is between MLD's and our second demonstration, since MLD's have not been studied with relatively fast-beating stimuli and it is not known whether they can produce unmasking. Egan (*10*) has used slowly beating stimuli to demonstrate MLD's, exploiting the principle that stimuli which differ slightly in frequency can be conceived of as stimuli with identical frequencies but with constantly changing phase relations. In his demonstration a signal is heard to fade in and out of noise with the beat frequency. No such fading occurs in our second demonstration. In addition, it should be noted that no cyclopean (visual) analog has yet been generated (*11*).

It can be argued that both demonstrations are "weakly cyclotean" according to the Julesz definition (*1*, pp. 17–21): Changes are present in a single stimulus that an instrument could detect to determine which of the simultaneous eight tones underwent sudden phase or frequency shift. The ear, however, is not such an instrument. Moreover, to generate the strongly cyclotean stimulus one need only shift more than one component (preferably all eight) in phase or in frequency, but making such changes identical in both ears except for the crucial melodic component.

MICHAEL KUBOVY
Department of Psychology,
Yale University,
New Haven, Connecticut 06520
JAMES E. CUTTING*
RODERICK MCI. MCGUIRE
Haskins Laboratories, New Haven,
Connecticut 06510, and *Yale University*

References and Notes

1. B. Julesz, *Foundations of Cyclopean Perception* (Univ. of Chicago Press, Chicago, 1971).
2. This neologism is constructed from Greek roots to be analogous to the term *cyclopean.* Since *ops* is the Greek root for eye and *oto* the root for ear, we feel that *cyclotean* is the proper term for this phenomenon. As yet we have been unable to find reference to such a mythical beast. One reason for this may be that the *cyclot* was a much less truculent, and hence much less memorable, creature.
3. B. Julesz and I. J. Hirsh, in *Human Communication: A Unified View,* E. E. David and P. Denes, Eds. (McGraw-Hill, New York, 1973), pp. 283–340.
4. First reported by J. C. R. Licklider, in *Information Theory, Third London Symposium,* C. Cherry, Ed. (Butterworth, London, 1956), pp. 253–368, and investigated by E. M. Cramer and W. H. Huggins, *J. Acoust. Soc. Am.* **30**, 413 (1958). Subsequent reports have been made by A. J. Fourcin, *Proceedings of the 4th International Congress of Phonetic Sciences* (Mouton, The Hague, 1962), pp. 355–359, and by N. Guttman, *J. Acoust. Soc. Am.* **34**, 1996(A) (1962).
5. The lowest note, D_4, was 300 hz, whereas the highest note, D_5, was adjusted to 601.5 hz to avoid harmonic relationships with D_4. The other six tones were left at even-tempered frequencies since their pairwise frequency ratios are all irrational.
6. F. S. Cooper and I. G. Mattingly, *J. Acoust. Soc. Am.* **46**, 115(A) (1969); also in *Haskins Laboratories Status Report on Speech Research,* SR 17/18 (1969), pp. 17–21.
7. With phase shifts of 1 msec for each of the eight sine waves, the degree to which opposite-ear sine waves are out of phase is not optimal, but varies with frequency. The amount of interaural phase differences at different frequencies should therefore result in different perceived spatial locations. Critical listening can give rise to a spatially varying cyclotean percept, but few listeners can detect it without being instructed what to listen for and without having previously listened to the second demonstration.
8. One subject, for example, was a New Zealander who reported hearing "Waltzing Matilda," not "Daisy." We attribute this misperception to his ethnocentricity and general musical inability, not to the subjective strength of the percept.
9. For discussions of binaural beats see J. C. R. Licklider, J. C. Webster, and J. M. Hedlun, *J. Acoust. Soc. Am.* **22**, 468 (1950); D. R. Perrot and M. A. Nelson, *ibid.* **46**, 1477 (1969); G. Oster, *Sci. Am.* **229**, 94 (Oct. 1973).
10. J. P. Egan, *J. Acoust. Soc. Am.* **37**, 1143 (1965).
11. Any attempt to generate such a pattern would probably rely on previous work by C. Blakemore [*Vision Res.* **10**, 1181 (1970)], who studied binocular combinations of gratings.
12. Supported by NICHD grant HD-01994 to the Haskins Laboratories. Parts of this report were read at the 87th meeting of the Acoustical Society of America, New York, 23–26 April 1974.
* Present address: Wesleyan University, Middletown, Conn., and Haskins Laboratories.

