proof of the existence of presynaptic as opposed to remote postsynaptic inhibition. However, we think that, when all the facts reported above are considered together, it becomes very difficult to escape the conclusion that presynaptic inhibition is operative here and that it functions to protect the first synapse of the reflex pathway from depression during tail-flip responses, thereby protecting the animal from maladaptive habituation.

The theoretical possibility of a protective mechanism based on presynaptic inhibition would be predicted from most currently favored explanations of presynaptic inhibition and synaptic depression (*17*). Similarly, protection from postsynaptic potentiation and temporal facilitation seem theoretically possible, and the latter has been found (*18*).

We believe the importance of these observations to be twofold. (i) Intrinsic changes of synaptic efficacy which play an important role in normal functioning are not obligatory. There are mechanisms which can operate to prevent them specifically when they would be maladaptive. (ii) The role of presynaptic inhibition in achieving such regulation of inherent plasticity suggests a new and perhaps rather general function for presynaptic inhibition in the nervous system.

FRANKLIN B. KRASNE
JOAN S. BRYAN

Department of Psychology,
University of California,
Los Angeles 90024

References and Notes

1. R. S. Zucker, D. Kennedy, A. I. Selverston, *Science* **173**, 645 (1971); R. S. Zucker, *J. Neurophysiol.* **35**, 599, 621, 638 (1972).
2. D. Kennedy, *Physiologist* **14**, 5 (1971).
3. A. I. Selverston and M. P. Remler, *J. Neurophysiol.* **35**, 797 (1972).
4. F. B. Krasne, *J. Exp. Biol.* **50**, 29 (1969); J. J. Wine and F. B. Krasne, *Proc. 77th Ann. Conv. Amer. Psychol. Ass.* (1969), p. 237.
5. J. J. Wine and F. B. Krasne, *J. Exp. Biol.* **56**, 1 (1972).
6. The methods used permit this conclusion only for tail flips mediated by medial or LG fibers. The tail flips which occur during swims composed of long sequences of flips are mediated by a nongiant system which has not been studied here. However, J. J. Wine and F. B. Krasne (in preparation) have found that inhibition of both LG and interneuron A can be activated by tail-flip motor neurons; we therefore consider it extremely likely that protection accompanies all tail-flip responses.
7. Stimulation and gross recording were carried out by hook or suction electrodes. Micropipettes were filled with 2.5*M* KCl. The LG's were impaled just rostral to septa in third or fourth abdominal ganglia; EPSP's were evoked by second-root shocks. Preparations were irrigated with a constant flow of cold, aerated Ringer solution and stimuli were kept well spaced whenever possible to minimize deterioration [for further details of methods, see (*1–4*)].
8. Shocks just suprathreshold for firing any giant fiber, delivered by pairs of platinum wires on the cord's dorsal surface, were used routinely. However, we used selective stimulation to verify that each giant fiber could by itself evoke protection from LG habituation and the early excitation and subsequent inhibition of interneuron A.
9. W. A. Spencer, R. F. Thompson, D. R. Neilson, *J. Neurophysiol.* **29**, 221 (1966); V. Castellucci, H. Pinsker, I. Kupfermann, E. R. Kandel, *Science* **167**, 1745 (1970); C. H. F. Rowell, *J. Exp. Biol.* **55**, 727 (1971).
10. A. M. Roberts, *J. Exp. Biol.* **48**, 545 (1968).
11. In extracellular experiments, interneuron A was identified by (i) its receptive field (*1, 2*), (ii) the large size of its action potential at the ventral surface of desheathed connectives, (iii) its low threshold for activation by electrical shocks to any of ipsilateral roots 1 to 4 of the last abdominal ganglion, and in some experiments by (iv) its large diameter and (v) position in the cord. In intracellular experiments criteria (ii), (iii), and (v) were used. Impalement was at the point where the axon enters the last ganglion.
12. J. Dudel, *Pfluegers Arch. Gesamte Physiol. Menschen Tiere* **277**, 537 (1963).
13. For example, J. C. Eccles, *The Physiology of Synapses* (Springer-Verlag, New York, 1964).
14. The fourth root of the last abdominal ganglion, which was used for these experiments, contains a single efferent fiber and otherwise appears to be entirely sensory (*15*). Neuropile about halfway laterally from the midline at the level of entrance of the first root—where the terminal tuft of the fourth-root fibers overlaps the dendritic arbor of interneuron A [(*15*); A. Selverston and D. Kennedy, *Endeavour* **28**, 107 (1969)]—was explored with 5- to 30-μm steel electrodes for points where antidromic potentials could be evoked that were (i) gradable with stimulus current (which was then set for an intermediate-sized response) and (ii) subject to change of size when evoked after the firing of a giant fiber. Such points were not difficult to find. These changes were gradable and therefore could not be solely due to the single, fourth-root efferent.
15. Cobalt dye studies of fourth root by Ron Calabrese (personal communication).
16. Work on presynaptic inhibition at neuromuscular synapses in crayfish has indicated that the effects of decreased membrane resistance are of major importance, whereas terminal depolarization is probably slight (*12*). Decreased excitability of sensory axons during presynaptic inhibition has been observed at eighth-nerve Mauthner cell synapses in goldfish [T. Furukawa, Y. Fukami, Y. Asada, *J. Neurophysiol.* **26**, 759 (1963)].
17. This follows if these induced changes of efficacy are due to events which depend upon Na^+-spike-elicited Ca^{2+} influx into terminals [W. J. Betz, *J. Physiol.* **206**, 629 (1970); R. Miledi and R. Thies, *ibid.* **212**, 245 (1971)], since presynaptic inhibition should reduce such influx (*12, 13*). If changes of efficacy are a consequence of events that do not depend on Ca^{2+} influx [R. G. Sherman and H. L. Atwood, *Science* **171**, 1248 (1971); J. Bruner and D. Kennedy, *ibid.* **169**, 92 (1970)], predictions are equivocal.
18. J. Dudel and S. W. Kuffler, *J. Physiol.* **155**, 543 (1961).
19. Supported by NINDS grant NS-08108. J.S.B. is a PHS trainee. We thank Drs. J. J. Wine, J. S. Liebeskind, D. Novin, G. Ellison, and A. Stuart for suggestions. We thank L. Chen for help in behavioral experiments.

