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IMMUNOLOGICAL EFFECTS OF AN INFLAMMATORY REACTION INDUCED IN THE CENTRAL NERVOUS SYSTEM

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The brain has been considered a privileged site in relation to transplantation immunity (Medawar, 1984; Raju & Crogan, 1977). The relatively long survival of intracerebrally transplanted grafts is believed to be due to an impairment in both the afferent and efferent arcs of the immune response due to a lack of lymphatic system within the brain (afferent privilege) and the presence of the blood-brain barrier (efferent privilege). The intercellular spaces within the brain parenchyma, however, have free communications with the subarachnoid space (SAS) and also with the lymphatic system of the head and neck regions (Földi, 1977), the CSF-lymphatic outflow being very rapid (Bradbury, 1981). The studies of organ distribution (Fig. 1) provide an additional evidence for the existence of a CSF-lymphatic outflow pathway for tracer (colloidal carbon) and cells (sheep erytrocytes) injected into the subarachnoid space. It is therefore difficult to see how lack of drainage into the lymphatic system can account for extended graft survival in the brain. Moreover, migration of macrophages from inflammed brain parenchyma into the perivascular space has also been described (McKeever & Balentine, 1978). It is still uncertain whether suppressor mechanisms both humoral and cellular (Raju & Crogan, 1977; Barker & Billingham, 1977) might be implicated in graft tolerance in the brain.

Evidence that bone-marrow derived macrophages (Bartlett, 1982; Hickey & Kimura, 1987) and sensitized lymphocytes (Lublin et al., 1983; Traugott et al., 1983) can pass an intact blood-brain barrier and infiltrate the brain parenchyma suggest that the most likely cause of extended graft survival in the brain is a low level of sensitization. In contrast, injections of soluble or particulate antigens into the brain parenchyma or subarachnoid space (Table I) induce higher systemic antibody responses than injection of the antigen into any of the sites commonly used for immunization (subcutaneous, intravenous, intraperitoneal). The enhanced immunogenicity of SAS introduced antigens was only observed with thymus-dependent and not with a type-2 thymus-independent antigen. These data indicate that the brain is not privileged with regard to humoral immunity. Therefore, leading to the idea that immune events generated in the subarachnoid space are poorly regulated by the systemic immune system, although being capable of inducing a local effective antigen presentation. This could explain why the injection of thymus-dependent (TD) antigens into the subarachnoid space increases both local and systemic immune responses. The effect is not so marked with thymus-independent antigens (TI) because they depend less on regulatory events of a systemic nature, due to their capacity of direct lymphocyte

