LETTERS

edited by Etta Kavanagh

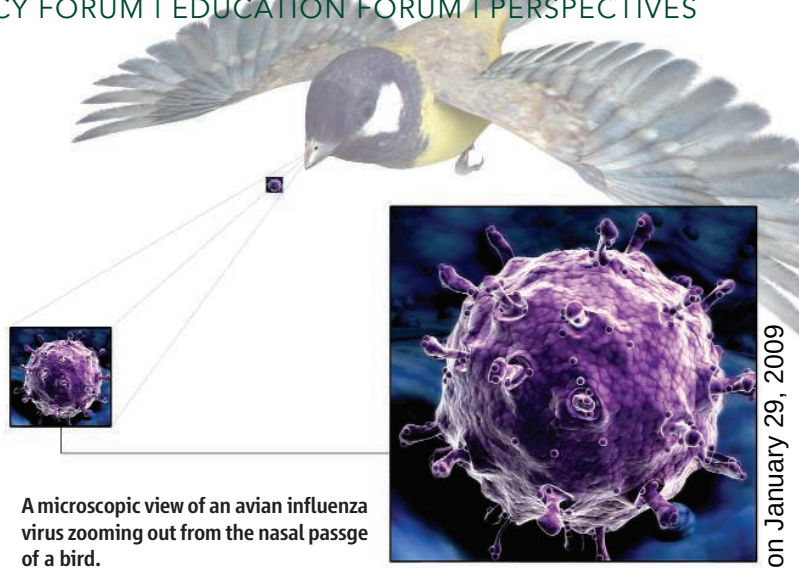
Veterinary Virologists Share Avian Flu Data

AVIAN INFLUENZA INFECTIONS CAUSED BY VIRUSES OF THE ASIAN HPAI H5N1 subtype have spread from East and Southeast Asia to Europe, the Middle East, and Africa. The virus is occurring in new ecosystems and infecting new hosts, resulting in novel host-pathogen interactions and genetic modifications. There is a lack of information on how the virus spreads across and within continents, including the role of wild birds. This hampers research into avian influenza, which is causing significant food security issues in developing countries, in addition to its pandemic potential.

Veterinary virologists have been working on avian influenza viruses for many years, and our collections of influenza virus isolates could be of great value to the international scientific community.

Within the Scientific Committee of OFFLU (the World Organization of Animal Health/United Nations Food and Agriculture Organization Network of Expertise on Avian Influenza), we have initiated the FLU-ID project. We will make available for genome nucleotide sequencing H5N1 contemporary isolates from several countries and relevant historical strains. This will be achieved in collaboration with the NIH Influenza Genome Project, and the full genetic sequences will be available in GenBank.

The Asian HPAI H5N1 virus is spreading very quickly. Real-time availability of genetic information is now possible and is essential for timely monitoring of viral evolution. These data will increase our knowledge of this pathogen and will help the appropriate selection of viral candidates for experimental studies, thus avoiding duplication of efforts and waste of resources.



A microscopic view of an avian influenza virus zooming out from the nasal passge of a bird.

We firmly believe that knowledge of the genetic profile of avian influenza viruses from animals is a prerequisite to understanding a complex disease that has already killed hundreds of millions of birds worldwide and that is threatening human lives. We are convinced that this initiative will contribute substantially to the efforts that are being carried out worldwide, and we invite other medical and veterinary virologists to join us.

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Investigating a Second Thymus in Mice

IN THE REPORT "EVIDENCE FOR A FUNCTIONAL second thymus in mice" (14 Apr., p. 284; published online 1 Mar.), G. Terszowski *et al.* provide definitive evidence that, as in a number of other species, the mouse has a cervical thymus in addition to the conventional thoracic one. In this regard, it is useful to remember what Law told us at a meeting held in 1964 (*1*):

"The completeness of thymectomies was always checked at necropsy by inspection with a dissecting microscope and by histologic sections taken from the upper mediastinum. Nevertheless many mice, particularly those of the BALB/c strain, developed normally, after a transient loss in weight and lymphopenia; at necroscopy remnants of the thymus tissue were not found. Since it is known that ectopic thymus tissue may be found within the thyroid, serial sections of the thyroid were often made, and thymus tissue was found in the region of the parathyroid area." (*2*).

