control strains in endogeneous GH levels, although mammalian GH treatments did produce significant changes in serum T3 and T4 levels within the K-strain. These results provide evidence that hormonal manipulations can significantly affect body growth, primary lymphoid organ development, and immune function in the dwarf strains studied and suggest these strains may be useful models for future studies on hormonal interactions and immune function.

The hormonal status of an animal may have profound effects on a variety of physiological and growth parameters. One approach in studying the functional interactions of specific hormones is to utilize model systems that are known to have impaired endocrine activity. The sex-linked dwarf strain of chickens (1) is such a model in that while thyroid activity is near normal (2–4) there is a decreased peripheral conversion of thyroxine (T4) to triiodothyronine (T3) resulting in a functionally hypothyroid condition (4). Abnormally fluctuating growth hormone (GH) levels (4) and decreased somatomedin levels (5) have also been reported in this strain. Furthermore, previous studies (6) have demonstrated impaired immune activity within the SLD strain which appears to be due, at least in part, to a decreased stimulation of immunoresponsive cells by low antigen dosages.

Investigations into the causes and effects of dwarfism in the Snell–Bagg (7–9) and Ames (10, 11) dwarf mice strains have demonstrated that the hormonal deficiencies which occur within these strains may have adverse effects on immune development and function. The almost total lack of anterior pituitary function within these strains frequently leads to the onset of a fatal wasting disease unless hormonal supplementation and/or special disease-free environments are provided (8, 11, 12). The avian dwarf model provides an alternative system for the investigation of the effects of a less severe but naturally occurring hormonal deficiency on both growth and development of immune function. Furthermore, the clear dichotomy of the avian immune system with

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a discrete primary lymphoid organ controlling B-cell development and function provides a means of more directly assessing hormonal effects on this population of immunoresponsive cells.

The purpose of the experiments described herein was to examine the effects of thyroxine and/or growth hormone supplementation on the dwarf chicken strains and to determine the suitability of these strains as a model system for investigations on the effects of these important hormones on growth and immune development.

Materials and Methods. *Experimental animals.* Three strains of male White Leghorn chickens developed and maintained at Cornell University were utilized in these experiments. These were the autosomal dwarf (ADW) strain (13), the sex-linked dwarf (SLD) strain (1), and a normal-growing control (K) strain. Day-old chicks from each strain were randomly assigned to treatment groups and housed in thermostatically controlled battery brooders with raised wire floors. A commercial mash chick starter ration (Agway Pacemaker Starter) and water were provided *ad libitum* and chicks were raised under a 15-hr L:9-hr D photoperiod. In experiments where housing was necessary beyond 6 weeks, chicks were transferred to grower batteries.

Experimental protocol. Experiments 1 and 2 were performed concurrently in two separate locations. The first was designed to assess the effects of hormonal supplementation on general growth parameters (i.e., body weight gain). The second experiment was of shorter duration and was primarily concerned with the effects of these hormonal treatments on immune development and function.

Experiment 1. Day-old male chicks from each of the three strains were randomly divided into four groups of nine chicks each and treated as follows: Group 1 served as the control and received only saline injections; Group 2 was fed a commercial chick starter ration for 1 week, after which it received the same ration supplemented with 1.0 ppm T4 and daily saline injections for the remainder of the experiment; Group 3 was fed the commercial chick diet and, beginning at 2 weeks of age, received daily subcutaneous injections of bovine growth hormone (GH) for the next 3 weeks; Group 4 received both the T4-supplemented diet and the daily GH injections as described above. Initial body weight measurements were taken at 1 week of age and at weekly intervals thereafter for the 9-week duration of the experiment.

