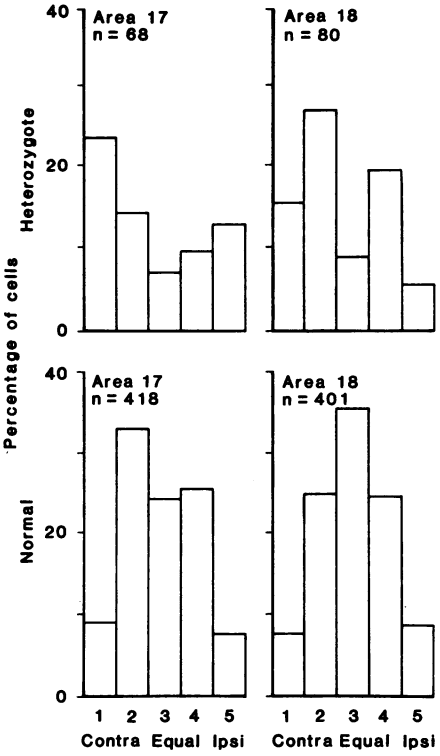
Fig. 3. Ocular dominance distributions of cells recorded within 15° of the representation of the vertical meridian in areas 17 and 18 of homozygous cats and of heterozygotes for albinism. Relatively few cells in areas 17 and 18 of heterozygotes are activated binocularly.



as the representation of the visual field in the LGNd and visual cortex, are abnormal in normally pigmented cats that are heterozygous for a recessive allele for tyrosinase-negative albinism. The retinal abnormalities we observed are similar to but less extreme than those reported for homozygous tyrosinase-negative albino and Siamese cats (*5, 6, 8, 10*). The abnormal representation of the visual field in areas 17 and 18 was close to the border between them. This is reminiscent of the pattern observed in the "Boston variety" of Siamese cats (*2–4*).

Our findings can be interpreted as evidence that the cause of the misdirected retinal projections in hypopigmented individuals is not related to reduced pigment in the retina but rather to some other unknown effect of a gene for albinism. However, the exact amount of retinal pigment in heterozygotes has not been quantified; it is possible that heterozygotes have a reduction in retinal pigment not revealed by qualitative inspection. Also, it may be that the time course of pigment production during development or some other effect of melanin pigment, not the amount of pigment produced, is critical for misrouting of retinal axons at the optic chiasm. Additional research is needed to clarify the mechanisms responsible for the visual system defects associated with albinism.

There are six well-characterized types of human oculocutaneous albinism, and evidence for several other types (*12*). Most common are types IA (tyrosinase-negative) and II (tyrosinase-positive). The frequency of type IA albinism in the United States is approximately 1:39,000 in the white population and 1:28,000 in the black population. The heterozygote frequency for this type of albinism is approximately 1 percent in the total population. The frequency of type II albinism is a little higher. Normally pigmented heterozygous individuals for these two types of albinism constitute approximately 2 percent of the population. If anomalies are also found in heterozygotes for type II albinism, then the frequency of individuals with abnormal optic projections would exceed 2 percent of the population (*13*). Thus our results suggest that visual anomalies similar to those in albinos may be present in the 1 to 2 percent of the human population carrying a recessive allele for albinism (*12*). While the functional significance of these abnormalities remains to be determined, the abnormal visual field representation and relatively low proportion of binocular cells in striate and extrastriate cortex of the heterozygote suggest an adverse effect on binocular depth perception (*14*). The presence of marked abnormalities in the heterozygote indicate that congenital nervous system defects associated with albinism (*15*), and possibly other genetically determined abnormalities, are far more widespread than previously believed.