12 June 1974

Relation between the Major Histocompatibility (B) Locus and Autoimmune Thyroiditis in Obese Chickens

Abstract. *Obese strain chickens develop circulating autoantibodies to thyroglobulin and lymphocytic infiltration of their thyroids during aging. Two alleles,* B^1 *and* B^4*, are found with high gene frequency at the major histocompatibility (B) locus. Greater pathology and higher antibody titers are observed in* B^1B^1 *and* B^1B^4 *birds than in their* B^4B^4 *siblings.*

In chickens the B blood group locus determines the major histocompatibility antigens (*1*). The Obese strain (OS) of White Leghorns has three alleles segregating at the B locus (*2*). The arbitrarily designated B^1 and B^4 alleles occur with nearly equal gene frequency in the population ($p = 0.50$, $q = 0.46$), while the B^3 allele occurs only rarely ($r = 0.04$). In mice, genes that segregate with alleles of the major histocompatibility (H-2) locus are known to influence the immune response to homologous thyroglobulin (*3*). More than 90 percent of OS chickens noninbred develop thyroiditis during aging (*4*). A study was conducted to determine whether the B genotype influences the susceptibility of OS chicks to genetically determined autoimmune thyroiditis (*5*).

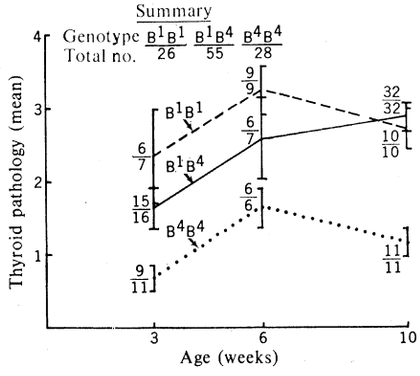

Fig. 1. Thyroid pathology of chicks from $B^1B^4 \times B^1B^4$ OS matings. The fraction at each point indicates the ratio of number of birds with lymphocyte infiltration of the thyroids to the total number of birds.

The chicks were obtained primarily from three different partially inbred OS families that were established within the noninbred closed OS flock or R. K. Cole at Cornell University. Chicks from these matings were > 40 percent inbred. Fertile eggs supplied from Cornell University were hatched and reared in our facilities (*6*). Two types of inbred matings were used: (i) heterozygous B^1B^4 males mated with B^1B^4 females to provide B^1B^1, B^1B^4, and B^4B^4 offspring in a 1 : 2 : 1 ratio and (ii) B^4B^4 homozygous matings within one family. A few noninbred OS chicks were produced from heterozygous B^1B^4 matings at our laboratory. B locus antigens were determined by hemagglutination tests of all chicks before they were killed. Groups of chicks were killed at either 3, 6, or 10 weeks of age.

Just before the animals were killed, a blood sample was taken from each, and the serum separated and frozen. The level of serum antibody to thyroglobulin was determined by a tanned-cell hemagglutination test (TCHT), with human red blood cells (RBC) coated with chicken thyroglobulin (*6*). The titer was defined as the $\log_2$ of the greatest dilution producing definite agglutination. Paired thyroid lobes were

also obtained from each chick at the time of death and these were prepared for histologic examination (*7*). Sections from at least four different levels of each thyroid were scored for the percentage of lymphocyte infiltration, with values ranging from 0 (no infiltration) to 4 (complete replacement of the gland by lymphoid cells), assuming 0.2 unit for each 5 percent increment of infiltration. This was done so that the precision of measurement would be increased, particularly at lower degrees of infiltration, and so that the mean score would reflect more accurately the percentage of lymphoid infiltration of the thyroid.