Experiment 2. A similar experimental design to that described above was again followed with 15 1-day-old male chicks per group. Treatments were: Group 1, serving as the control, was fed a chick starter diet and received daily subcutaneous injections of the vehicle buffer; Group 2 was fed 1.0 ppm T4-supplemented diet from hatching and given control buffer injections; Group 3 was fed unsupplemented chick ration and given daily subcutaneous injections of ovine GH; and Group 4 received both the T4-supplemented diet and daily ovine GH injections. Injections, both control and treatment, were begun at 1 week of age and continued until the experiment was terminated. At 3 weeks of age, all animals received a primary immunizing dose of suspended SRBC. One week later, blood samples were collected and analyzed for antibody and hormone levels. At 29 days of age, final body weights were recorded, the animals were sacrificed, and all thymic tissue and the bursa of Fabricius were removed and cleaned of adherent tissue prior to obtaining organ weights.

Immunization and antibody titration. Chicks were immunized at 3 weeks of age by an intracardial injection of the primary test antigen, sheep erythrocytes (SRBC). A 1.0% suspension of SRBC in 0.01 *M* phosphate buffer containing 0.85% saline, pH 7.4, was prepared and a 0.2 ml immunizing dose was used for all injections. Blood samples were drawn by cardiac puncture 7 days after the primary immunization. The sera of these samples were individually analyzed for circulating anti-SRBC antibody and for hormone levels. Antibody was measured by the microhemagglutination technique (14) and titer was expressed as the $\log_2$ of the reciprocal of the highest dilution of an individual antiserum that produced visible agglutination of the test antigen.

Hormone treatments and serum hormone determinations. Thyroxine (T4) supplementation was accomplished by adding powdered 3,3',5,5'-tetraiodo-L-thyronine (Sigma Chemical Co.) to 1 kg of chick starter ration and mixing thoroughly to achieve an even distri-

bution of T4. This was then added to a larger volume of starter ration and mixed again to produce a final concentration of 1.0 ppm thyroxine. This level of T4 has been previously demonstrated to significantly elevate plasma T4 levels in the chicken (15). Bovine growth hormone (Miles Laboratories) treatments consisted of daily subcutaneous injections (sc) of 200 μg (0.8 IU/mg) in alkaline saline/kg body weight. Ovine growth hormone (provided by the National Pituitary Agency) was administered by daily sc injections of 290 μg (0.56 IU/mg) in 0.01 *M* borate-buffered saline (BBS, pH 9.0)/kg body wt. All injections were given during the same time period daily.

Thyroxine and triiodothyronine (T3) hormone levels were measured in duplicate serum samples using commercially available radioimmunoassay kits (Amersham Corp.). Endogeneous avian GH concentrations were determined in duplicate at two concentrations in a single RIA using the specific homologous RIA developed by Harvey and Scanes (16).

Statistical treatment of data. All samples were coded and randomized for antibody and hormone determinations. The data were organized into the respective strain and treatment groups only after the samples had been read and recorded. Analysis of variance was performed to determine if strain or treatment effects existed within the different parameters examined. Planned comparisons were further analyzed by Student's *t* test to determine the significance of individual strain or treatment effects. The growth data were transformed to the natural logarithm of the body weight gain which allowed regression analysis of the total growth curves and comparisons of slopes, adjusted means, and elevations of the regression lines (17).

Results. Following data transformation, the growth data of Experiment 1 (Table I) for all strains and treatment groups could be represented by individual straight lines ($r > 0.90$, $P < 0.01$) and multiple regression analysis of the growth curves within a strain revealed no significant differences ($P > 0.05$) in the overall growth curves due to treatment. The growth data were further examined by analysis of total body weights within treatment groups during the growth period. No significant effects ($P > 0.05$) due to treatment were seen in the control K-strain. Within the ADW strain, however, a significant enhancement of growth ($P < 0.05$) during the final week of the treatment period was seen due to either GH or T4 supplementation (Table I).

Examination of the SLD final body weights from the first experiment revealed a trend toward stimulated body growth by both the T4 and T4/GH treatments, although neither treatment produced a significant growth stimulation ($P > 0.05$). The results of the second experiment (Table I) support the growth-promoting effects of T4 within the SLD. This experiment, even though of a relatively short duration, resulted in significant increases ($P < 0.05$) in body weight when birds of the SLD strain were treated with either T4 or T4/GH. This result is consistent with the trends observed in the first experiment.