References and Notes

1. C. L. Sheridan, *J. Comp. Physiol. Psychol.* **59**, 292 (1965); R. D. Lund, *Science* **149**, 1506 (1965); R. A. Giolli and M. D. Guthrie, *J. Comp. Neurol.* **136**, 99 (1969); R. W. Guillery, *Brain Res.* **14**, 739 (1969); R. W. Guillery and J. Kaas, *J. Comp. Neurol.* **143**, 73 (1971); D. Creel, *Nature (London)* **231**, 465 (1971a); *J. Comp. Physiol. Psychol.* **77**, 161 (1971b).
2. D. H. Hubel and T. N. Wiesel, *J. Physiol. (London)* **218**, 33 (1971).
3. J. H. Kaas and R. W. Guillery, *Brain Res.* **59**, 61 (1973); R. W. Guillery, *Sci. Am.* **230**, 44 (May 1974).
4. C. Shatz, *J. Comp. Neurol.* **171**, 205 (1977).
5. J. Stone, J. E. Campion, J. Liecester, *ibid.* **180**, 783 (1978).
6. M. L. Cooper and J. D. Pettigrew, *ibid.* **187**, 313 (1979).
7. M. L. Cooper and G. G. Blasdel, *ibid.* **193**, 237 (1980).
8. A. G. Leventhal and D. J. Creel, *J. Neurosci.* **5**, 795 (1985).
9. R. A. King and C. J. Witkop, *Am. J. Hum. Genet.* **29**, 164 (1977).
10. A. G. Leventhal, *J. Neurosci.* **2**, 1024 (1982).
11. J. Stone, B. Dreher, A. G. Leventhal, *Brain Res. Rev.* **1**, 345 (1979).
12. R. A. King and D. P. Olds, *Am. J. Med. Genet.* **20**, 49 (1985).
13. C. J. Witkop, Jr., W. C. Quevedo, Jr., T. B. Fitzpatrick, in *The Metabolic Basis of Inherited Disease*, J. B. Stanbury *et al.*, Eds. (McGraw-Hill, New York, ed. 5, 1983), pp. 301–346.
14. R. Blake and H. V. B. Hirsch, *Science* **190**, 1114 (1975).
15. G. Bock and K. Steel, *Hear. Res.* **13**, 201 (1984); J. Conlee, T. Parks, C. Romero, D. Creel, *J. Comp. Neurol.* **225**, 141 (1984); D. Creel, *Pharmacol. Biochem. Behav.* **12**, 969 (1980).
16. Supported by PHS grants EYO 4951 to A.G.L., NRSA EYO 5767 to D.J.V., and the Medical Research Service of the Veterans Administration.

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Glucocorticoids Potentiate Ischemic Injury to Neurons: Therapeutic Implications

Abstract. *Sustained exposure to glucocorticoids, the adrenocortical stress hormones, is toxic to neurons, and such toxicity appears to play a role in neuron loss during aging. Previous work has shown that glucocorticoids compromise the capacity of neurons to survive a variety of metabolic insults. This report extends those observations by showing that ischemic injury to neurons in rat brain is also potentiated by exposure to high physiological titers of glucocorticoids and is attenuated by adrenalectomy. The synergy between ischemic and glucocorticoid brain injury was seen even when glucocorticoid levels were manipulated after the ischemic insult. Pharmacological interventions that diminish the adrenocortical stress response may improve neurological outcome from stroke or cardiac arrest.*

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Glucocorticoids (GS's) are secreted by the adrenal cortex in response to stress; in adults they increase circulating energy substrates, stimulate cardiovascular tone, alter cognition, and inhibit costly anabolism such as growth, reproduction, and the immune and inflammatory responses (*1*). Although such actions are central to successful adaptation to acute physical stress, prolonged stress or hypersecretion of GC's has deleterious consequences, including myopathy, steroid diabetes, hypertension, infertility,

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and immunosuppression (*2*). It has become apparent that excessive GC's are also toxic to neurons because pharmacological doses of GC's produce hippocampal damage in the rat (*3*). Furthermore, the hippocampus loses neurons with age (*4–7*), and GC's are implicated in this process because adrenalectomy at midage prevents the loss of neurons while prolonged exposure to elevated GC titers exacerbates it (*5, 6*). The hippocampus is preferentially sensitive to these steroid effects, perhaps because it contains the highest concentration of GC receptors of any brain region.

Recent work has examined the mechanisms of GC neurotoxicity in the hippocampus. Two neurotoxins that preferentially damage the hippocampus by different mechanisms—kainic acid, an excitotoxin, and 3-acetylpyridine, an antimetabolite—are both more damaging in rats exposed to high GC titers and less damaging in adrenalectomized rats (*8*). This suggests that the highly catabolic GC's induce a general metabolic vulnerability in these neurons and thus compromise their ability to survive various toxic insults (*8*). In the present report, we have extended these observations by demonstrating that elevated GC titers enhance and adrenalectomy attenuates ischemic damage to brain neurons.