2 April 1973; revised 3 August 1973

Rapid Viral Induction of Plasmacytomas in Pristane-Primed BALB/c Mice

Abstract. *Strain BALB/c mice were injected intraperitoneally with 0.5 milliliter of pristane, and 39 to 56 days later they were infected with Abelson murine leukemia virus, which is a lymphosarcomagenic variant of Moloney virus. Fifty-eight percent of the mice developed lymphosarcoma, and 28 percent developed immunoglobulin-producing plasmacytomas within 20 to 93 days (77 to 149 days after the pristane injection). Two of 57 control mice developed plasmacytomas at days 138 and 166 after a single injection of pristane; no plasmacytomas were found in mice treated with virus alone.*

The immunoglobulin-producing, transplantable murine plasmacytomas have proved valuable in elucidating the structure and function of antibodies and the mechanisms by which they are synthesized (*1*). Although spontaneous plasmacytomas are rare, they can be induced in BALB/c mice by the intraperitoneal implantation of various materials, including solid plastics, mineral oils, and chemically pure oils such as 2,6,10,14-tetramethylpentadecane (pristane). These agents induce a diffuse peritoneal granuloma in which plasmacytomas develop after 150 to more than 600 days (*1–3*). Endogenous viruses have been suspected of playing a role in plasmacytoma development. However, aside from the presence of C-type and intracisternal A-type particles (*4*), little

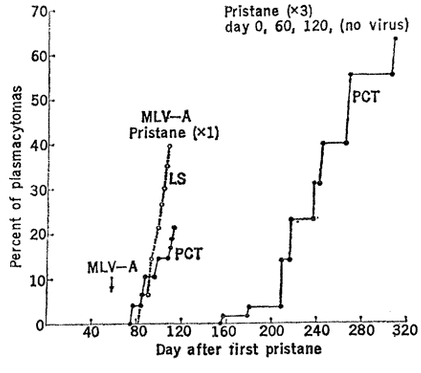

Fig. 1. Cumulative percentage of mice given a single intraperitoneal injection of pristane on day 0 and infected with Abelson virus (*MLV-A*) on day 57 that developed lymphosarcomas (*LS*) or plasmacytomas (*PCT*) in experiment 2. For comparison the cumulative percentage of mice in a previous experiment that developed plasmacytomas following three intraperitoneal injections of pristane given on days 0, 60, and 120 is shown.