In the second experiment, humoral immune function was assessed by the ability of each strain and treatment group to produce antibody in response to the T-dependent antigen, SRBC. As is apparent from Fig. 1, the untreated SLD chickens produced significantly less circulating antibody ($P < 0.01$) than the untreated K-strain control. Those of the SLD strain receiving T4 supplements also were significantly ($P < 0.001$) below T4-treated K-strain controls in antibody production but did not differ significantly ($P > 0.05$) from untreated SLD controls. Daily GH injections of the SLD, however, resulted in circulating antibody levels that were not significantly different ($P > 0.05$) from the K-strain animals receiving the same treatment and that were significantly higher ($P < 0.005$) than the untreated SLD group. Finally, the combined T4 and GH treatment did not significantly increase ($P > 0.05$) the SLD antibody response over the untreated control, resulting in a humoral response that was significantly less ($P < 0.05$) than that of the K-strain group receiving the same treatment.

Examination of the treatment effects on antibody production within the K and ADW strains revealed no significant changes ($P > 0.05$) from the untreated controls within either strain. Last, no differences ($P > 0.05$) were found between the humoral immune responses of the K-strain and the ADW within any of the treatment groups.

To further assess the effects of hormonal treatments on immune development, the pri-

TABLE I. EFFECTS OF GH AND/OR THYROXINE ON BODY GROWTH

Age (weeks)	K-Strain body wts (g)				SLD Strain body wts (g)				ADW Strain body wts (g)			
	Control	T_4[a]	GH	T_4/GH	Control	T_4	GH	T_4/GH	Control	T_4	GH	T_4/GH
Expt 1												
1	65 ± 2[b]	65 ± 2	65 ± 2	65 ± 2	56 ± 3	56 ± 3	56 ± 2	56 ± 2	48 ± 2	48 ± 2	48 ± 2	48 ± 1
2	110 ± 4	108 ± 4	106 ± 4	106 ± 4	97 ± 6	95 ± 6	90 ± 4	93 ± 4	79 ± 4	74 ± 3	83 ± 1	72 ± 2
3	175 ± 8	169 ± 5	171 ± 8	165 ± 9	132 ± 11	129 ± 8	127 ± 6	130 ± 6	113 ± 5	111 ± 4	123 ± 2	107 ± 4
4	260 ± 11	252 ± 8	261 ± 13	264 ± 13	162 ± 13	189 ± 15	161 ± 10	193 ± 10	166 ± 8	162 ± 7	180 ± 5	156 ± 7
5	352 ± 15	335 ± 11	371 ± 15	334 ± 19	244 ± 23	245 ± 21	241 ± 16	255 ± 14	232 ± 12	234 ± 10	246 ± 7	212 ± 9
6	469 ± 18	456 ± 16	479 ± 23	454 ± 28	295 ± 31	310 ± 28	304 ± 20	327 ± 19	278 ± 16	304 ± 12	308 ± 11	286 ± 11
7	571 ± 20	548 ± 24	581 ± 24	563 ± 32	352 ± 40	406 ± 31	369 ± 25	420 ± 17	329 ± 20	391 ± 11**	382 ± 13*	354 ± 14
8	692 ± 26	688 ± 32	728 ± 27	696 ± 36	450 ± 47	487 ± 34	471 ± 19	508 ± 21	378 ± 25	443 ± 15*	451 ± 16*	396 ± 16
9	823 ± 28	774 ± 29	859 ± 31	796 ± 38	520 ± 54	563 ± 40	549 ± 21	596 ± 23	457 ± 28	508 ± 25	531 ± 19*	465 ± 18
Expt 2												
0	39 ± 1[c]	40 ± 1	39 ± 1	40 ± 1	34 ± 1	34 ± 1	34 ± 1	34 ± 1	33 ± 1	34 ± 1	33 ± 1	33 ± 1
1	56 ± 2	59 ± 2	55 ± 1	55 ± 1	45 ± 3	50 ± 2	47 ± 2	51 ± 3	45 ± 2	46 ± 1	44 ± 1	47 ± 2
2	105 ± 4	101 ± 4	100 ± 3	94 ± 4	83 ± 5	87 ± 5	83 ± 3	86 ± 4	71 ± 5	76 ± 3	74 ± 2	74 ± 4
3	173 ± 6	152 ± 6	170 ± 4	164 ± 6	142 ± 9	142 ± 8	138 ± 6	143 ± 6	115 ± 7	117 ± 4	117 ± 2	118 ± 6
4	261 ± 7	273 ± 10	264 ± 7	253 ± 9	191 ± 10	220 ± 9*	208 ± 9	226 ± 8*	163 ± 11	170 ± 6	174 ± 3	174 ± 8