Experimental and clincial ischemic brain damage can present several distinct morphological patterns depending on the particular conditions of the hypoxia-ischemia (*9, 10*). Cerebral infarction, which is typically associated with prolonged, focal brain ischemia, is characterized by irreversible damage to neurons, glia, and other supporting cell types in brain. In contrast, transient global ischemia, such as that accompanying cardiac arrest and resuscitation, principally injures specific populations of neurons known to be highly vulnerable to ischemia. The pyramidal cells in the CA1 zone of the hippocampus, small- and medium-sized neurons in the striatum, neocortical neurons in layers 3,5, and 6, and the cerebellar Purkinje cells are among those neurons most susceptible to ischemic injury. We elected to test the effect of GC's in an animal model of ischemia in which only populations of selectively vulnerable neurons are injured (*10, 11*) so that the interaction between ischemia and GC's could be compared in populations of neurons with high or low concentrations of GC receptors.

Male Wistar rats weighing 250 to 350 g were deprived of food overnight and then subjected to 20 minutes of forebrain ischemia by means of the four-vessel occlusion method (*11*). Blood flow was reestablished to the brain by release of the carotid artery clasps, and the rats were randomly divided into three groups. (i) Ten animals were sham-adrenalectomized and injected subcutaneously with 10 mg of corticosterone (the GC of the rat) at the time of reperfusion and every 24 hours thereafter (CORT group). Corticosterone was dissolved in sesame oil, which releases the steroid slowly and elevates circulating titers for up to 20 hours (*6*) to levels observed after major stress. (ii) Ten rats were adrenalectomized within 3 minutes of reperfusion and allowed free access to 0.9 percent NaCl solutions as drinking water (ADX group). Given a half-life of circulating corticosterone of approximately 15 minutes (*12*), blood titers would be below 1 μg per 100 ml within 90 minutes of adrenalectomy, even in rats subjected to the stress of ischemia. (iii) Ten rats were sham-adrenalectomized and injected subcutaneously with vehicle [intact group (INT)]. Two rats each from the CORT and INT groups and three rats from the ADX group developed seizures after cerebral reperfusion and died; all remaining animals showed no behavioral signs of convulsions.

At 72 hours after cerebral reperfusion, the animals were killed either by decapitation or by perfusion-fixation with formaldehyde–acetic acid–methanol (1:1:8). Both sets of brains were processed, sectioned, and stained (*13*) for examination with a light microscope. Regional neuronal injury was graded independently in each hemisphere without examiner knowledge of the experimental conditions on a scale of 0 to 3, where 0 represents normal brain, 1 represents 1 to 10 percent damaged neurons, 2 represents 11 to 50 percent damaged neurons, and 3 represents greater than 50 percent damaged neurons (*11, 14, 15*). Irreversible damage was concluded to have occurred in neurons showing ischemic cell change or homogenizing change (*9*). A χ^2 analysis of the numbers of hemispheres showing each category of damage was used to determine whether there was an overall treatment effect. Mann-Whitney tests with correction for tie scores were then used to determine whether this was due to corticosterone administration or to adrenalectomy.

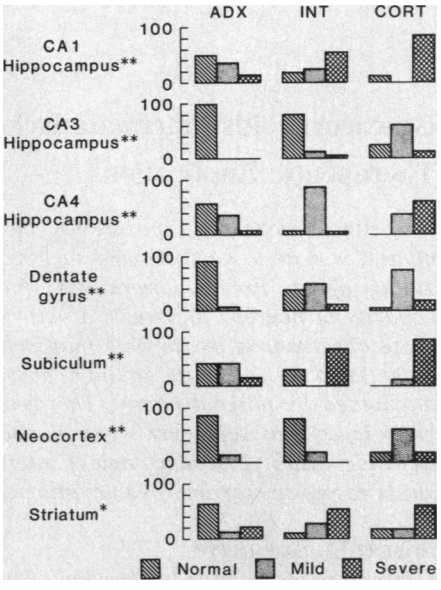

Fig. 1. Regional brain damage in rats subjected to 20 minutes of forebrain ischemia and 72 hours of postischemia reperfusion. Abbreviations: ADX, adrenalectomized rats (n = 7); INT, intact rats (n = 8); CORT, corticosterone-treated rats (n = 8). Brain damage is expressed as the percentage of total hemispheres (ADX, 14; INT, 16; CORT, 16) that were normal (grade 0) or had mild (grade 1) or severe (grades 2 to 3) damage. (*) $P < 0.05$, (**) $P < 0.01$ indicate a significant treatment effect (two-tailed χ^2 analysis).

