Blood-brain barrier permeability in rats exposed to electromagnetic fields used in wireless communication

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Biological effects of *radio frequency* electromagnetic fields (EMF) on the blood-brain barrier (BBB) have been studied in Fischer 344 rats of both sexes. The rats were not anaesthetised during the exposure. All animals were sacrificed by perfusion–fixation of the brains under chloralhydrate anaesthesia after the exposure. The brains were perfused with saline for 3–4 minutes, and thereafter perfusion fixed with 4% formaldehyde for 5–6 minutes. Whole coronal sections of the brains were dehydrated and embedded in paraffin and sectioned at 5 μm. Albumin and fibrinogen were demonstrated immunohistochemically and classified as normal versus pathological leakage. In the present investigation we exposed male and female Fischer 344 rats in a Transverse Electromagnetic Transmission line chamber to microwaves of 915 MHz as continuous wave (CW) and pulse-modulated with different pulse power and at various time intervals. The CW-pulse power varied from 0.001 W to 10 W and the exposure time from 2 min to 960 min. In each experiment we exposed 4–6 rats with 2–4 controls randomly placed in excited and non-excited TEM-cells respectively. We have in total investigated 630 exposed rats at various modulation frequencies and 372 controls. The frequency of pathological rats is significantly increased ($p < 0.0001$) from $62/372$ (ratio: 0.17 ± 0.02) for control rats to $244/630$ (ratio: 0.39 ± 0.03) in all exposed rats. Grouping the exposed animals according to the level of specific absorbed energy (J/kg) give significant difference in all levels above 1.5 J/kg. The exposure was 915 MHz microwaves either pulse modulated (PW) at 217 Hz with 0.57 ms pulse width, at 50 Hz with 6.6 ms pulse width or continuous wave (CW). The frequency of pathological rats (0.17) among controls in the various groups is not significantly different. The frequency of pathological rats was $170/481$ (0.35 ± 0.03) among rats exposed to pulse modulated (PW) and $74/149$ (0.50 ± 0.07) among rats exposed to continuous wave exposure (CW). These results are both highly significantly different to their corresponding controls ($p < 0.0001$) and the frequency of pathological rats after exposure to pulsed radiation (PW) is significantly less ($p < 0.002$) than after exposure to continuous radiation (CW).

1. Introduction

The mammalian brain is protected from potentially harmful compounds in the blood by the so called blood-brain barrier (BBB). It is a selectively permeable, hydrophobic barrier that is readily crossed by small, lipid-soluble molecules [19,24]. Certain lipid-insoluble molecules such as glucose also readily crosses the cell layers constituting the barrier through carrier proteins that have a high affinity with specific molecules.

Although knowledge of the barrier's adaptive role is far from complete, there is a growing consensus that it serves not only to restrict entry of toxic polar molecules into the brain. It also serves as a regulatory system that stabilises and optimises the fluid environment of the brain's intracellular compartment [19,24].

The intact BBB protects the brain from damage, whereas a dysfunctioning BBB, as induced by epileptic seizures or extreme hypertension, allows influx of normally excluded hydrophilic molecules into the brain tissue. This might lead to cerebral oedema, increased intracranial pressure and in the worst case, irreversible brain damage.

The normal selective permeability of the blood-brain barrier (BBB) can be altered in several neuropathological conditions and experimental situations. The BBB opens during an acute hypertensive episode [30], in epileptic seizures [15,31], and during therapeutic X-ray irradiation [16].

Several authors have reported that electromagnetic exposure alters BBB permeability [1–4,7,8,10–12,17,20,21,32, 33]. Other authors have reported difficulties in confirming these findings [11,14,22,23,35–38]. The lack of agreement among investigators might be due to lack of an assay of BBB permeability that combines sensitivity and specificity.

Shivers et al. [29] observed during exposure to clinical magnetic resonance imaging (MRI) procedures an amplified vesicle-mediated transport of horseradish peroxidase across the endothelium to the extracellular compartment of the brain parenchyma of the rat. They did not, however, report on effects of the exclusive field components. The mechanism involved, however, points strongly to facilitation of *pinocyosis*-like transport of albumin through BBB [18].

In the present investigation we have studied the permeability of BBB to endogenous albumin and fibrinogen during exposure to microwaves. We exposed rats to 915 MHz microwaves as continuous wave (CW) and pulse-modulated at the various repetition rates (4–217 s^{-1}). Preliminary results are previously reported by Salford et al. [25–28].