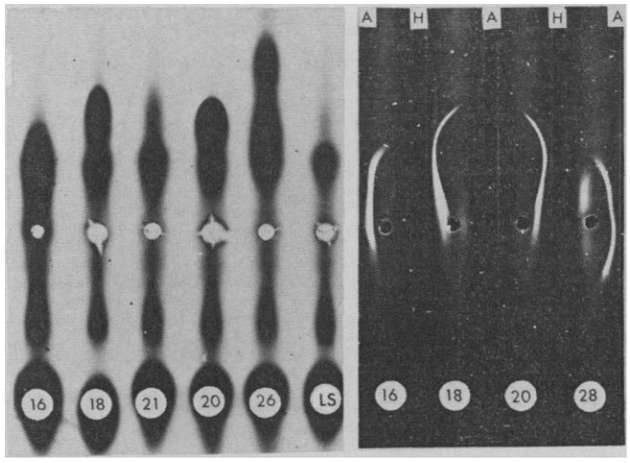

Fig. 2. (Left) Agar gel electrophoresis at *p*H 8.2 of ascites from five mice that developed plasmacytomas (ABPC 16, 18, 20, 21, and 26) following a single injection of pristane and MLV-A infection. The specimen labeled LS which has a normal pattern is ascites from a mouse that developed lymphosarcoma. The major cathodically migrating protein in this ascites is siderophilin (between the origin and the top of the figure). Myeloma proteins migrated cathodically also and differed from each other in electrophoretic mobility. ABPC 26 ascites contained two components; the more cathodic is kappa chain and the other is an IgA myeloma protein. (Right) Immunoelectrophoresis of ascites from mice with tumors ABPC 16 (IgA), 18 (IgH, also called γ2b), 20 (IgH), and 28 (IgA). Rabbit antiserum to mouse IgA (A) and IgH (H) were placed in respective troughs. The ABPC 28 ascites contains a major IgA component and a minor IgH component; the latter could be due to a normal IgH immunoglobulin in the ascites, a second myeloma protein, or a cross-reaction of the rabbit antiserum to mouse IgH with the ABPC 28 myeloma protein. (ABPC designates a plasmacytoma induced by pristane and the Abelson virus.)

direct evidence supports this hypothesis.

In 1969, Abelson and Rabstein (*5*) isolated a lymphosarcomagenic virus from a BALB/c mouse that had been treated with prednisolone from birth and infected with Moloney leukemia virus at 28 days of age. This virus induces nonthymic lymphosarcomas within as short a time as 3 to 4 weeks when injected into newborn or adult BALB/c mice. Like certain other pathogenic variants of murine leukemia viruses, the Abelson virus (MLV-A) appears to consist of a mixture of Moloney leukemia virus and a lymphosarcoma virus in a Moloney virus envelope (*6*). In addition, most preparations of MLV-A, including those used here, contain the lactic dehydrogenase virus (LDV) (*7*).

We have found that MLV-A infection of pristane-primed BALB/c mice induces both lymphosarcomas and plasmacytomas after a short latent period. Young adult BALB/c mice were injected intraperitoneally with 0.5 ml of pristane (*8*), and 39 or 59 days later they were infected by the same route with MLV-A (Table 1) (*9*). Of 38 mice infected with MLV-A in the absence of pristane, 16 (42 percent) developed tumors, all of which were lymphosarcoma. In the 92 pristane-primed mice that were given MLV-A, 54 (58 percent) developed lymphosarcoma and 26 (28 percent) developed plasmacytoma; one of these animals developed both types of tumor. The latent periods were similar for the two types of tumor (Table 1 and Fig. 1); the shorter latent periods in experiment 2 are probably due to the higher dose of virus rather than to the longer interval between pristane and virus. Two (3.5 percent) plasmacytomas developed in the 57 mice receiving pristane alone, at 138 and 166 days after the injection of pristane.

The lymphosarcomas that occurred in the mice that were given virus without pristane were typical of the Abelson disease, arising in lymph nodes and bone marrow. Mice commonly developed paraplegia, and at autopsy large tumor masses were frequently observed in the spine. The thymus rarely contained tumor. In pristane-treated mice the lymphosarcomas developed in both the lymphoreticular organs and oil granulomas, and were associated with ascites. Histologically the predominant cell in the lymphosarcomas was lymphoid in character with a lobated nucleus, as previously described for Abelson disease (*5*). In the lymph nodes the lymphosarcoma cells grew predominantly in the medullary cord regions and tended to compress the cortical tissue of the node.

The plasmacytomas were histologically similar to those that develop late in mice that have received pristane or

Table 1. Induction of plasmacytomas (PCT) and lymphosarcomas (LS) by MLV-A in pristane-treated BALB/c mice.