In all brain regions examined, the severity of damage after hypoxic-ischemic injury varied significantly as a function of corticosterone levels (two-tailed χ^2 test; $P < 0.05$ for striatum, $P < 0.01$ for all other brain regions) (Figs. 1 and 2). Prolonged elevation of corticosterone titers to a level observed during major stress significantly enhanced damage (relative to intact animals) in the subiculum, CA3 and CA4 zones of the hippocampus, and neocortex (two-tailed Mann-Whitney test; Z = 2.2, 2.6, 2.9, and 3.2, respectively; $P < 0.05$, 0.01, 0.01, and 0.01, respectively). Comparisons were made in anterior dorsal hippocampus; data from posterior dorsal hippocampus were quantitatively similar. Conversely, adrenalectomy in the immediate aftermath of ischemia was protective of neurons because ADX rats had significantly less damage compared to intact animals in the subiculum, CA1 and CA4 zones of the hippocampus, dentate gyrus, and striatum (Z = 2.2, 2.5, 2.3, 2.6, and 2.5, respectively; $P < 0.05$, 0.05, 0.05, 0.01, and 0.05, respectively).

A number of possible mechanisms by which glucocorticoids could endanger neurons in the aftermath of hypoxia-ischemia can be eliminated. Differences in the severity of ischemia between the three groups of animals cannot account for the corticosteroid effect because the animals were randomized and the GC levels manipulated after cerebral recirculation. The effect of altered circulating CG's on cerebral blood flow in animals after ischemia is currently unknown.

However, physiological variables showed only minor (arterial oxygen tension) or nonsignificant differences (mean arterial pressure, carbon dioxide tension, *p*H, body temperature, and hematocrit) between rats given corticosterone or adrenalectomy after ischemia (*16*). These data suggest that the observed corticosteroid effect is not attributable to altered respiratory or cardiovascular mechanisms. Finally, GC-induced hyperglycemia (*16*) is unlikely to be an important factor in this phenomenon because elevation of blood and brain glucose levels after reperfusion of previously ischemic brain does not alter the severity of ischemic brain damage (*14*).

Whether the augmentation of ischemic brain injury by corticosterone is receptor-mediated is unclear. GC receptors are concentrated in the hippocampus more heavily than in other brain regions (*17*), and there is evidence that their concentrations correlate with the capacity of GC's to modulate neuronal injury through kainic acid and 3-acetylpyridine (*8*). However, our results show that, although GC potentiation of ischemic injury was most pronounced in the hippocampus, GC's also modulated damage in the striatum and neocortex, which are regions with low to moderate concentrations of GC receptors (*17, 18*). It is possible that, after transient ischemia, surviving neocortical and striatal neurons are sufficiently compromised that even minimal receptor-mediated GC effects could tip the balance toward irreversible injury. Alternatively, GC's may act on injured neurons in a non–receptor-mediated fashion (for example, by being incorporated into cell membranes and altering membrane fluidity or resistance). Although precedence for such GC action exists, it is considered to represent only a minor route of action (*19*).

Regardless of the precise mechanisms of action, GC's appear to induce a general vulnerability in brain neurons because they impair the ability of neurons to survive after various metabolic insults, including injections of kainic acid and 3-acetylpyridine. Kainic acid is thought to interact with the glutamate neurotransmitter system, and 3-acetylpyridine disrupts the electron transport chain and inhibits synthesis of adenosine triphosphate (ATP). Ischemic injury to neurons is likely to result from a combination of molecular abnormalities including ATP depletion (*20*), disturbed excitatory amino acid effects (*10, 21*), and accumulation of intracellular calcium (*20, 22*). With regard to the last abnormality, corticosteroids may influence calcium influx at the synapse (*23*) and thereby modulate postsynaptic neuronal injury.

Ischemic injury to selectively vulnerable neurons in animals progresses for many hours (in the striatum) to days (in the neocortex and hippocampus) after the restoration of cerebral blood flow (*15*). The implication of these data is that neurons remain viable for prolonged periods after transient ischemia and eventually succumb to events initiated by reperfusion of the brain. Our results support this notion in that modification of GC titers after the ischemic interval significantly altered the final outcome of brain injury.

A number of clinical implications emerge from this study. Glucocorticoid treatment of ischemic brain infarction and edema in experimental animals and in humans has in most instances showed no beneficial effect (*24*); in several instances the outcome was worse in the GC-treated subjects (*24*). Our results indicate that GC's must be used with the greatest caution in the clinical treatment of ischemic brain edema.

