References
1. L. Gabunia *et al.*, *Grabungsergebnisse Archaeolog. Korrespond.* **29/4**, 451 (1999).
2. L. Gabunia, *Jahr. RGZM* **39**, 185 (1992).
3. ——— and A. Vekua, *Nature* **373**, 509 (1995).

Early Mouse Models of Human Diseases

The News Focus article "The rise of the mouse, biomedicine's model mammal" by David Malakoff (14 Apr., p. 248) highlights the mouse as a mammalian model for human diseases, with the emphasis being on the provision of mouse strains and mutants by suppliers. In this otherwise fine survey of the role of the mouse as a prototype of human genetics and physiology, there is, however, little mention of the numerous mouse mutations as counterparts of human diseases that were already discovered in the early part of the 20th century. For instance, mouse pituitary dwarfism was discovered by Snell in 1929 (*1*). A^y, the top-dominant allele of the agouti coat color series, was discovered by the French geneticist Cuénot in 1905 (*2*). Many animals with the A^y gene become remarkably obese and thus offered an early model for human obesity (*3*). At least six genes were known early in the century to produce neurological and labyrinthine disturbances, the prototype being the Japanese waltzing mouse (*4*).

An outstanding resource that would have been valuable to mention is the volume by Hans Grüneberg titled *The Genetics of the Mouse* (*5*), a scholarly treatise about the mouse, including detailed descriptions of mouse mutants, gene action, genetic strains, and cancer genetics. It was first published in 1943 and enlarged greatly for the second edition in 1952, which includes more than 1700 references. Modern physiologists and geneticists should be aware of this gold mine of information about mouse mutants, many of which can still be obtained and studied using modern biochemical and molecular techniques. These mutants exhibit many abnormalities, including those in the central nervous system, the eye, blood and blood-forming organs, skin, and skeleton.

My criticisms should not detract from the thrust of the article, which is that the mouse should be recognized as the prime mammalian model of human genetics and physiology.

Frederick H. Kasten
Department of Anatomy and Cell Biology, James H. Quillen College of Medicine, East Tennessee State University, Johnson City, TN 37614–0582, USA. E-mail: fhkasten@mounet.com

References
1. G. D. Snell, *Proc. Natl. Acad. Sci. U.S.A.* **15**, 733 (1929).
2. L. Cuénot, *Arch. Zool. Exp. Gen.* (4e ser.) **3**, cxxiii (1905).
3. F. H. Kasten, *Science* **115**, 647 (1952).
4. R. M. Yerkes, *The Dancing Mouse* (Macmillan, New York, 1907).
5. H. Grüneberg, *The Genetics of the Mouse* (Martinus Nijhoff, The Hague, ed. 2, 1952).

Antipsychotics and Working Memory in Schizophrenia

Patients with schizophrenia suffer from substantial cognitive deficits, notably in the realm of memory functioning (*1*), which warrants considerable research efforts aimed at developing pharmacological treatment strategies. S. A. Castner, G. V. Williams, and P. S. Goldman-Rakic describe in their Report (17 Mar., p. 2020) the reversal of antipsychotic-induced working memory deficits in monkeys by stimulation of short-term dopamine D1 receptors. They suggest that the results of their study may have therapeutic implications for schizophrenia. However, the putative implications of their results for treatment of cognitive dysfunction in schizophrenia may be somewhat overstated.

Castner and colleagues propose that chronic haloperidol treatment should induce

Circle No. 28 on Readers' Service Card

severe working memory impairments. Although they cite some studies that reported haloperidol-induced cognitive impairment in patients with schizophrenia, most studies do not indicate that haloperidol influences cognitive function significantly, as three recent reviews of the literature have concluded (*2–4*). In a review on the adverse neurobiological effects of long-term use of neuroleptics, Jeste *et al.* conclude that "persistent cognitive impairment associated with long-term use of typical neuroleptics has not been well documented" (*5*, p. 201). In addition, two well-controlled studies that appeared after these reviews also indicate that haloperidol does not worsen working memory performance in schizophrenia patients (*6*, *7*). Indeed, in a multicenter, double-blind study with random assignment, Purdon *et al.* (*7*) observed a near-significant improvement on the Wisconsin Card Sorting Test (decline in number of perseverative errors) after 12 months of treatment with haloperidol (effect size −0.46, $P = 0.06$).