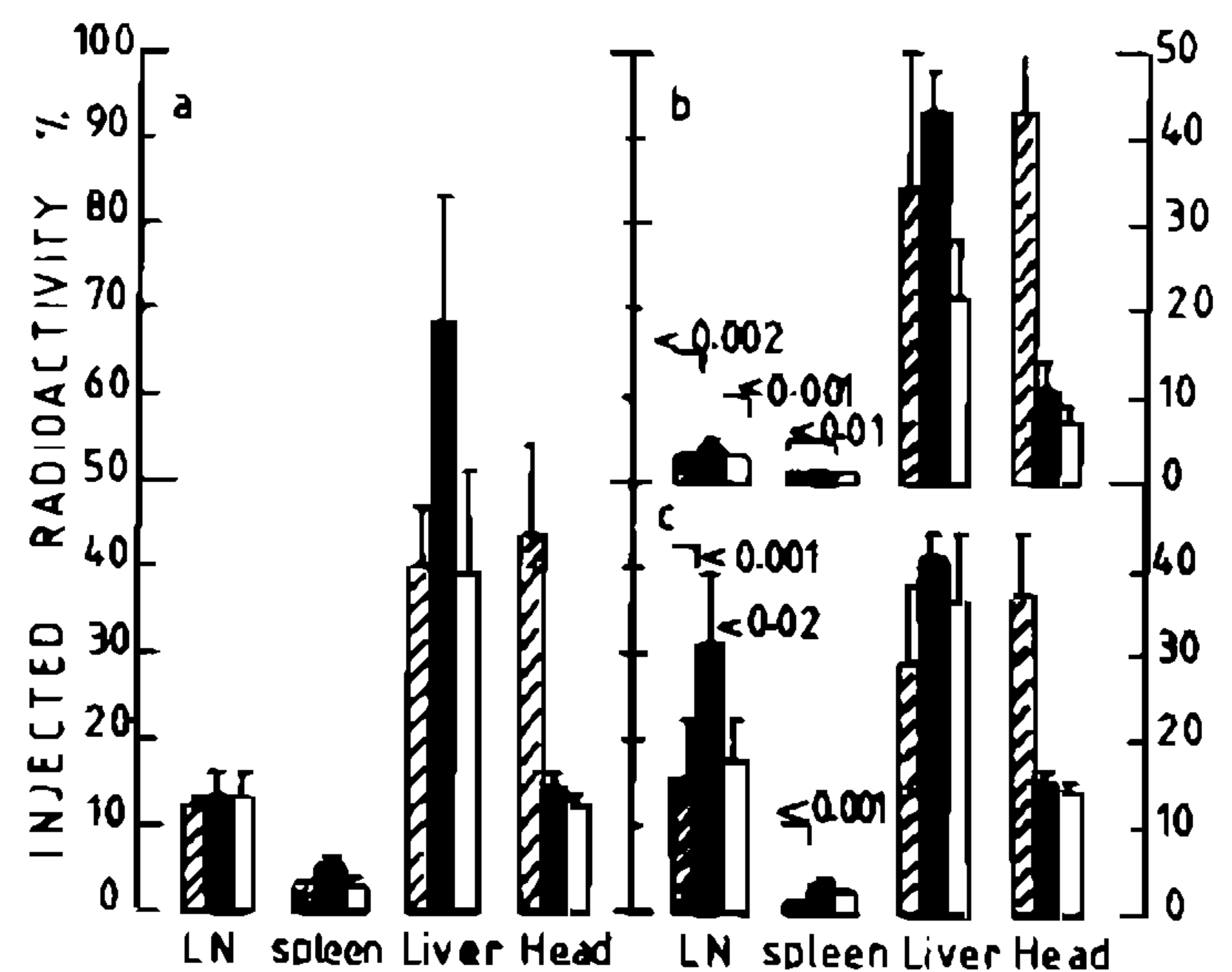

Fig. 1: Organ distribution of labelling erythrocytes injected into the subarachnoid space. Groups of five adult (CBA x C_{57}BL) F_1 mice were treated with colloidal carbon on days -3 -1 before injection of 2 x 10^6 chromium-labelled SRBC into the subarachnoid space. The animals were killed 30 minutes (▨), 20 hours (■), and 96 hours (□) after ^{51}Cr-SRBC injection into the subarachnoid space. Radioactivity is expressed as percentage of the injected dose. a) control groups injected only with ^{51}Cr-SRBC; b) mice treated with 10 μg of colloidal carbon SAS; c) mice receiving colloidal carbon ip (10 mg) and SAS (10 μg). *p* values calculated by the Student's t-test refers to the control group (a).

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TABLE I

Antibody production following antigenic challenge by different routes

Route of Immunization	IgG-PFC/spleen		
	SRBC	TNP-BSA	TNP-Ficoll
SAS	4,76 ±0,07	4,29 ±0,08	4,36 ±0,12
IBP	4,38 ±0,21	NT	NT
IP	4,28 ±0,13 P <0,02	3,80 ±0,14 P <0,02	4,34 ±0,06
SC	1,90 ±0 P <0,001	3,31 ±0,17 P <0,001	NT

Groups of four (CBA x C_{57}BL) F_1 mice were primed and challenged with 2×10^6 SRBC, 100 μg TNP_{12}-BSA or 10 μg TNP-Ficoll. The antigens were injected SC (subcutaneous), Ip (intra-peritoneal); IBP (intra-brain parenchyma) or SAS (subarachnoid space). Indirect spleen PFC were determined seven days after rechallenge and are expressed as mean log10 ±SE. P values (Student's T test) refer to the respective SAS group. NT - not tested.

activation. Alternatively, the effect observed following immunization with T-dependent antigens into the subarachnoid space could also in part be due to the release from the inflammed tissue, of substances with adjuvant activity (Quirico-Santos & Valdimarsson, 1982) and/or a disturbance on the immuno-neuroendocrine network (Besedovsky & Sorkin, 1977). In this context, it should be mentioned that similar increase in the antibody production was observed (Quirico-Santos & Valdimarsson, 1987) when the antigen was injected intraperitoneally and the brain lesioned by stab wound or X-irradiation (400 R). Therefore, a serie of studies were conducted in order to determine the possible influence of a cerebral inflammatory reaction on immune parameters.

Pulse-labelling studies of cell accumulation within the central nervous system following local inflammatory reaction induced with antigen (ovalbumin), brain trauma (26 G needle lesion) or inflammatory substances (endotoxin, muramil dipeptide, carrageenan) demonstrate (Fig. 2) that a consistent increase in mononuclear cell accumulation in the brain parenchyma and spinal cord was only observed following endotoxin (LPS) injection into the subarachnoid space. This response was still increasing four days after treatment. Recently, Cybulsky et al. (1986) reported that interleukin-1 (IL-1) was very potent in increasing leucocyte emigration into tissue. It is quite possible that the effect observed with LPS was related to its capacity to induce lymphokine production within the central nervous system.

Astrocytes and C6 glioblastoma cells are known to produce *in vitro* IL-1 like factors