The nature of the experimental brain injury reported here is similar to the brain injury associated with cardiac arrest and resuscitation. It was shown that the stress of focal brain ischemia (stroke) elevated circulating GC levels (*25*), and it is likely that stress in the aftermath of global brain ischemia (cardiac arrest) will do the same. Thus, what is currently viewed as "expected" neuronal damage in response to focal or global ischemia may, in fact, represent ischemic damage worsened by the acute hypersecretion of glucocorticoids. Should our finding that the GC milieu can modify brain injury minutes to hours after transient ischemia prove to be relevant to humans, then transient inhibition of corticosteroid synthesis or treatment with GC-receptor antagonists may be effective in lessening clinical brain damage from stroke or cardiac arrest.

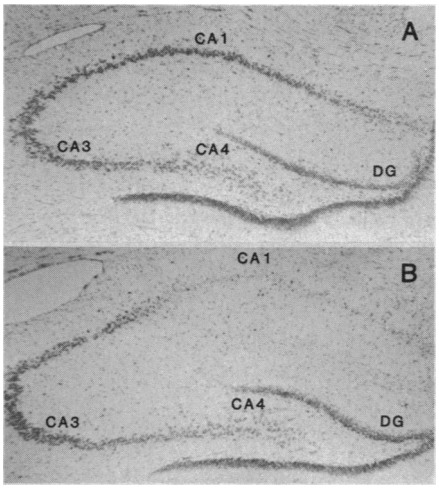

Fig. 2. Representative low-power photomicrographs of dorsal hippocampus from animals in the ADX(A) and CORT(B) groups subjected to 20 minutes of forebrain ischemia and 72 hours of postischemic reperfusion. The pyramidal zones CA1, CA3, and CA4 are labeled; DG, dentate gyrus. Neurons were mostly preserved (grade 1) in the CA1 zone in (A) and were virtually completely lost (grade 3) in (B). These sections were taken from brains fixed in formaldehyde–acetic acid–methanol and stained with cresyl violet.

References and Notes

1. F. Yates, D. Marsh, J. Maran, in *Medical Physiology*, V. Mountcastle, Ed. (Mosby, St. Louis, 1980), pp. 1558–1601; A. Munck, P. Guyre, N. Holbrook, *Endo. Rev.* **5**, 25 (1984); T. Cupps and A. Fauci, *Immunol. Rev.* **65**, 133 (1982).
2. D. Krieger, *Cushing's Syndrome* (Springer-Verlag, Berlin, 1982), pp. 1–142.
3. K. Aus der Muhlen and H. Ockenfels, *Z. Zellforsch.* **93**, 126 (1969).
4. P. W. Landfield, L. Braun, T. Pitler, J. Lindsey, G. Lynch, *Neurobiol. Aging* **2**, 265 (1981); K. Brizzee and J. Ordy, *Mech. Aging Dev.* **9**, 143 (1979).
5. P. W. Landfield, R. K. Baskin, T. A. Pitler, *Science* **214**, 581 (1981); R. M. Sapolsky, L. C. Krey, B. S. McEwen, *Proc. Natl. Acad. Sci. U.S.A.* **81**, 6174 (1984).
6. R. M. Sapolsky, L. C. Krey, B. S. McEwen, *J. Neurosci.* **5**, 1222 (1985).
7. ———, T. C. Rainbow, *ibid.* **4**, 1479 (1984).
8. R. M. Sapolsky, *ibid.* **5**, 1228 (1985); *Brain Res.*, in press.
9. J. B. Brierley, in *Greenfield's Neuropathology*, W. Blackwood and J. A. N. Corsellis, Eds. (Arnold, London, 1976), pp. 43–85.
10. W. A. Pulsinelli, *Prog. Brain Res.*, **63**, 1 (1985).
11. ——— and J. B. Brierley, *Stroke* **10**, 267 (1979); W. A. Pulsinelli and T. E. Duffy, *J. Neurochem.* **40**, 1500 (1983). All surgical procedures were performed under 2 to 3 percent halothane anesthesia. The vertebral arteries in the anesthesized rats were electrocauterized, a ligature to occlude collateral blood vessels was inserted through the neck, and reversible clasps were placed around both common carotid arteries without interrupting carotid blood flow. Twenty-four hours later, severe forebrain ischemia was produced by tightening the carotid artery clasps and the cervical ligature. Cerebral blood flow was restored 20 minutes later by releasing the carotid clasps.
12. R. M. Sapolsky, L. C. Krey, B. S. McEwen, *Exp. Gerontol.* **18**, 55 (1983).
13. The brains from decapitated rats were rapidly removed and frozen in dry ice. Two animals in each group were anesthesized and killed by perfusion-fixation with formaldehyde–acetic acid–methanol. The frozen brains were sectioned (20 μm) in a cryostat, dried on a hot plate, and then fixed in 95 percent ethanol. The perfusion-fixed brains were sectioned (7 μm) after they were embedded in paraffin. Brain sections from all animals were stained with hematoxylin and eosin; only those sections obtained from the perfusion-fixed brains and intended for photography were stained with cresyl violet.
14. W. A. Pulsinelli, S. Waldman, D. Rawlinson, F. Plum, *Neurology* **32**, 1239 (1982).
15. W. A. Pulsinelli, J. B. Brierley, F. Plum, *Ann. Neurol.* **11**, 491 (1982); T. Kirino, *Brain Res.* **239**, 57 (1982).
16. These data are available upon request from the authors. Blood sugar values ranged from 175 ± 24 to 220 ± 25 mg/dl (mean ± standard error of the mean) in CORT animals throughout the first 24 hours after reperfusion; blood sugar in ADX animals ranged between 86 ± 9 and 148 ± 17 mg/dl.
17. B. S. McEwen, in *Curr. Top. Neuroendocrinol.* **2**, 23 (1982).
18. C. Defiore and B. Turner, *Brain Res.* **278**, 93 (1983).
19. J. Baxter and G. Rosseau, in *Glucocorticoid Hormone Action*, J. Baxter and G. Rosseau, Eds. (Springer-Verlag, Berlin, 1979), pp. 1–12.
20. B. K. Siesjo, *J. Cereb. Blood Flow Metab.* **1**, 155 (1981).