Castner and colleagues have provided strong evidence that haloperidol can induce working memory deficits in monkeys, which can be reversed by short-term dopamine D1 receptor stimulation. However, as haloperidol does not seem to impair working memory significantly in patients with schizophrenia, the clinical implications of their findings remain unclear.

André Aleman
Edward H. F. de Haan
Psychological Laboratory, Department of Psychonomics, Utrecht University, Heidelberglaan 2, 3584 CS, Utrecht, Netherlands

References and Notes

1. A. Aleman, R. Hijman, E. H. F. De Haan, R. S. Kahn, *Am. J. Psychiatry* **156**, 1358 (1999).
2. D. J. King, *Br. J. Psychiatry* **57**, 799 (1990).
3. A. M. Mortimer, *Pharmacol. Biochem. Behav.* **56**, 789 (1997).
4. T. Sharma, *Br. J. Psychiatry* **38** (suppl.), 44 (1999).
5. D. V. Jeste, J. B. Lohr, J. H. Eastham, E. Rockwell, M. P. Caligiuri, *J. Psychiatr. Res.* **32**, 201 (1998).
6. M. A. Lee, K. Jayathilake, H. Y. Meltzer, *Schizophr. Res.* **37**, 1 (1999).
7. S. E. Purdon *et al.*, *Arch. Gen. Psychiatry* **57**, 249 (2000).

Response

As noted by Aleman and de Haan, patients with schizophrenia suffer from substantial cognitive deficits, an observation that motivated the work on nonhuman primates described in our Report "Reversal of antipsychotic-induced working memory deficits by short-term dopamine D1 receptor stimulation." In our study we found that the typical antipsychotic drug, haloperidol, impaired working memory performance in normal monkeys, whereas according to the clinical literature, chronic haloperidol treatment tends to have only minimal or no effect on cognitive functioning in patients with schizophrenia. However, it was not our intention to suggest that the memory impairments in patients are necessarily due to their antipsychotic drug treatment. Rather, our study emphasized that conventional neuroleptics, such as haloperidol, appear to have a heretofore unrecognized, behaviorally relevant action at the D1 dopamine receptor, in addition to their well-known effect on the D2 dopamine receptor subtype.

We tested and confirmed the hypothesis that down-regulation of the D1 receptor produced by experimental means, in this case by chronic haloperidol treatment, might be associated with the emergence of cognitive impairment. Given the evidence from recent imaging studies (*1*) that D1 receptors are reduced in the prefrontal cortex of both medicated and unmedicated patients with schizophrenia, our results could have significant implications for cognitive dysfunction in this disorder in that the haloperidol-induced deficits were reversed by a selective D1 agonist. Thus, our findings suggest that, whether produced by chronic haloperidol treatment or an endogenous pathophysiological process, D1

with KPL's new Detector™ Systems!

Eliminate background and get consistent, publication-quality results blot after blot! With KPL's new, non-isotopic Detector Systems you can get sensitivity that rivals ^{32}P in far less time.

Choose from our full line of Detector Kits for DNA, RNA and protein detection. Detector Kits give superior performance by combining the sensitivity of chemiluminescence with KPL's optimized reagents.

KPL's Detector Kits
- Southern Blotting
- Northern Blotting
- Probe Labeling
- Western Blotting

Don't settle for mediocre blots. Try Detector Kits and let KPL clean up your assay! Contact us today and take advantage of our discount offer!