Differences in severity of disease between chicks of a given genotype from heterozygous OS families, whether from five inbred or three noninbred matings, were not obvious, and hence the data were pooled into B^1B^1, B^1B^4, and B^4B^4 groups. The histological results (mean ± standard error of the mean) presented in Fig. 1 indicate that at 3, 6, and 10 weeks of age the thyroids of B^1B^1 and B^1B^4 chicks had significantly greater lymphocyte infiltration than did thyroids from B^4B^4 chicks. There were no significant differences between the thyroid pathology of B^1B^1 and B^1B^4 chicks at these times, although at 3 weeks of age the B^1B^4 mean was lower. The TCHT titers of these chicks are shown in Fig. 2. The B^1B^1 and B^1B^4 chicks had significantly higher titers than B^4B^4 chicks at 6 and 10 weeks of age. The B^1B^1 chicks had higher titers than B^1B^4 chicks at 6 weeks, but at 10 weeks the difference was not statistically significant ($0.1 > P > .05$).

Thirteen chicks produced from three homozygous B^4B^4 inbred matings were killed at 3 weeks, 11 at 6 weeks, and 19 at 10 weeks of age. The birds that were 3 and 6 weeks of age had histological and TCHT scores similar to those recorded for B^4B^4 chicks from the heterozygous matings in Figs. 1 and 2. However, the 10-week-old birds had a mean pathological score of 2.0 ± 0.2, and a mean TCHT titer of 3.0 ± 0.5, which are significantly higher than those recorded in Figs. 1 and 2. Two-thirds of the birds in each group were females. The birds with severe pathologic changes and elevated antibody titers from the homozygous sire family were in each of the three dam families studied, but were principally in one of two hatch groups. The reason for more

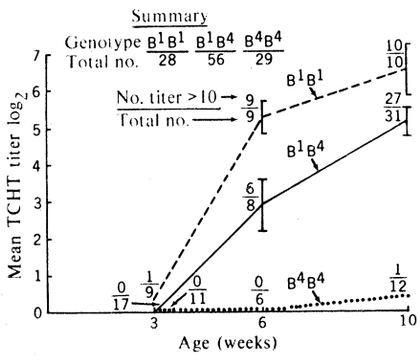

Fig. 2. Titer of antibody to thyroglobulin of chicks from $B^1B^4 \times B^1B^4$ OS matings.

severe thyroiditis in the B^4B^4 chicks from homozygous than heterozygous parents is unknown. However, thyroiditis in the presence of the B^4 allele appears to be dependent on, or modified by, environmental conditions and/or other genetic factors. Results of other studies (in preparation for publication) indicate 6-week-old B^4B^4 chicks from B^4B^4 OS × B^1B^4 OS noninbred matings have significantly less pathology and lower TCHT antibody titers than their B^1B^4 siblings. Moreover, when a B^1B^1 male was mated to the same B^1B^4 females, the 3- and 6-week-old siblings had similar pathology and TCHT antibody titers.

Observations from heterozygous matings indicate that B^1B^1 and B^1B^4 chicks are more susceptible to early onset of thyroiditis than their B^4B^4 siblings. It is possible that this susceptibility may result from the action of immune response (Ir) genes linked to the B locus, perhaps through expression of a recognition site on thymus derived (T) lymphocytes specific for a particular antigenic determinant of the thyroglobulin molecules (*3*, *8*). However, since neonatal thymectomy is known to accelerate the development of spontaneous thyroiditis in OS chickens (*9*) we suggest that another population of T cells may also exist, in which the action of the stimulated T lymphocytes may be to suppress autoimmune recognition. Alternatively, if viruses are involved in initiating the autoimmune process, other possibilities must also be considered (*10*). Preliminary evidence suggests that B genotypes influence susceptibility to Marek's disease in chickens (*11*), and an R_1 isoantigen has been associated with susceptibility to avian leukosis-sarcoma viruses of subgroup B (*12*). However, attempts to detect a virus in OS chickens have been unsuccessful (*13*).