21. A. Francis and W. A. Pulsinelli, *Brain Res.* **243**, 271 (1982); R. P. Simon *et al.*, *Science* **226**, 850 (1984); W. A. Pulsinelli, *Stroke* **16**, 144 (1985).
22. W. K. Hass, in *Cerebral Vascular Disease*, J. S. Meyer *et al.*, Eds. (Excerpta Medica, Amsterdam, 1981), pp. 3–17.
23. P. Sze, *Am. Soc. Neurochem. Abst. 225* (1985).
24. D. Anderson and R. Crawford, *Stroke* **10**, 68 (1979); F. Plum, E. Alvard, J. Posner, *Arch. Neurol.* **9**, 571 (1963); M. Dyken and P. White, *J. Am. Med. Assoc.* **162**, 1531 (1956).
25. J. H. Feibel, P. M. Hardi, R. G. Campbell, M. N. Goldstein, R. J. Joynt, *J. Am. Med. Assoc.* **238**, 1374 (1977).
26. We thank B. McEwen and F. Plum for helpful suggestions. Supported by NIH grant NS-03346 and by a postdoctoral grant from the National Institute of Aging (R.S.). R.S. is a Mathers Fellow of the Life Science Research Foundation.

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Persistent Noncytopathic Infection of Normal Human T Lymphocytes with AIDS-Associated Retrovirus

Abstract. *Infection of normal peripheral blood T cells by the acquired immune deficiency syndrome (AIDS)–associated retrovirus (ARV) was evaluated in long-term cultures of helper-inducer T cells (T4 cells). Cells that were inoculated with ARV and maintained in medium supplemented with interleukin-2 remained productively infected with this virus for more than 4 months in culture, although they showed no cytopathic effects characteristic of acute ARV infection. The presence of replicating virus was demonstrated by reverse transcriptase activity of culture fluids and by viral antigens and budding particles detected on cells by immunofluorescence and electron microscopy. Virus produced in these cultures remained infectious and could induce cytopathic effects and viral antigens in uninfected lymphoid cells. The finding that normal lymphocytes may be productively infected by an AIDS retrovirus in the absence of cell death suggests that a range of biologic effects may occur after infection in vivo.*