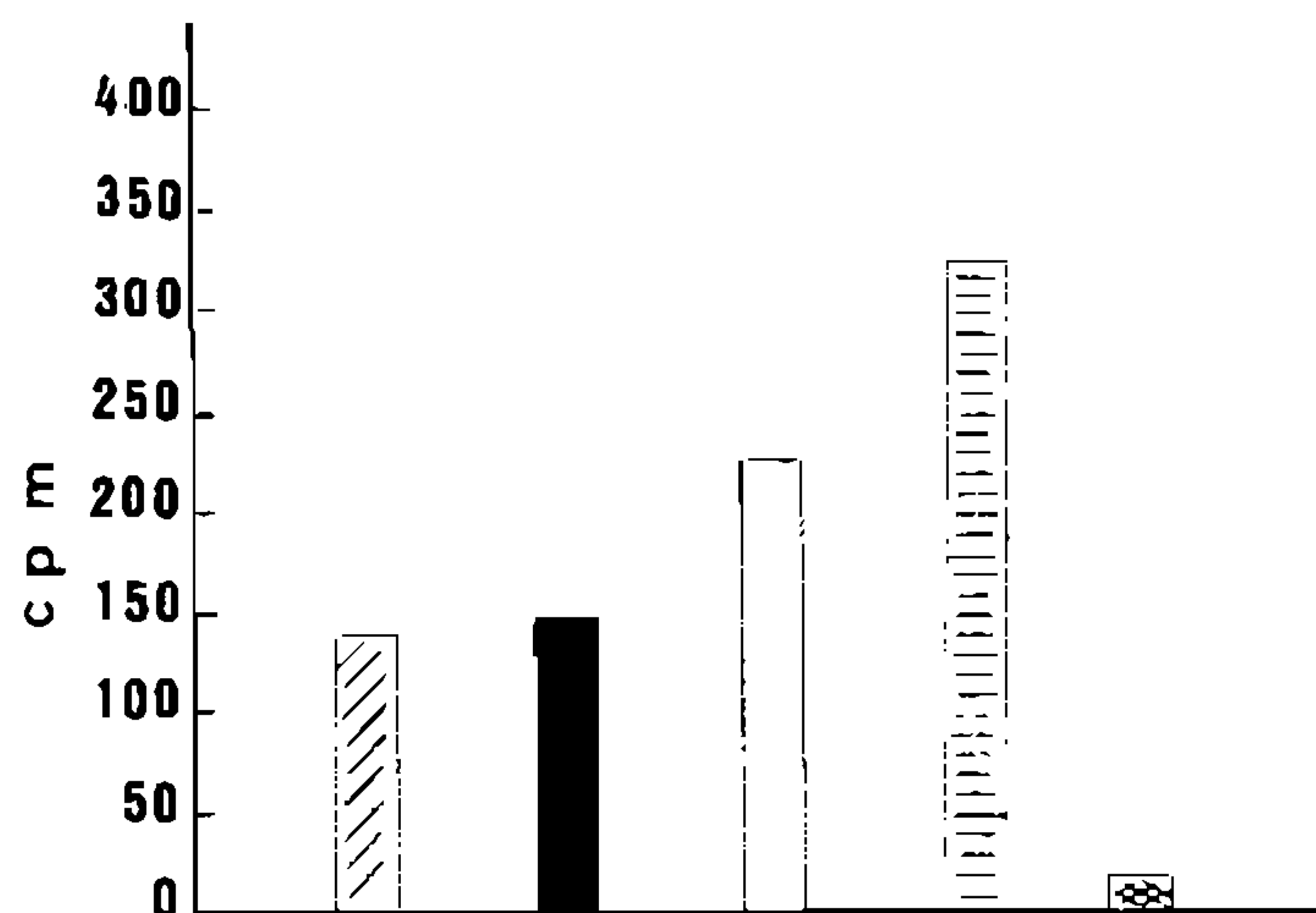

Fig. 2: Effect of CNS inflammation on local mononuclear cell accumulation. Inflammatory reaction were induced in groups of five Balb/c mice injected SAS with 1 μg muramil di-peptide (MDP, Sigma Chem. Co); 10 μg endotoxin (LPS E.011:827, Sigma), 100 μg Carrageenan iota (Sigma) or 10 μg PHA. Chromium-labelled mononuclear cells (^{51}Cr-MNC) from mesenteric and cervical lymphnodes were injected 24h before killing. Mice were sacrificed 96 hours after induction of CNS inflammation, and the incorporation of radioactivity measured in the brain tissue. Control group (▨) received saline into the SAS. (■) MDP; (□) Carrageenan; ▤ LPS; ▩ PHA.

(Fontana et al., 1982) being considered as the major source of lymphokine production in the brain tissue (Tobler et al., 1984). Moreover, following intraperitoneal injection of LPS, a marked lymphokine production is observed by the brain tissue compared with spleen, kidney or thymus (Fontana et al., 1984).

The evidence that IL-1 may regulate normal growth and differentiation of astrocytes, thus support its involvement in the development of reactive gliosis, and scar formation (Giulian & Lachman, 1985). Astrocytes are morphological-

ly interconnected between endothelial cells of the brain vessels and neurons. Such location may favor the entrance of mononuclear cells within the brain parenchyma during local inflammatory reactions or even in the abscence of mechanical disturbance of the blood-brain barrier (Hickey & Kimura, 1987). However, following brain injury or inflammation, growth-promoting substances which are synthesized within the brain tissue by macroglial cells (Giulian et al., 1985; Merril, 1987), might play an important role in the activation of immunological events within the CNS.

Although antibody-producing cells have been demonstrated in the brain tissue following local antigenic challenge (Quirico-Santos & Valdimarsson, 1985), the experiments with chromium-labelled monuclear cells (^{51}Cr-MNC) suggest that lymphocytes from the peripheral blood accounts for only a small proportion of cells present in the brain parenchyma (Fig. 2) under these experimental conditions. Furthermore, experiments with ^{51}Cr-SRBC demonstrated that this cell accumulation was not a reflection of increased local blood flow (data not shown). It should be mentioned that this effect was not detected following either antigen, mitogen (PHA) or inflammatory substances such as thyoglycolate, casein or carrageenan injected into the subarachnoid space. However, it cannot be ruled out that the effects observed following SAS antigenic challenge, brain trauma or the inflammatory substances LPS and MDP, could be related to an increase in lymphokine production by the lymphoid tissue. Moreover, preliminary studies (Table II) points to an increase in the numbers of spleen mononuclear cells, with predominance of lymphoblasts, 72 and 120 hours after SAS injection of MDP and LPS.