[a] Hormonal treatments administered as described under Methods.
[b] Means of 9 chicks/treatment ± SEM.
[c] Means of 15 chicks/treatment ± SEM.
* Significantly different from the control within that strain, $P \leq 0.05$.
** Significantly different from the control within that strain, $P \leq 0.01$.

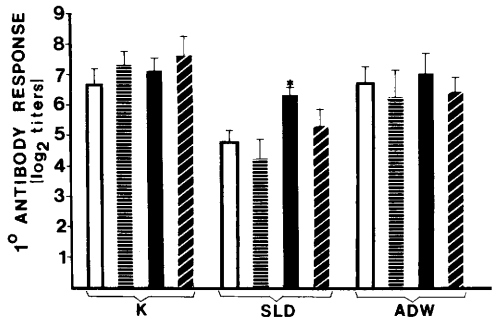

FIG. 1. The antibody response of the control K-strain and the autosomal and sex-linked dwarf strains to SRBC. Each bar represents the mean circulating antibody titer for 15 males with the SEM indicated. Open bars represent the control treatment group; the horizontal slashed bars represent the T4 supplemented group; the solid bars represent the GH treatment group; and the diagonally slashed bars represent the T4/GH treatment group. Data are those derived from Experiment 2. Levels of significance are represented by the (*) as compared to the control treatment within that strain: $*P < 0.005$.

mary lymphoid organs were collected and weighed. These data are presented in Fig. 2. It should be noted that all organ weights are adjusted for body weights to facilitate direct comparisons between strains. Treatments utilizing T4 supplementation (T4 alone or T4 and GH) produced significant increases ($P < 0.05$ and $P < 0.01$, respectively) in SLD thymic weights (Fig. 2A). No other treatment effects on thymic growth were detected within any of the strains ($P > 0.05$). However, there were strain differences within treatment groups when compared to the control K-strain. The thymic weights of the ADW were consistently lower in all treatment groups and significantly so ($P < 0.05$) both in the T4-treated and in the GH-treated groups. In those treatment groups of the SLD that had increased thymic weights (T4-treated and T4/GH-treated), there were also significant increases ($P < 0.05$ and $P < 0.01$, respectively) over the K-strain control.

The hormonal treatments also affected bursal growth with the greatest effect once again observed in the SLD strain. As may be seen in Fig. 2B, when GH was administered either separately or in combination with T4, highly significant increases ($P < 0.005$ and $P < 0.001$, respectively) in bursal growth were produced within the SLD strain. There were no significant treatment effects ($P < 0.05$) on bursal weights observed within the control K-strain. Supplementation with both T4 and GH resulted in a decreased bursa weight per body weight ratio ($P < 0.05$) within the ADW strain. This decreased ratio provided the only significant difference in bursal growth ($P < 0.05$) between strains. Absolute bursal weights, however, when not adjusted for body weight were not significantly different between the treatment groups of the ADW.

The results of the serum hormonal analysis are presented in Table II. Thyroxine supplementation resulted in highly significant increases ($P < 0.001$) of serum T4 within all groups receiving that treatment. GH treatment