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A group of newly recognized human retroviruses termed lymphadenopathy-associated virus (LAV) (*1*), human T-cell lymphotropic virus type III (HTLV-III) (*2*), or AIDS-associated retrovirus (ARV) (*3*) has been strongly implicated in the etiology of the acquired immune deficiency syndrome (AIDS). This disease is clinically characterized by the progressive loss of T lymphocytes of the helper phenotype (T4 lymphocytes), as defined by the monoclonal antibodies OKT4 or Leu-3a (*4*). These AIDS-associated retroviruses have shown a tropism for T4 lymphocytes in vitro, possibly through a specific interaction with the 62,000 molecular weight glycoprotein antigen CD4 (*5–8*). Infection of T4 cells with these viruses results in cell death. This observation supports the role for these viruses in the pathogenesis of AIDS (*3, 5, 9*). However, in view of the prolonged period between viral exposure and disease (*10*), as well as the functional abnormalities in isolated T4 cells from patients with AIDS (*11*), the possibility exists that noncytotoxic infection of T4 cells may also occur. Such an observation has been made for established T-cell lines (*3, 9*). To evaluate more fully the range of biologic effects that follow viral infection, we evaluated infection of normal human T4 lymphocytes by ARV and report the stable production of this virus in long-term cultures of these cells.

The experimental conditions and results are summarized in Fig. 1. T lymphocytes were enriched for T4 cells by affinity chromatography and cultured in phytohemagglutinin (PHA) for 3 days. Cells were then incubated for 4 hours with filtered fluid containing ARV-2 (*3, 12*), washed, and suspended in medium supplemented with lectin-free interleukin-2 (IL-2; 10 percent by volume). Cytopathic effects, including the presence of multinucleated cells and degenerative cellular forms characteristic of acute ARV (or HTLV-III/LAV) infection (*3, 5, 9*), were observed between 5 and 12 days after the addition of virus. The presence of retrovirus was documented during this period both by reverse transcriptase (RT) activity in culture supernatants and by ARV antigens detected in lymphocytes by immunofluorescence (IFA) (*3, 12*); for the latter assay, serum from a patient with AIDS-related complex was used as a source of antibody. Up to 35 percent of cells showed viral antigens by IFA at this time. Simultaneously, more than 90 percent of these lymphocytes ceased to react with the OKT4 monoclonal antibody, as has been described for other T4-positive lymphocytes and cell lines infected with the AIDS retrovirus (*5, 6, 12*). Control (uninfected) T4 cells cultured under identical conditions continued to show more than 85 percent

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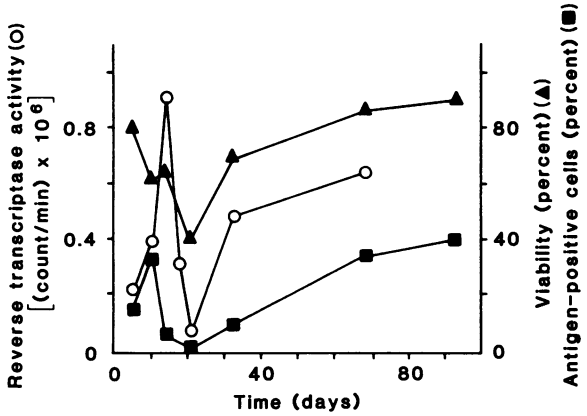

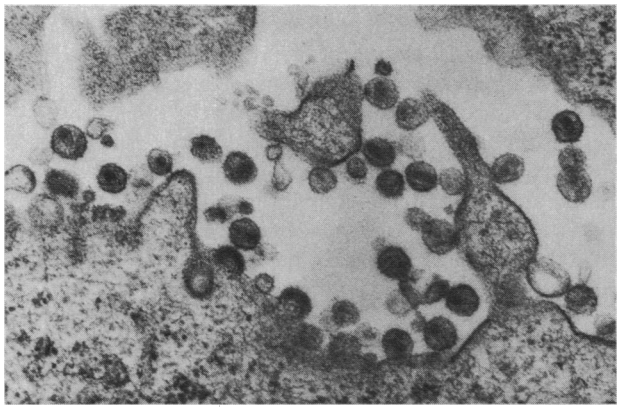

Fig. 1 (left). Persistance of ARV infection in cultures of T4 lymphocytes (*15*). Results of a representative experiment are shown. Fig. 2 (right). Electron micrograph of ARV-infected T4 cells from long-term cultures. T cells 93 days after infection with ARV-2 are shown (× 90,000); the numerous budding and mature particles are characteristic of ARV.