Law's group did not have the sophisticated technical tools to prove that the ectopic cervical thymus produced lymphocytes in the same way as the thoracic thymus. But a close look at the picture they published does show lymphocytes and a demarcation between medulla and cortex, suggesting that the cervical thymus could at least function in organizing itself as the thoracic one. In my early work with neonatally thymectomized mice, I found that mice of the Balb/c strain were not as adversely affected by neonatal thoracic thymectomy as mice of other strains (*2*). As Law suggested, this could well have been due to the existence of an ectopic cervical thymus—indirect evidence that such an ectopic tissue was indeed functional. Although this may be so, I have never believed that neonatal thoracic thymectomy could be associated with a complete absence of all thymus-derived lymphocytes (now known as T cells).

Thoracic thymectomy at 4 to 6 weeks of age prevented leukemia induced by x-irradiation in C57BL mice and by carcinogenic hydrocarbons in DBA/2 mice (*3*). In my own leukemia work, thoracic thymectomy at 4 to 5 weeks of age completely prevented leukemia in C3Hf mice that had been inoculated at birth with the Gross virus, and grafting neonatal thoracic thymus tissue as late as 6 months after thymectomy restored leukemia development in inoculated mice (*4*–*6*). From these findings, one might surmise that the cervical thymus is not susceptible to leukemogenesis. A more likely possibility, however, is that

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for leukemia development, the cervical thymus is too small to be relevant. Here it is worth noting that T cell export from the thoracic thymus is proportional to the total thymic mass (*7*) and that according to Terszowski *et al.*, the cellularity of the cervical thymus is only 1/500th of that of the thoracic thymus.

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Response

WE THANK MILLER FOR THE INTERESTING POINTS he raises and his historical perspective. Miller claims that a meeting report from 1964 by Law *et al.* (*1*) provided "indirect evidence that such an ectopic tissue was indeed functional." Law *et al.* presented a histological section from a mouse neck described as "thymus tissue located at the site of the parathyroid gland" (*1*). A histological section cannot provide conclusive evidence that the observed tissue was a T cell–producing thymus.

In hindsight, for contemporary immunologists, the Law *et al.* data could have presented a worthwhile starting point to conclusively address the possibility that mice have functional thymus in their neck. "Tools to prove that the ectopic cervical thymus produced lymphocytes in the same way as the thoracic thymus" have been available for more than 20 years. We were, however, unaware of the histological section reported in 1964. A simple explanation for why cervical thymus tissue was ignored for more than 40 years is that it was considered nonfunctional. Now, Miller writes that "it had been known for decades that BALB/c mice have an ectopic cervical thymus" (*2*). This is a surprisingly late statement given that, throughout the years, thoracic thymectomy was a major tool to study the role of the thymus in immunology, and given the possibility that cervical thymi were not restricted to BALB/c mice.

We are less concerned about the possibility that T cells can be generated prior to thoracic thymectomy. It is the issue of the de novo generation of T cells after thoracic thymectomy that is relevant in the light of cervical thymi. Many investigators have been concerned about the completeness of the surgical removal of the thoracic thymus. As a result, the thoracic cavity is often reexamined at the end of the experiments [e.g., (*3*)]. We have suggested that functional cervical thymus may provide an alternative explanation for ongoing thymopoiesis after thoracic thymectomy.

With regard to leukemogenesis, Miller proposes that the cervical thymus is not susceptible, or too small to be relevant for leukemia development. While this may be the case, the primary function of the thymus is to support the body with immunologically functional T cells, and, as far as we can tell, the cervical thymus is not too small to do that.

Notably, further differences exist comparing Miller's view and our own data. First, the anatomical positions of neck thymi throughout the ventral region of the mouse neck (fig. 1R in our Report) are quite distinct from the exclusive location in the vicinity of the parathyroid. Second, cervical thymi are not restricted to BALB/c mice. Third, the cervical thymus, although in major aspects a "pocket version" of the chest thymus, shows some special features such as its developmental delay until after birth and a different ratio of mature to immature thymocytes. Further experiments will be required to fully elucidate the role of the bona fide neck thymus in mice.