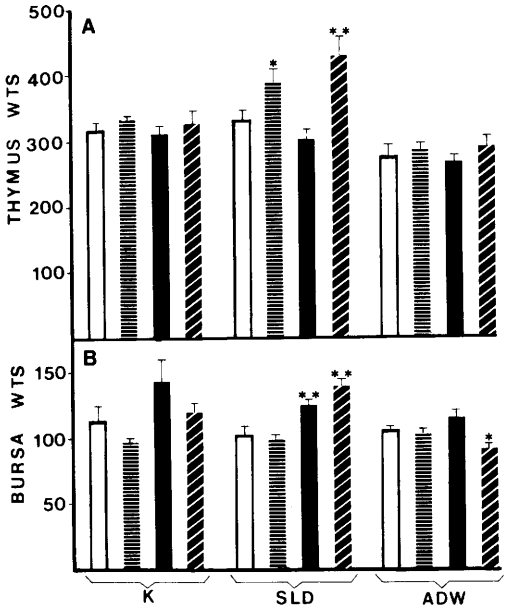

FIG. 2. (A) The effect of GH and T4 supplementation on thymic growth in the control and dwarf strains. (B) The effect of GH and T4 supplementation on bursal growth in the control and dwarf strains. For all organ weight determination, each bar represents the mean of 12–15 determinations with the SEM indicated. Open bars represent the control treatment group; the horizontal slashed bars represent the T4 supplemented group; the solid bars represent the GH treatment group; and the diagonally slashed bars represent the T4/GH treatment group. Data are those derived from Experiment 2. Levels of significance are represented by the (*) as compared to the untreated control within that strain: $*P < 0.005$; $**P < 0.001$.

TABLE II. EFFECT OF GH AND/OR THYROXINE TREATMENTS ON SERUM HORMONE CONCENTRATIONS

	Hormone concentrations (ng/ml)									
	K-Strain			SLD-Strain			ADW-Strain			
	T_3	T_4	GH	T_3	T_4	GH	T_3	T_4	GH
Control	2.8[a] ± 0.3	46.1 ± 4.9	297.5 ± 45.0	1.0 ± 0.1	37.9 ± 3.8	270.8 ± 29.8	2.1 ± 0.1	40.4 ± 4.2	—
T_4[a]	4.0** ± 0.4	115.0*** ± 8.5	226.9 ± 46.0	1.4* ± 0.1	141.0*** ± 15.0	244.3 ± 51.1	2.7* ± 0.2	106.8*** ± 14.6	—
GH	2.1 ± 0.2	62.2* ± 5.2	206.3 ± 38.4	0.7* ± 0.1	46.6 ± 3.3	283.4 ± 35.7	1.9 ± 0.2	53.2 ± 6.6	—
T_4/GH	1.6** ± 0.1	160.1*** ± 13.7	325.1 ± 51.9	1.1 ± 10.1	102.6*** ± 9.4	338.7 ± 39.6	2.4 ± 0.5	104.5*** ± 8.9	—

[a] Serum values are means of 10–12 samples/treatment ± SEM.
[b] Hormonal treatments administered as described under Methods.
* Significantly different from the control within that strain, $P < 0.05$.
** Significantly different from the control within that strain, $P < 0.01$.
*** Significantly different from the control within that strain, $P < 0.001$.

also produced somewhat elevated T4 levels in all strains, although this was significant ($P < 0.05$) only within the K-strain. The T4/GH treatment of the K-strain resulted in serum T4 levels that were significantly higher ($P < 0.01$) than either the SLD or ADW within that treatment group.

Examination of serum T3 levels from these strains demonstrated that the SLD strain had significantly less T3 ($P < 0.005$) in all treatment groups when compared to the K-strain, while the ADW had somewhat reduced levels ($P < 0.05$) in only the T4-supplemented group (Table II). Furthermore, T4-treatment resulted in significantly elevated T3 levels in all strains ($P < 0.01$ for the K-strain, $P < 0.05$ for the SLD and ADW strains) as compared to the respective untreated controls. The serum T3 levels of the K-strain T4/GH treatment group was significantly lower ($P < 0.01$) than that of the untreated control from this strain. This effect was not seen in either of the dwarf strains.

Finally, avian growth hormone levels were analyzed in the K and SLD strains. Since the homologous avian GH RIA shows little reactivity (<1.0%) for mammalian GH, it is primarily endogenous GH that is being detected. While there was some fluctuation of GH levels between strain and/or treatment groups (Table II), no significant differences ($P > 0.05$) due to either strain or treatment were found.