KPL
Your Detection Resource

© 2000 KPL

Call 800-638-3167 • 301-948-7755 • www.kpl.com

Circle No. 29 on Readers' Service Card

HUMAN EMBRYONIC AND FETAL TISSUE

- Exclusively for biomedical research at universities and nonprofit scientific institutions.
- The laboratory has studied normal and abnormal development and provided tissue for 35 years.
- Most tissues are available for study.
- Tissues can be supplied from most gestational stages and from normal or abnormal specimens.
- Immediate processing includes rapid fixation, LN_2, balanced salt or medium as requested.
- Tissues shipped nationwide by overnight air are suitable for molecular biology, enzymology, receptor study, electron microscopy, etc.

For further information:

Phone 800-583-0671
FAX 800-583-0668

Please include an abstract of proposed research, preferably on PHS 398.

Circle No. 9 on Readers' Service Card

receptor deficits could account for the cognitive impairments observed in schizophrenia or, in many cases, the lack of restitution of cognitive function in response to drugs. If this hypothesis is correct for even a subgroup of patients, then the finding that D1-mediated impairment can be reversed by a selective D1 agonist has clinical implications. Although our study supports an important role of the D1 receptor in optimizing cognitive function in the nonhuman primate, its role in schizophrenia or other conditions of dopamine deficiency, such as aging and Parkinson's disease, deserves further investigation.

Stacy A. Castner
Graham V. Williams
Patricia S. Goldman-Rakic
Section of Neurobiology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510, USA. E-mail: castner@kafka.med.yale.edu, graham.williams@yale.edu, and Patricia.goldman-rakic@yale.edu

References

1. Y. Okubo *et al.*, *Nature* **385**, 634 (1997).

CORRECTIONS AND CLARIFICATIONS

Letters: "Many modes of movement," letter by A. Carl Leopold (23 June, p. 2131). The second author of this letter, Mordecai J. Jaffe, was omitted as a result of an editorial error. He is at the Boyce Thompson Institute of Plant Research, Ithaca, NY 14853, USA.

News of the Week: "Penn report, agency heads home in on clinical research" by Eliot Marshall (2 June, p. 1558). It was incorrectly reported that a company in which the University of Pennsylvania and researcher James Wilson hold an interest (Genovo Inc. of Sharon Hill, Pennsylvania) supplied reagents for a gene therapy trial at the university. The university, not the company, provided the reagents.

Research Article: "Timing the ancestor of the HIV-1 pandemic strains" by B. Korber *et al.* (9 June, p. 1789). The Web address in reference 23 is missing a "~" character. The correct address is http://www.santafe.edu/~btk/science-paper/bette.html

Perspectives: "Absorbing phenomena" by S. E. and P. R. Buseck (12 May, p. 989). The source of the image on page 990 was reference 15, not reference 14 as stated in the credit.

ScienceScope: "Unconventional committee" (12 May, p. 941). Harvey Bialy's last name was misspelled.

DNA samples

DNA samples from a

global collection network

We can meet your sample needs from inventory or by exercising our Global Collection Network on your behalf. We are adding samples, disease states, and collection sites on a regular basis.

GenomicsCollaborative

has a growing collection of ***DNA*** *and* ***serum*** *matched to* ***phenotypic data*** *from patients with high prevalence diseases. These samples are available to support your research.*

Some examples of samples we currently have, and are actively collecting, in the following disease states are:

- *Cardiovascular disease (hyperdipidemia, hypertension, AMI stroke)*
- *Cancers (Breast, Ovarian, Colon, Prostate, Leukemia, Lymphoma)*
- *Diabetes*
- *Asthma*
- *Renal failure*

All material is:

- *Collected under IRB approved protocols and compliant with GCP*
- *Processed and stored under GCP conditions*

For information regarding our current inventory of samples and disease states please contact us.

GenomicsCollaborative

1-877-GENOMIX, extension 248 (877-436-6649)
email: getsamples@DNArepository.com
www.DNArepository.com

Circle No. 19 on Readers' Service Card