TABLE II

Effect of CNS inflammation on the spleen cell numbers

Groups	CNS inflammation	Spleen MNC x 10^6		
		24h	72h	120h
Control	–	19,3	23,2	24,5
Trauma	Transcranial lesion	28,6	20,0	19,2
Endotoxin	10 μg LPS	19,3	23,2	39,3
MDP	1 μg	17,0	26,6	57,3
Carrageenan	100 μg	22,3	16,0	32,0

Inflammatory reaction were induced in Balb/c mice with inflammatory substances injected SAS or with a 26 G transcranial stab lesion. The spleen cellularity were assessed 24, 72 and 120 hours after treatment.

Attempts to block TD antigen processing within the brain by injecting colloidal carbon into the subarachnoid space, did not cause a significant reduction on the antibody production (Table III) despite the fact that these cells had taken up the carbon (data not shown). This suggests the existence of cells in the brain that are relatively more effective in antigen presentation than in phagocytic function. The presence of Ia positive dendritic cells have been demonstrated in the choroid plexuses and meninges of normal adult rats (Hart & Fabre, 1981). Moreover a strong systemic immune response (Hickey & Kimura, 1987) and also gamma interferon (Wong et al., 1985) are known to induce extensive expression of MHC class I and II molecules on non-neuronal cells.

The demonstration that *in vitro* astrocytes (Fierz et al., 1985), oligodendrocytes (Cashman & Noronha, 1986) and also Schwann cells (Wekerle et al., 1986) in the peripheral nervous system are able to present antigen to cloned T cells suggest, also *in vivo*, a significant role in antigen processing and local activation of the afferent arc of the immune response.

Attempts for blocking the mononuclear phagocytic system both inside and outside the brain (Table III) by intraperitoneal and SAS injections of colloidal carbon, INCREASED the numbers of systemic antibody producing cells (PFC). The experiments in organ distribution (Table IV) indicate that the brain is able to trap antigens for prolonged periods. Thus in addition to a better antigen presentation by non-neuronal cells, the enhanced antibody response observed following SAS antigen injections, might also in part be explained by its persistence in the brain tissue and slow release to the draining cervical lymphoid tissue.

TABLE III

Effect of colloidal carbon treatment on antibody production

Route of Immunization	Carbon treatment	Direct spleen PFC/10^7
IP	–	3,45 ± 0,09
	–	2,41 ± 0,14 P < 0,001
SAS	–	3,93 ± 0,08
	IP	3,94 ± 0,06 NS
	SAS	3,84 ± 0,14 NS
	IP/SAS	4,00 ± 0,07 NS

(CBA x C_{57}BL)F_1 mice were treated with colloidal carbon either ip (10mg) and/or SAS (10μg) on days -3-1 before immunization with 2×10^6 SRBC ip or SAS. The numbers of IgM spleen PFC determined five days later. P values (Student's T-test) refers to the control non-treated group. NS-not significant.

TABLE IV

Persistence of labelled erythrocytes in the brain tissue of normal and carbon-treated mice

Carbon-treatment	Time after ^{51}Cr-SRBC injection		
	30 min	24 h	96 h
Control not-treated	34 ± 6	7 ± 0,7	7 ± 1
SAS	29 ± 6	7 ± 1	3 ± 0,7
IP/SAS	28 ± 3	13 ± 1 P < 0,001	11 ± 1 P < 0,002

(CBA x C_{57}BL) F_1 mice were treated with colloidal carbon 10 mg ip and/or 10 μg SAS on days -3-1 before injection of 2×10^6 labelled SRBC into the subarachnoid space. The proportion of Chromium-labelled SRBC in the brain tissue was detected 30 min, 24 h, 96 h after SAS injection.

Injections of TD antigens into the subarachnoid space, not only induced a higher systemic antibody production, but were also capable of breaking down a tolerant state. The induction of systemic low-zone tolerance (LZT) to a carrier protein is known to be long lasting, sensitive to cyclophosphamide treatment, stable in adoptive transfer experiments and suitable for studing suppression of carrier specific T helper cells (Brüner & Kölsch, 1981). Abrogation of this type of tolerance can be achieved with treatment that selectively impairs suppressor mechanisms or enhance helper cell function. Injection of brain extract or infliction of brain injury by a transcranial stab wound (26 G needle) or irradiation (400 R) of the head, proved (Table V) as effective as cyclophosphamide in breaking down LZT. Additional experiment using another type of tolerance (oral tolerance) to high doses of protein fed antigen to suppress both humoral and cell-mediated immunity (Bruce & Ferguson, 1986) show that manipulation of the CNS could also abrogate (Table VI) this type of tolerance. Moreover, antigenic challenge within the CNS proved more effective ($p < 0.001$) than other treatment in terminating oral and systemic tolerance. Altogether these results thus suggest that antigen processing by brain cells is more significant in activating the afferent arc of the immune response, than the release from the inflammed (lesioned) brain tissue, of substance with adjuvant activity.