Discussion. T3 and T4 supplementation do not stimulate body growth in broiler chickens (15, 18). Treatment of sex-linked dwarf chicken strains with iodinated casein (19, 20) has also been investigated and found to produce somewhat variable results but no major growth promoting effects were seen as was also the result of T4 treatments in this study. At least part of the reason for the relative limited effectiveness of these treatments in the SLD has become more clear. Scanes *et al.* (4) have recently demonstrated a significantly diminished 5′-monodeiodinase activity within this strain, resulting in reduced serum T3 levels and a functional hypothyroidism. The data presented here further support that observation with (i) significantly lower T3 levels in the untreated SLDs as compared to the K-strain and (ii) a lower conversion of T4 to T3 in the T4-supplemented SLD group. The fact that there was a body weight increase in the

T4-treated SLD is consistent with some growth stimulation resulting from the low level conversion of T4 to T3.

In mammals it has been demonstrated that the thyroid hormones have a thymotropic effect (12), that immune responsiveness may be decreased by thyroidectomy and restored by thyroxine treatments (21), and that exogeneous thyroxine both *in vitro* and *in vivo* may have direct stimulatory activity on lymphocytes (22). In birds, studies using a thiouracil-induced hypothyroidism (18, 23) have also shown the necessity of thyroid function in supporting optimal levels of immune responsiveness. The role of the thyroid hormones in regulating and modifying immune activity has been investigated in the obese-line chicken strain (24) where T4 supplementation produced a significant reduction in the onset of autoimmune disease.

The decreased humoral immune activity reported in the SLD strain (6) immediately suggests a possible link between endocrine and immune function. In the present study, however, no significant change in antibody responsiveness was seen in any of the treatments involving T4 supplementation to the SLD strain. Whether this is due to the inability of the strain to utilize T4 effectively as discussed above or whether humoral immune function is refractory to any additional thyroidal stimulation in this strain is the subject of current investigations. The data do show, however, that T4 supplementation significantly enhances thymic growth. The effect that this may have on immunocompetency within the SLD strain is presently unclear.

The results of mammalian GH administration in the dwarf strains provide evidence that this hormone is active in the intact avian system. Several previous studies have examined the effect of mammalian GH in birds, primarily in chicken strains demonstrating normal growth characteristics. In general, no significant effects on overall body growth or body composition have been reported (25–28), even when dosages of two to three levels of magnitude greater than those reported here were used. These results have led some to conclude that mammalian GH is inactive in the avian system, presumably due to species specificity (25, 29). However, treatment of the hypophysectomized pigeon with mammalian GH (either alone or in combination with other hormones) demonstrated that a growth-enhancing effect could occur within the avian species (30). This suggests that when the endogeneous source of GH is eliminated, the avian system becomes much more responsive to exogeneous mammalian GH. Both in this system and in the intact chicken (25, 31), the effects of mammalian GH within the avian species have been more readily demonstrated when combined with other hormonal treatments.

Several investigations have shown that while mammalian GH may not generally exert detectable effects on body growth within members of the avian species, effects do occur at the organ and tissue level that are comparable to those seen in mammalian systems. Increased RNA and protein synthesis have been stimulated by administration of low levels of bovine GH to broilers (27) and slight stimulation of bursa growth accompanied by significant increases in adrenal weights have been produced in young chickens by large dosages of bovine GH (26). Furthermore, in the hypophysectomized duck, treatment with mammalian GH has produced elevations in plasma glucose, insulin, free fatty acids, and circulating levels of nonprotein nitrogen (32, 33).

Almost certainly, a major factor in this study which allowed the detection of more generalized effects of mammalian GH in an intact avian model was the availability of two dwarf strains which demonstrate an increased sensitivity to hormonal manipulations. The possibility of increased dwarf strain responsiveness is further supported by the ineffectiveness of the same treatments within the control K-strain. These results are consistent with the observations of others using normal growing strains. In this study, significant stimulation of general body growth in the ADW and of bursal growth and antibody responsiveness in the SLD can be directly attributed to the GH treatments. Furthermore, as may be seen from the data, there are several instances of apparent synergism where the treatments combining T4 and GH produced more of an effect than either treatment administered separately (i.e., body weight gain and thymic growth in the SLD).