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BDNF in Anxiety and Depression

ADAPTING THE SOCIAL DEFEAT PARADIGM DEVELoped by one of our groups (*1*), O. Berton and colleagues comprehensively evaluated the role of brain-derived neurotrophic factor (BDNF) in mouse social stress ("Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress," Reports, 10 Feb., p. 864). Although their molecular data convincingly link chronic social defeat to activated mesolimbic BDNF, their behavioral and pharmacological data might benefit from some reconsideration.

For example, social avoidance in 10-day stressed mice that lose BDNF (interpreted by Berton *et al.* as depression) more correctly resembles "social anxiety" in the original model, where evident depression developed only after 20 days of social stress (*1*). Unaltered anxiety (versus depression) cannot be confirmed by 2.5 mg/kg chlordiazepoxide, a dose insufficient to affect anxiety in most published studies using C57BL/6 mice (*2*, *3*). Moreover, reduced avoidance produced by chronic administration of antidepressants is not specific to depression, but is more likely due to their well-known anxiolytic effects in animals and humans (*4*, *5*).

Indeed, other data implicate BDNF in animal and human anxiety (*6*–*9*). Consistent with this, we have recently shown that loss of one BDNF gene allele increases anxiety in serotonin transporter (SERT) knockout mice (*10*). Implying that both BDNF and serotonergic systems interact in modulation of anxiety, these data may explain anxiogenic effects of social defeat corrected by SERT-modulating drugs. In addition, BDNF signaling improves both short-term and long-term memory (*6*, *9*)—a phenomenon that may also contribute to the learned social aversion reported by Berton *et al.*

Finally, although Berton *et al.* suggest that BDNF inactivation leads to antidepressant effects, there are numerous data on opposite, antidepressant effects of BDNF in brain (*11*–*13*). Clearly, further studies are necessary to examine the role of BDNF in stress responses. Modeling transitions from anxiety to depression (*1*), use of longer social and nonsocial stressors, and specific targeting of neuromediatory systems beyond dopamine may help further elaborate BDNF's important role in brain stress-related disorders.

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Response

KUDRYAVTSEVA AND HER COLLEAGUES HAVE made significant contributions in developing the social defeat paradigm in mice (*1*). Our work was also influenced by earlier research demonstrating that social defeat in mice induces lasting submissiveness or social avoidance upon sensory exposure to a nonaggressive animal (*2*). We essentially repeated these earlier findings and went on to show that social avoidance, induced by repeated social defeat, is an extremely durable phenomenon, which can be normalized by chronic, but not acute, treatment with antidepressants. We agree with Kalueff *et al.* that the duration of the chronic social defeat, which was not addressed in our study, is a critical dimension for future investigations.

Kalueff *et al.* raise an important point concerning the human syndrome to which social defeat paradigms have the most relevance. The

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persistent social avoidance induced by chronic social defeat stress could be relevant to several human syndromes, including depression, social phobia (anxiety), and post-traumatic stress disorder. The distinction between anxiety and depression is not well understood (*3*): Anxiety and depression syndromes share several overlapping symptoms. Our demonstration that chronic antidepressant administration reverses the persistent social avoidance induced by social defeat could be consistent with any of these clinical syndromes, all of which show some responsiveness to antidepressants. We also showed that chlordiazepoxide, given acutely or chronically, does not reverse this social avoidance, but this finding does not clarify the distinction between anxiety and depression because benzodiazepines are ineffective for the long-term treatment of any of these syndromes. Much more work is needed in humans to identify bona fide etiologic and pathophysiologic subtypes of these syndromes before we can appreciate with any confidence which syndrome is closest to social defeat in mice.

It should not be surprising that a molecule like BDNF, and many others, exert different or even opposite effects on behavior depending on the neural circuitry in question. There is indeed considerable evidence for antidepressant-like effects of BDNF in hippocampal circuits (*3*–*6*), but also growing evidence for prodepression-like effects in the mesolimbic dopamine system [our Report; (*7*, *8*)]. This underscores the importance of establishing the molecular underpinnings of complex behavior within the context of carefully delineated neural circuits in the brain. The selective knockout of BDNF within the mesolimbic dopamine circuit, accomplished in our study by use of viral-mediated expression of Cre recombinase within a highly discrete brain region, provides one exciting tool with which to accomplish this critical task for psychiatric neuroscience.