In an attempt to verify the possible influence of a CNS inflammatory reaction on the cellular immune response, two well-established

TABLE V

Effect of CNS modulation on low-zone tolerance

BSA reactivity	NIM treatment	Anti-TNP IgG spleen PFC/10^7	Significance T-test P <
Primed	–	3,31 ± 0,10	
TOL	–	2,07 ± 0,13	0,001
TOL	Cyclophosphamide	3,12 ± 0,15	0,001
TOL	Transcranial STAB	2,68 ± 0,16	0,02
TOL	Head x-irradiation (400 R)	3,10 ± 0,10	0,001
TOL	Brain extract	3,25 ± 0,14	0,001

(CBA x C_{57}BL) F_1 mice pre-treated with 2,5 mg hydrocortisone acetate ip, received seven consecutive injections of 10 μg monomeric BSA ip. Cyclophosphamide treatment (10 mg/ip) and brain injury (stab or X-irradiation) were performed 48 hours before antigenic challenge (100 μg TNP-BSA ip). Brain extract (Fraction I, Folchi-partition) were injected ip together with TNP-BSA. Controls (primed group) that received 2,5 mg hydrocortisone acetate and TNP-BSA (1 mg) ip, were treated for five consecutive days with saline ip. Anti-TNP spleen PFC were determined six days after TNP-BSA challenge. TOL: tolerant mice.

TABLE VI

Abrogation of oral tolerance by CNS modulation

Group	BSA Challenge	NIM treatment	Spleen PFC		Significance T-test P <
			/10^6 cells	/spleen	
Non tolerant	IP	–	68,4 ± 14	1552 ± 111	
Tolerant	IP	–	14,4 ± 3	556 ± 136	0,001
Tolerant	SAS	TNP-BSA 100 μg SAS	59,6 ± 19	2018 ± 523	0,001
Tolerant	IP	Transcranial STAB	24,9 ± 9	1128 ± 389	0,02
Tolerant	IP	LPS 10 μg SAS	51,3 ± 23	2420 ± 110	0,001

Groups of five Balb/c adult mice received 20 mg of BSA intragastric. The animals were challenged seven days later with 100 μg TNP-BSA ip or SAS in association with NIM treatment. The numbers of spleen PFC were detected five days later. Results are expressed as GM ± SF.

models were selected: tumour growth and host-versus-graft (HVG) reaction. The data reported in the literature regarding the effect of various stressors on the growth pattern of chemically induced tumour, is contradictory (Justice, 1985). Initially it was chosen a methyl-cholantrene (Mec-2) induced fibrossarcoma. The cells were injected subcutaneously in the back of Balb/C adult mice, and the pattern of tumour growth followed. Neither brain trauma (Fig. 3) nor inflammatory substances (Fig. 4) could alter the pattern of tumour growth; although a trend towards increasing growth was observed in those mice submitted to brain trauma five days before the injection of Mec-2 tumour cells. Further experiments using a spontaneous Balb/C thymoma are in progress to study the effect neuroimmunomodulation (NIM) on the growth pattern of this tumour.

In contrast, NIM had some effect on HVG reactions. Semi-allogeneic cells (Balb/C x C57BL) F1 were injected into the footpad of parental mice, and the increase in the weight of the draining popliteal lymph node compared to the contralateral one. The results (Table VII) show a consistent increase ($p < 0.001$) in the HVG reaction in the ipsilateral popliteal lymph node of mice submitted to a transcranial stab lesion. This was time-dependent as the effect was *ONLY* observed when the CNS modulation occurred at the time of antigenic challenge. Injection of inflammatory substrances (LPS, MDP, carrageenan) into the subarachnoid space, caused a reduction in the HVG reaction, though a significant ($p < 0.05$) inhibition could only be observed with carrageenan. A similar reduction in HVG reaction has also been previoulsy de-