Group	Pristane (0.5 ml)*	MLV-A given on day†	Virus pool‡	Total No. of mice	No. of mice that developed		Average latent period§ (with range)	
					LS (%)	PCT (%)	LS	PCT
				Experiment 1				
A	—	39	1	14	2 (14)	0 (0)	73 (58–89)	
B	+			17	0 (0)	0 (0)		
C	+	39	1	16	10 (62)	4 (24)	70 (40–129)	59 (46–73)
				Experiment 2				
A-1	—	57	2	16	10 (60)	0 (0)	44 (36–55)	
A-2	—	57	2F	8	4 (50)	0 (0)	42 (32–47)	
B	+			24	0 (0)	2 (8)		95 (81–109) ‖
C-1	+	57	2	32	20 (62)	8 (25)	55 (30–120)	49 (21–93)
C-2	+	57	2F	14	6 (43)	5 (36)	40 (30–48)	46 (20–82)
				Experiment 3				
B	+			16	0 (0)	0 (0)		
C	+	39	3	30	18 (60)	9 (30)	37 (26–67)	47 (28–58)

* Pristane was injected intraperitoneally when the mice were approximately 2 months old; +, pristane given; —, none given. † Days after pristane. ‡ MLV-A pools 1 and 2 were 1.7 percent and 10 percent extracts of primary lymphosarcomas, respectively. Pool 2F was an 0.45-mμ Millipore filtrate of pool 2. Pool 3 was a 10 percent extract of a transplanted lymphosarcoma. Infectivity titers (per 0.1 ml) were as follows: pool 1, $10^{4.9}$ plaque-forming units (PFU) and $10^{1.8}$ tumor (lymphosarcoma)-producing units, 50 percent positive (TPD_{50}); pool 2, $10^{5.7}$ PFU and $10^{2.6}$ TPD_{50}; and pool 2F, $10^{5.2}$ PFU; pool 3, 1.6×10^{5} PFU and 10^{2} TPD_{50}. § The latent period was defined as the number of days from MLV-A infection to development of ascites, lymphadenopathy, paraplegia, or solid tumor. The mice in experiment 1 were observed for 169 days after virus injection and 208 days after administration of pristane; the mice in experiment 2, for 114 days after virus and 170 days after pristane; and the mice in experiment 3, 99 days after virus and 138 days after pristane. ‖ The latent period for these tumors was 138 and 166 days after pristane.

other mineral oils alone. They involved the oil granuloma and were associated with ascites that contained the characteristic large plasmacytoma cells.

Twenty-three of the 26 primary plasmacytomas produced a myeloma protein. The heavy chain class of immunoglobulins (IgC_H) was immunoglobulin A (IgA) in 18 (69 percent) cases and immunoglobulin G (IgG, γ2a or γ2b) in 5 (11.8 percent). The myeloma proteins differed from each other in electrophoretic mobility (see Fig. 2). The restriction of immunoglobulin production to a single class, and the individuality of the electrophoretic mobility suggest, but do not prove, that these tumors are monoclonal.

Seven of the plasmacytomas have at this time been transplanted to new recipients. The transplants were made into pristane-treated mice in order to rapidly establish the tumors in transplant (*10*). In the five cases tested so far the myeloma proteins produced in the transplanted tumors were identical in class and electrophoretic mobility to the proteins produced in the respective primary host.

The ascites and serum from pristane-treated mice that developed lymphosarcomas have also been studied in both agar gel electrophoresis and immunoelectrophoresis, and no myeloma proteins have been observed.

The oil-primed peritoneum is clearly necessary for development of plasmacytomas in this system, since no plasmacytomas have been reported by others or observed by us in unprimed mice given MLV-A. Since mineral oil alone will eventually induce plasmacytomas, the question arises of the principal role of the virus: that is, is it a direct transforming agent, or merely a helper or accelerator of a process that would occur in any case? A plausible interpretation of our results is that MLV-A infection induces transformation of plasma cells or their precursors, while the role of pristane might be either to increase the number or susceptibility of the target cell population, or to induce microenvironmental changes in the peritoneum that are essential for the growth of transformed cells into detectable plasmacytomas (*10*).

As mentioned previously, our MLV-A preparations contain at least three different viral components. Any one or any combination of these might be the plasmacytomagen.

Several applications of this system are readily apparent. The marked reduction in the induction time for plasmacytomas will facilitate determining factors involved in the pathogenesis of plasmacytomas. Of major importance is the possibility of inducing plasmacytomas that produce antibodies to a given specific antigen. Because of the rapidity of the process, it should be possible to use the virus to investigate the genetic basis of the vastly different susceptibilities of different mouse strains for oil-induced plasmacytoma formation. Finally, the discovery that a virus can induce plasmacytomas in the oil-primed mouse provides a system for looking for other viruses, especially endogenous ones, that can do the same.