The results of the experiments with the SLD strain support the conclusion that GH sup-

plementation can significantly enhance immune development and function in a strain which has been demonstrated to be immunodeficient (6). This is a somewhat unexpected result since previous studies utilizing other varieties of the sex-linked dwarf (5, 34, 35) have found endogenous GH serum levels to be at least equal those of control strains. The same result was obtained in this and in a previous (4) study of the SLD. Also, the sex-linked dwarf appears to have normal pituitary organization as determined by conventional histochemical analysis (19). The observed immunostimulatory effects of a heterologous GH lend support to the possibility that the immunoreactive endogenous growth hormone may have limited biological activity or that the tissues may have decreased responsiveness to the circulating GH. The second possibility appears to be less likely due to recent findings that the receptor levels within these three strains are not significantly different (unpublished observations, F. Levine, C. Scanes, and J. Marsh).

The stimulatory action of GH on immune development has been amply demonstrated in the mammalian system both through its thymotropic effects (8, 9, 12) and through direct effects on lymphocytes (36, 37). The majority of the present evidence supports the view that hypopituitary function is the primary cause of immunodeficiencies seen both in the Snell–Bagg (8, 9, 12) and in the Ames (10, 11) dwarf mice strains. Furthermore, it has been shown that the depressed immune function of the Snell–Bagg dwarf can be restored to essentially normal levels by GH or GH and thyroxine supplementation (8, 12). Study of GH activity on immune development in the avian system allows one to extend those observations made in mammals due to the presence of a second primary lymphoid organ, the bursa of Fabricius. Both stimulation and suppression of bursal growth have been produced by hormone treatments (26, 38, 39). There have been no previous demonstrations of which the authors are aware, however, where hormonal treatments have resulted in an enhancement of humoral immune function *and* bursal growth. The data presented here strongly suggest a bursotrophic function for GH within the SLD strain in a manner analogous to the demonstrated thymotrophic and general lymphoid-stimulating activity seen in mammals.

Finally, the interactions seen between GH and thyroid hormones allow for some conclusions and speculation. The enhanced effectiveness seen in several of the combined GH and T4 treatments is consistent with the concept that thyroid hormones function in a "permissive" manner, causing target tissues to exhibit increased responsiveness to other hormones. There are, however, several recent reports indicating that thyroid hormones and GH may also interact at the regulatory level (40, 41). In chickens, thyrotropin releasing hormone (TRH) has been shown to stimulate the pituitary release of not only thyroid stimulating hormone (TSH) but also GH (42). Furthermore, exogeneously administered GH and TSH appear to synergize in the stimulation of T4 release from the thyroid (43). This interaction is further demonstrated by the experiments of Grau and Stetson (44) showing that chronic GH treatments may exert thyrotropic effects. Within the normal-growing K-strain controls, continued GH treatments resulted in significant increases in serum T4 levels and this trend was also apparent within the SLD and ADW strains. Likewise, treatment of the K-strain with T4 and GH resulted in increased serum T4 when compared to those treated with only T4. Finally, there were consistently detectable and often significant decreases in serum T3 levels within those treatments involving GH administration. This suggests that either GH is facilitating the uptake and utilization of T3 or that it is regulating the T4:T3 ratio by affecting either peripheral conversion or thyroidal synthesis. Accepting that T3 is the major biologically active product of the thyroid (45) but that T4 may be important in the feedback control of TRH release (46), a regulatory role in which GH affects the balance of T4 and T3 would be consistent with the interrelated functions of these important developmental hormones.

In conclusion, these results demonstrate that mammalian GH can exert definite enhancing effects on bursal growth and immune function as well as stimulating general body growth within dwarf strains of the avian species. Likewise, treatments with thyroxine were also shown to stimulate general body growth

and thymic growth within the SLD strain. Finally, there are also indications that exogeneously administered GH may interact with and regulate the availability and expression of the thyroid hormones.

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