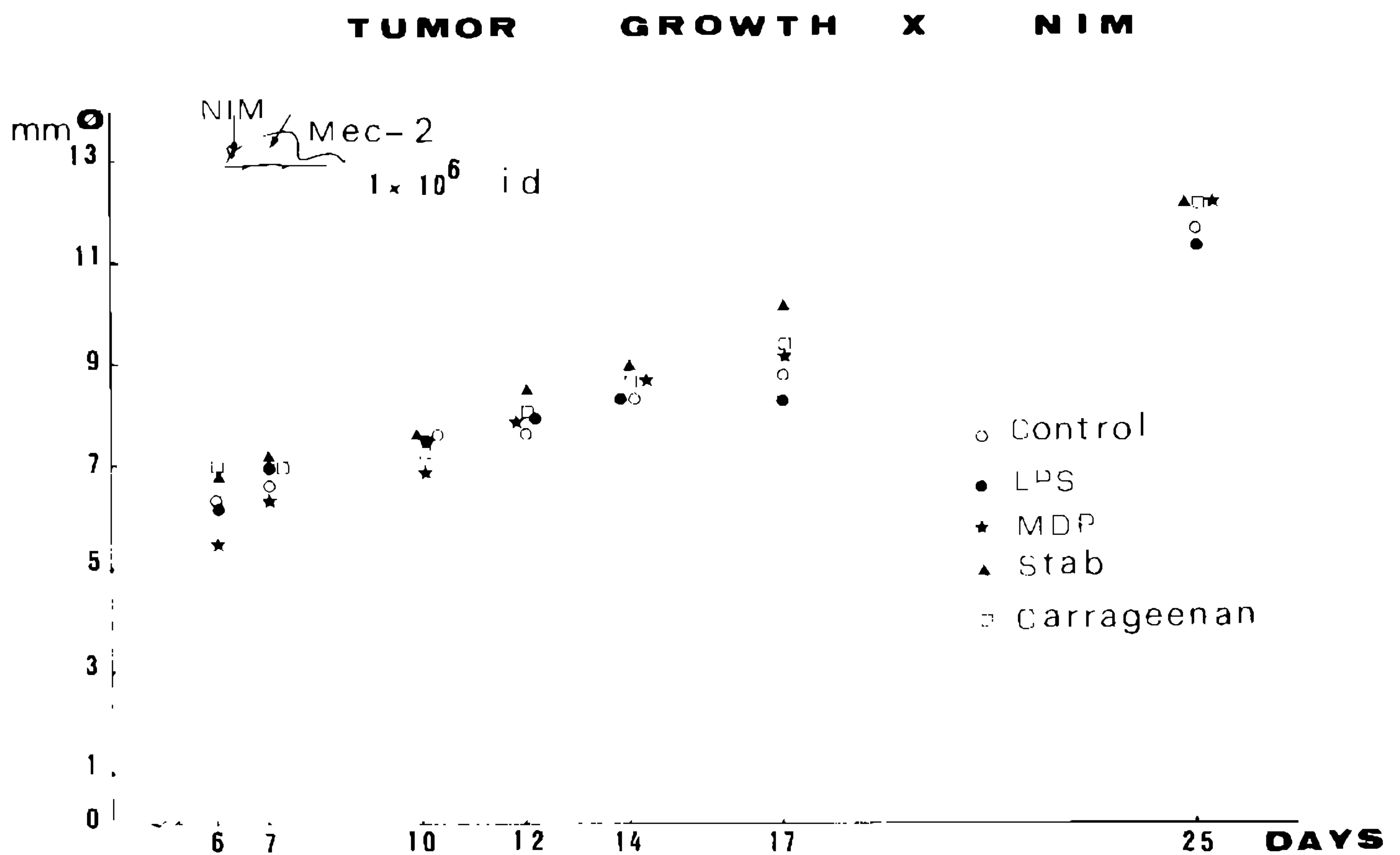

Fig. 3: Tumour growth pattern following CNS inflammation. Injection of 1 x 10^6 cells from a chemically induced fibrosarcoma were injected in the back of Balb/c mice in association with SAS injection of inflammatory substances (LPS, 10 μg; MDP, 1 μg; carrageenan, 100 μg; or a transcranial brain lesion (26 G needle). Control (O) mice were only anaesthesized by ether at the time of tumour challenge. Each point represent a mean of ten mice.

TABLE VII

Effect of CNS manipulation on the HVG reaction

Experimental groups	Popliteal lymph node weighing		Significance (T-test) P <
	Contralateral	Ipsilateral	
Control	1,0 ± 0,1	3,52 ± 0,5	
LPS	1,2 ± 0.14	2,7 ± 0,32	
MDP	1,1 ± 0,12	2,88 ± 0,27	
Carrageenan	1,1 ± 0,2	2,18 ± 0,35	0,05
Brain-STAB	1,3 ± 0,12	5,12 ± 0.52	0,001
6-OHDOPA	1,1 ± 0,18	3,6 ± 0,43	

Balb/c mice received 5 x 10^6 semi-allogeneic (Balb/c x $C_{57}BL$) F_1 cells in the footpad. Transcranial brain lesion (26 G needle), SAS injection of 6-OHdopamine (100 μg) or inflammatory substances (LPS, 10 μg; MDP, 1 μg; Carrageenan, 100 μg) were performed on the same day. HVG reaction were assessed four days later by the weighing of popliteal lymph node.

scribed (Rumjanek et al., 1977) following intraperitoneal administration of carrageenan.

The very significant effect seen with brain trauma, could suggest the involvement of a neuroendocrine regulation of lymphocyte traffic into the lymph node, although central depletion of catecholaminergic neurons with 100 μg of 6 OH-dopamine injected into the subarachnoid space, did not influence the HVG reaction. However, Moore (1984) using a sheep model of cannulated popliteal lymph node, demonstrated that neurotransmitters could modulate the outflow of lymphocytes from the lymph node. Bombesin, methione-enkephalin and serotonin increasing the outflow and VIP, neurotensin arresting the cels within the node.

At the moment, additional experiments are being conducted to verify if the enhanced reaction observed following brain lesion is at the level of cell traffic or cell proliferation within the lymph node.

The data reported herein may have important implications for certain diseases affecting the central nervous system, including multiple sclerosis, SSPE and meningitis. A common feature in these diseases is oligoclonal synthesis of immunoglobulin within the CNS (Mehta et al., 1982; Waksman, 1985; Forsberg et al., 1986). Moreover, extensive intrathecal immune response has also been observed for prolonged periods, in a patient with myasthenia gravis, but without any signs of active disease (Kam-Hansen, 1986). Intense local antibody production seen after cerebral infarcts (Roström et al., 1981) suggest that brain injury may lead to a local polyclonal B cell activation and then contribute to the development of autoimmune processes.

Astrocytes have been implicated as an important cell for activation of local CNS immunological events. In addition to antigen presentation to T cells (Fierz et al., 1985), and to mitogen induced polyclonal T cell activation (Schnyder et al., 1986) further evidences for the production of IL-1 (Giulian & Lachman, 1985) and also IL-3 like factors (Frei et al., 1985) suggest that astrocytes may also play *in vivo* an importat role in the maintenance and expansion of local hemopoietic and pluripotent stem cells (Bartlett, 1982) during CNS inflammation.