To our knowledge, this is the first demonstration that incidence of a genetically determined autoimmune disease is influenced by the major histocompatibility (*B*) genes in a noninbred population (*14*). We propose that immune response genes at, or closely linked to, the major histocompatibility locus may be relevant in spontaneous diseases having a demonstrable autoimmune basis.

LARRY D. BACON
Department of Immunology and Microbiology, Wayne State University School of Medicine, Detroit, Michigan 48201

JOSEPH H. KITE, JR.
Center for Immunology and *Department of Microbiology, State University of New York at Buffalo 14214*

NOEL R. ROSE
Department of Immunology and Microbiology, Wayne State University School of Medicine

References and Notes

1. W. E. Briles, W. H. McGibbon, M. R. Irwin, *Genetics* **35**, 633 (1950); L. W. Schierman and A. W. Nordskog, *Science* **134**, 1008 (1961); W. P. Jaffe and E. M. McDermid, *ibid.* **137**, 984 (1962).
2. R. K. Cole, *Genetics* **53**, 1021 (1966); L. D. Bacon, J. H. Kite, Jr., N. R. Rose, *Transplantation* **16**, 591 (1973).
3. A. O. Vladutiu and N. R. Rose, *Science* **174**, 1137 (1971).
4. R. K. Cole, J. H. Kite, G. Wick, E. Witebsky, *Poultry Sci.* **49**, 839 (1970).
5. The results for the largest family of chicks were presented in a preliminary report [L. D. Bacon, J. H. Kite, Jr., N. R. Rose, *Fed. Proc.* **32**, 1026 (1973)].
6. E. Witebsky, J. H. Kite, Jr., G. Wick, R. K. Cole, *J. Immunol.* **103**, 708 (1969).
7. J. H. Kite, Jr., G. Wick, B. Twarog, E. Witebsky, *ibid.*, p. 1331.
8. H. O. McDevitt, *Transplant. Proc.* **3**, 1321 (1971); V. Tomazic, N. R. Rose, D. C. Shreffler, *J. Immunol.* **112**, 965 (1974).
9. P. Welch, N. R. Rose, J. H. Kite, *J. Immunol.* **110**, 575 (1973).
10. N. R. Rose, J. H. Kite, Jr., A. O. Vladutiu, V. Tomazic, L. D. Bacon, *Int. Arch. Allergy Appl. Immunol.* **45**, 138 (1973).
11. W. E. Briles and W. L. Oleson, *Poultry Sci.* **50**, 1558 (1971); R. N. Brewer, C. H. Moore, L. W. Johnson, *ibid.* **48**, 1790 (1969); B. M. Longenecker, F. Pazderka, G. R. J. Law, R. F. Ruth, *Fed. Proc.* **32**, 996 (1973).
12. L. B. Crittenden, W. E. Briles, H. A. Stone, *Science* **169**, 1324 (1970).
13. T. D. Flanagan, A. L. Barron, J. H. Kite, Jr., E. Witebsky, *Avian Dis.* **14**, 613 (1970); R. F. Ziegel, A. L. Barron, J. H. Kite, Jr., E. Witebsky, *ibid.*, p. 617.
14. M. B. A. Oldstone, F. J. Dixon, G. F. Mitchell, H. O. McDevitt, *J. Exp. Med.* **137**, 1201 (1973); A. D. Vladutiu and N. R. Rose, *Immunogenetics*, in press.

15. This work was performed at the Center for Immunology at the SUNYAB. Supported by NIH research grant CA-02357 and General Research Grant RRO 5400. We thank S. Kozmycz for excellent technical assistance, and Dr. R. K. Cole, Department of Poultry Science, Cornell University, for providing us with the OS fertile eggs.

29 April 1974; revised 21 June 1974