MICHAEL POTTER
Laboratory of Cell Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014

MARSHALL D. SKLAR
WALLACE P. ROWE
Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health

References and Notes

1. M. Potter, *Physiol. Rev.* **52**, 631 (1972).
2. R. M. Merwin and G. H. Algire, *Proc. Soc. Exp. Biol. Med.* **101**, 437 (1959); M. Potter and C. L. Robertson, *J. Nat. Cancer Inst.* **25**, 847 (1960); R. M. Merwin and L. W. Redmon, *ibid.* **31**, 998 (1962); M. Potter and C. R. Boyce, *Nature* **193**, 1086 (1962); P. N. Anderson and M. Potter, *ibid.* **222**, 994 (1969).
3. M. Potter and R. C. MacCardle, *J. Nat. Cancer Inst.* **33**, 497 (1964).
4. A. F. Howatson and E. A. McCulloch, *Nature* **181**, 1213 (1958); A. J. Dalton, M. Potter, R. M. Merwin, *J. Nat. Cancer Inst.* **26**, 1221 (196→ J. Watson, P. Ralph, S. Sarkar, M. Cohn, *Proc. Nat. Acad. Sci. U.S.A.* **66**, 344 (1970).
5. H. T. Abelson and L. S. Rabstein, *Cancer Res.* **30**, 2213 (1970); L. S. Rabstein, A. F. Gazdar, H. C. Chopra, H. T. Abelson, *J. Nat. Cancer Inst.* **46**, 481 (1971).
6. Lymphosarcoma induction by MLV-A virus pools is eliminated by neutralization with antiserum to Moloney virus. Addition of excess Moloney or Gross leukemia virus after neutralization does not restore its lymphosarcomagenic activity.
7. LDV virus determination was made by Dr. J. Parker, Microbiological Associates, Inc., Bethesda, Maryland.
8. Pristane was purchased from Aldrich Chemical Company, Milwaukee, Wisconsin.
9. MLV-A virus was obtained from Dr. L. S. Rabstein, Microbiological Associates, Inc. The original virus pool was passaged in newborn BALB/c mice and new virus pools were prepared from induced lymphosarcomatous tissue.
10. M. Potter, J. G. Pumphrey, J. L. Walters, *J. Nat. Cancer Inst.* **49**, 305 (1972); M. Potter and J. L. Walters, *ibid.*, in press.

15 May 1973; revised 12 July 1973

Cooperative Tool Use by Captive Hamadryas Baboons

Abstract. *A bonded pair of hamadryas baboons developed cooperative tool use without training. The male could get food with the tool but first had to get the tool from an adjoining cage which he could not enter. The female learned to give him the tool. Cooperation was temporarily disrupted by the terminal phase of the female's estrous inflation.*

Cooperation is common in many insects, birds, and mammals (*1*). However, it usually occurs in highly evolved protective, reproductive, and subsistence patterns and is not indicative of a capacity to cooperate in the face of novel environmental demands. Laboratory studies of cooperative problem-solving can expose such plasticity and reveal the dynamics of learned cooperative behavior. Rhesus monkeys can be trained to use the anticipatory affective or orienting responses of another rhesus as conditioned stimuli for operant discriminations (*2*), but other attempts to produce cooperative problem-solving by monkeys, even with patient training, have been generally unsuccessful (*3*). Chimpanzees are capable of cooperative problem-solving (*4, 5*), and Menzel (*6*) has reported spontaneous cooperative tool use by captive chimpanzees. I describe here cooperative problem-solving, involving tool use, by untrained monkeys.

In a previous experiment (*7*), a subadult male of a captive harem of hamadryas baboons (*Papio hamadryas*) learned, without training, to use an L-shaped tool to procure a pan of food which was out of reach. The tool use was learned by instrumental trial-and-error, resulting fortuitously from exploratory manipulation of the tool. The same harem, containing the tool-using male, was used in the present experiment. During this experiment, the harem consisted of eight animals: male-1, the harem leader, adult male estimated to be over 40 years old; female-1, adult female, estimated to be 10 years old; male-2, the tool user, young adult male born 20 April 1967; female-2, young adult female born 11 August 1968; female-3, young adult female born 21 August 1969; male-3, juvenile male born 9 May 1970; female-4, juvenile female born 30 January 1971; male-4, infant male born 14 February 1972. Male-1 and female-1 were the parents of all the other animals. Female-2 had formed a sexual bond with