It is conceivable that local CNS responses may proceed for longer periods because the traffic of lymphoid cells in and out of the brain is difficult. Alternatively antigen presentation within the CNS may be more efficient in activating the afferent arc of immune response, possibly due to the role played also *in vivo* by astrocytes and microglia, together with other local CNS macrophages (e.g. intraventricular macrophages, Bleier et al., 1975).

There is extensive evidence (Renoux et al., 1983; Blalock, 1984; Livnat et al., 1985; Roszman & Brooks, 1985; Maestroni et al., 1987) that the neuroendocrine system can modulate various immunological functions in an intergrate manner. Immunological events also influence the activity of the neuroendocrine system (Besedovsky et al., 1983). In addition, systemic responses would be made to last longer, because the local CNS responses are persistent and maintain a slow traffic of cells, antibody and neuroendocrine substances from the brain into the periphery, thus continuously hindering the regulatory adaptations of the system.

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REFERENCES

BARKER, F.C. & BILLINGHAM, R.E., 1977. Immunologically privileged sites. *Adv. Immunol., 25* :1-53.

BARTLETT, P.F., 1982. Pluripotent hemopoietic stem cells in adult mouse brain. *Proc. Natl. Acad. Sci., USA, 79* :2722-5.

BESEDOVSKY, H. & SORKIN, E., 1977. Network of immune-neuroendocrine interactions. *Clin. Exp. Immunol., 27* :1-12.

BESEDOVSKY, H.; DEL REY, A.; SORKIN, E.; DA PRADA, M.; BURRI, R. & HONEGGER, C., 1983. The immune response evokes changes in brain noradrenergic neurons. *Science, 221* :564-6.

BLALOCK, J.E., 1984. The immune system as a sensory organ. *J. Immunol., 132* :1067-70.

BLEIER, R.H.; ALBRECHT, R. & CRUCE, J.A.F., 1975. Supraependymal cells of hypothalamic third ventricles: identification as resident phagocytes of the brain. *Science, 189* :299-301.

BRADBURY, M., 1981. Lymphatics and the central nervous system. *Trends in Neuroscience, 4* :100-1.

BRUCE, M.G. & FERGUSON, A., 1986. Oral tolerance to ovalbumin in mice: studies of chemically modified and "biologically filtered" antigen. *Immunology, 57* :627-30.

BRÜNER, K. & KÖLSCH, E., 1981. Maintenance of lowzone tolerance to bovine serum albumin by T suppressor cells. *Cell Immunol., 62* :463-47.

CASHMAN, N.R. & NORONHA, A., 1986. Acessory cell competence of ovine oligodendrocytes in mitogenic activation of human peripheral T cells. *J. Immunol., 136* :4460-3.

CYBULSKY, M.I.; GOLDITZ, I.G. & MOVAT, H.Z., 1986. The role of interleukin-1 in neutrophil leukocyte emigration induced by endotoxin. *Am. J. Pathol., 124* :367-72.

FIERZ, W.; ENDLER, B.; RESKE, K.; WEKERLE, H. & FONTANA, A., 1985. Astrocytes as antigen-presenting cells. I – Induction of Ia antigen expression on astrocytes by T cells via immune interferon and its effect on antigen presentation. *J. Immunol., 134* :3785-93.

FÖLDI, M., 1977. Pre-lymphatic-lymphatic drainage of the brain. *Am. Heart J., 93* :121-4.

FONTANA, A.; KRISTENSEN, F.; DUBS, R.; GEMSA, D. & WEBER, E., 1982. Production of prostaglandin E and interleukin-1 like factor by cultured astrocytes and C6 glioma cells. *J. Immunol., 129* :2413-9.

FONTANA, A.; WEBER, E. & DAYER, J.M., 1984. Synthesis of interleukin-1/endogenous pyrogen in the brain of endotoxintreated mice: a step in fever induction? *J. Immunol., 133* :1696-8.

FORSBERG, P.; KAM-HAMSEN, S. & FRYDÉN, A., 1986. Production of specific antibodies by cerebrospinal fluid lymphocytes in patients with herpes zoster, mumps meningitis and herpes simplex virus encephalites. *Scand. J. Immunol., 24* :261-71.

FREI, K.; BODMER, S.; SCHWERDEL, C. &FONTANA, A., 1985. Astrocytes of the brain synthesize interleukin 3-like factors. *J. Immunol., 135* (6) :4044-7.

GIULIAN, D. & LACHMAN, L.B., 1985. Interleukin-1 stimulation of astroglial proliferation after brain injury. *Science, 228* :497-9.

GIULIAN, D.; TOMOZAWA, Y.; HINDMAN, H. & ALLEN, R.L., 1985. Peptides from regenerating central nervous system promote specific populations of macroglia. *Proc. Natl. Acad. Sci., USA, 82* :4287-90.

HART, D.N.J. & FABRE, J.W., 1981. Demonstration and characterization of Ia positive dendritic cells in the interstitial connective tissues of rat heart and other tissues, but not brain. *J. Exp. Med., 153* :357-61.