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Stardust Mission Results: Hot in Cold

THE NEWS OF THE WEEK ARTICLE "MINERALS point to a hot origin for icy comets" by R. A. Kerr (17 Mar., p. 1536) highlighted the recent results from the Stardust mission, which sampled dust from comet Wild 2. The subsequent finding that a major portion of the dust was crystalline and had formation temperatures in excess of 1400 K appears to be surprising, because comets are icy objects that formed some 5 to 40 Astronomical Units (AU) from the sun and were never exposed to such temperatures.

This "hot" in "cold" structure suggests that some solar nebula material was processed in the hot, innermost regions of the solar nebula and transported to the cooler outer regions. Supporting evidence for this idea is provided by observations of young stellar objects (YSOs), which indicate that similar crystalline dust is formed in the inner disk regions, within 1 or 2 AU of a star (*1*).

It was first suggested in 1990 (*2*) that crystalline olivine dust could have formed in an early solar bipolar outflow and was then transported to other regions of the solar nebula. These high-speed jets are produced from and flow perpendicular to the inner regions of the disks that surround young stars. They may exist for millions of years and typically eject about 10% of the material that accretes onto a star (*3*). A solar mass ($M_\odot$) YSO will subsequently eject around 0.1 $M_\odot$ of material of which 10^{-3} $M_\odot$ will probably be "rock-like." If only 10% of this rock-like material falls back to the nebula, then we have 10^{-4} $M_\odot$ of high-temperature, processed material in the solar nebula, an amount that is approximately equal to the total rock mass of the Solar System (*4*). This argument (*5*) plus other lines of evidence suggest that a significant portion of the dust in the solar nebula may have been processed by a solar jet (*6*, *7*).

The Stardust results are consistent with this jet flow model, which may provide a potentially coherent and predictive framework for understanding the formation and transport of rocky material in the solar nebula.

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Show Me the Dog

THE NEWS FOCUS ARTICLE "NEW SIGNS OF ANcient life in another martian meteorite?" (R. A. Kerr, 31 Mar., p. 1858) repeats the allegation that the 1911 Nakhla meteorite fall in Egypt killed a dog. Kevin Kichinka argues persuasively that this is more likely fiction than fact (*1*). The essence of the argument is that there is no corroboration of the "dog" story and that the stones fell around the town of El Nakhla el Baharia and none fell on Denshal, where the dog is reported to have been struck. So, no dog, no tail—er, tale.

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CORRECTIONS AND CLARIFICATIONS

News of the Week: "Genomes throw kinks in timing of chimp-human split" by E. Pennisi (19 May, p. 985). Contrary to what was stated in the article, Innan's analysis neither supported nor refuted hybridization between chimp and human ancestors.

Reports: "Chronology for the Aegean Late Bronze Age 1700–1400 B.C." by S. W. Manning *et al.* (28 Apr., p. 565). There was an error in the acknowledgment note (*47*). The correct full name for NERC is the Natural Environmental Research Council.

Special Section on Influenza: Perspectives: "Predictability and preparedness in influenza control" by D. J. Smith (21 Apr., p. 392). In reference (*8*), the journal is incorrect. The reference should read "C. E. Mills, J. M. Robins, C. T. Bergstrom, M. Lipsitch, *PLoS Med.* **3**, e135 (2006)."

Research Articles: "Atomic description of an enzyme reaction dominated by proton tunneling" by L. Masgrau *et al.* (14 Apr., p. 237). There was an error in Fig. 2C. The intermediate labeled as "VI" should have been labeled "VII."

2005 Visualization Challenge: "Photography" by C. Gramling (23 Sept. 2005, p. 1991). The First Place image "Autumn Color, Estonian Bog" should also have been credited to Susan W. Aber of Emporia State University. (This credit has been corrected in the HTML version of the article on *Science* Online.)

Research Articles: "Integration of spatial and temporal information during floral induction in *Arabidopsis*" by P. A. Wigge *et al.* (12 Aug. 2005, p. 1056). The ArrayExpress accession number was incorrect. It should be E-TABM-21.

Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 6 months or issues of general interest. They can be submitted through the Web (www.submit2science.org) or by regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.