HICKEY, W.F. & KIMURA, H., 1987. Graft-vs-host disease elicits expression of class I and class II histocompatibility antigens and the presence of scattered T lymphocytes in rat central nervous system. *Proc. Natl. Acad. Sci., USA, 84* :2082-6.

JUSTICE, A., 1985. Review of the effects of stress on cancer in laboratory animals: importance of time of stress application and type of tumor. *Psychol Bull, 98* (1) :108-38.

KAM-HANSEN, S., 1986. Asymptomatic oligoclonal CSF IgG and progressive increase of intrathecal IgG synthesis in a patient with myasthenia gravis treated with thymectomy. A 4-years follow-up. *J. Neurol. Sci., 75* :285-92.

LIVNAT, S.; FELTEN, S.T.; CARLSON, S.L.; BELLINGER, D.L. & FELTEN, D.L., 1985. Involvement of peripheral and central catecholamine systems in neural-immune interactions. *J. Neuroimmunol., 10* :5-30.

LUBLIN, F.D.; TIPPETT, D.L. & MAURER, P.H., 1983. Central nervous system and blood lymphocytes in experimental allergic encephalomyelitis. *J. Clin. Lab. Immunol., 10* :139-42.

MAESTRONI, G.J.M.; CONTI, A. & PIERPAOLI, W., 1987. Role of the pineal gland in immunity: II Melatonin enhances the antibody response via an opiatergic mechanism. *Clin. Exp. Immunol., 68* :869-76.

McKEEVER, P.E. & BALENTINE, J.D., 1978. Macrophage migration through the brain parenchyma to the perivascular space following particle ingestion. *Am. J. Pathol, 93* :153-164.

MEDAWAR, P.B., 1948. Immunity to homologous grafted skin. III The fate of skin homografts transplanted to the brain, subcutaneous tissue and to the anterior chamber of the eye. *Br. J. Exp. Pathol., 29* :58-69.

MEHTA, P.D.; PATRICK, B.A. & TORMAR, H., 1982. Measles specific IgG in CSF and serun from patients with subacute sclerosing panencephalitis. *Immunology, 46* :423-8.

MERRIL, J., 1987. MACROGLIA: Neural cell responsive to lymphokines and growth factors. *Immunology Today, 8* (5) :146-50.

MOORE, T.C., 1984. The modulation by prostaglandins of increases in lymphocyte traffic induced by bradykinin. *Immunology, 51* :455-60.

QUIRICO-SANTOS, T. & VALDIMARSSON, H., 1982. T-dependent antigens are more immunogenic in the subarachnoid space than in other sites. *J. Neuroimmunol., 2* :215-22.

QUIRICO-SANTOS, T. & VALDIMARSSON, H., 1985. Antibody production in the brain tissue of mice immunized into the central nervous system. *Brazilian J. Med. Biol. Res., 18* :217-22.

QUIRICO-SANTOS, T. & VALDIMARSSON, H., 1987. Modulation of systemic antibody response and tolerance by brain injury. *Annals New York Acad. Sci. (USA), 496* :384-7.

RAJU, S. & CROGAN, J.B., 1977. Immunologic study of the brain as a privileged site. *Transpl. Proc. vol. IX* :1187-91.

RENOUX, G.; BIZIERE, K.; RENOUX, M. & GUILLAUMIN, J.M., 1983. The production of T-cell-inducing factors in mice is controlled by the brain neocortex. Scand. *J. Immunol., 17* :45-50.

RÖSTROM, B.; LINK, H. & NORRBY, R., 1981. Antibodies and oligoclonal immunoglobulins in CSF from patients with acute cerebrovascular disease. *Acta Neurol. Scand., 64* :225-40.

ROSZMAN, T.L. & BROOKS, W.H., 1985. Neural modulation of immune function. *J. Neuroimmunol., 10* :59-69.

RUMJANEK, V.M.; WATSON, S.R. & SLIJIIVIC V.S., 1977. A reevaluation in the role of macrophages in carrageenan-induced immunossupression. *Immunology, 33* :423-32.

SCHNYDER, B.; WEBER, E.; FIERZ, W. & FONTANA, A., 1986. On the role of astrocytes in polyclonal T cell activation. *J. Neuroimmunol., 10* :209-18.

TOBLER, J., BORBILY, A.A., SCHWYZER, M. & FONTANA, A., 1984. Interleukin-1 derived from astrocytes enhances slow wave activity in sleep EEG of the rat. *Eur. J. Pharmacol., 104* :191-2.

TRAUGOTT, U.; REINHERZ, E.L. & RAINE, C.S., 1983. Multiple sclerosis – Distribution of T cells, T cell subsets and Ia positive macrophages in lesions of different ages. *J. Neuroimmunol., 4* :201-21.

WAKSMAN, B., 1985. Mechanisms in multiple sclerosis. *Nature, 318* :104-5.

WEKERLE, H.; SCHWAB, M., LININGTON, C. & MEYERMANN, R., 1986. Antigen presentation in the peripheral nervous system: Schwann cells present endogenous myelin autoantigens to lymphocytes. *Eur. J. Med., 16* :1551-7.

WONG, G.H.W.; BARTLETT, P.F.; CLARK-LEWIS, J.; McKIMM-BRESCHKIN, J.L. & SCHRADER, J. W., 1985. Interferon gamma induces the expression of H-2 and I-a antigens on brain cells. *J. Neuroimmunol., 7*: 255-78.