Our model does not make use of radioactive tracers and does not supply foreign substances or anaesthetics to the

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rat during exposure. Instead it uses the animals own albumin, that does not penetrate the intact BBB. The passage of even minute amounts of albumin from the capillaries through an opened BBB into the surrounding brain tissue is revealed by our histopathological technique. This also allows for the identification of exactly in which constituents (neurones, glial cells, extracellular space) of the surrounding brain, where the albumin is situated. The perfusion–fixation method washes out all blood and its albumin content from the brain vessels including the capillaries. This facilitates the identification of albumin that has leaked out through the opened BBB into the brain.

2. Material and methods

2.1. Exposure in a TEM-cell

A Transverse Electromagnetic transmission line cell (TEM-cell) used for the RF exposure of rats was designed by dimensional scaling from previously constructed cells at the National Bureau of Standards (Crawford, 1974). TEM-cells are known to generate uniform TEM-fields for standard measurements.

The cell is enclosed in a wooden box that supports the outer conductor and central plate. The outer conductor is made of brass-net and is attached to the inner walls of the box. The centre plate, or septum, is constructed of aluminium and is held up by teflon braces which are screwed at the inner side walls.

To allow access to the inside of the cell both ends can be removed. The inside of the cell is ventilated through 18 holes (diam. 18 mm) in the side walls and top of the box and the brass-net of 50 mesh allows air to circulate. These holes are also used for examination of the interior during exposure. Probes for monitoring temperature inside the cell or of test object are inserted through these holes.

The rats are placed in plastic trays to avoid contact with the central plate and outer conducter. The bottom of the tray is covered with absorbing paper to collect urine and faeces.

The rats were exposed to 915 MHz electromagnetic radiation continuous wave and pulse-modulated with different repetition rates. The modulated RF-radiation consists of square wave shaped pulses with durations of 0.57, 4 or 6 ms and intensities (in Watts) during the presence of the pulse. Transmitted and absorbed power was measured at continuous wave exposure with and without rats in the TEM-cell. From these measurements the average SAR in the whole rat was calculated to be 1.2 ± 0.4 W/kg per watt of input power. This value was in good agreement with the theoretical estimate of 1.6 W/Kg per watt of input power that was used in the evaluation of the experiment [5,9,13,34].

2.2. Albumin and fibrinogen immunohistochemistry

Fischer 344 rats of both sexes, weighing 119–555 g (median: 202 g; 25% quartiles: 175 g; 75% quartiles: 273 g) were used in these experiments (own breeding). The rats were not anaesthetised, during the exposure.

Both controls and exposed animals were sacrificed by perfusion–fixation of the brains under chloralhydrate anaesthesia between 20 minutes and 2 hours after the exposure. The brains were perfused with saline for 3–4 minutes, thereafter fixed in 4% formaldehyde for 5–6 minutes and immersion fixed in 4% formaldehyde for more than 24 hours. Whole coronal sections of the brains (3, 7 and 11 mm from the tip of the frontal pole) were dehydrated and embedded in paraffin and sectioned at 5 m. The chloralhydrate anaesthesia is necessary to avoid stress and blood pressure rise during perfusion–fixation procedure. Also for ethical reason no animals were sacrificed without chloralhydrate anaesthesia.

Albumin was demonstrated with the IgG fraction of rabbit anti-rat albumin (Cappel Research Products, Organon Teknika, Västra Frölunda, Sweden) diluted 1:16,000. Fibrinogen was demonstrated with rabbit anti-human fibrinogen (Dacopatts AB, Hägersten, Sweden), diluted 1:500. Incubation time for both was over night at 4°C.

Biotinylated swine anti-rabbit IgG was used as a secondary antibody. Then avidin, peroxidase conjugated, was coupled to the biotin and visualised with DAB (diaminobenzidine), counterstained with Meyer-HTX [6]. Standard control procedures were used for both albumin and fibrinogen.

The numbers of immunopositive extravasates were recorded under a microscope. None or occasional minor leakage was rated as normal, whereas one larger or several leakages were regarded as pathological. Immunopositive sites were, however, disregarded when localised in the hypothalamus, basally from the median eminence and laterally including the nucleus lateralis hypothalami, in the immediate vicinity of the third ventricles. These structures are well known for their insufficient blood-brain barrier and within any part of of the choroid plexus of the ventricles consitently shows immunopositivities, mostly of a diffuse type, in the strain used in the present experiments.

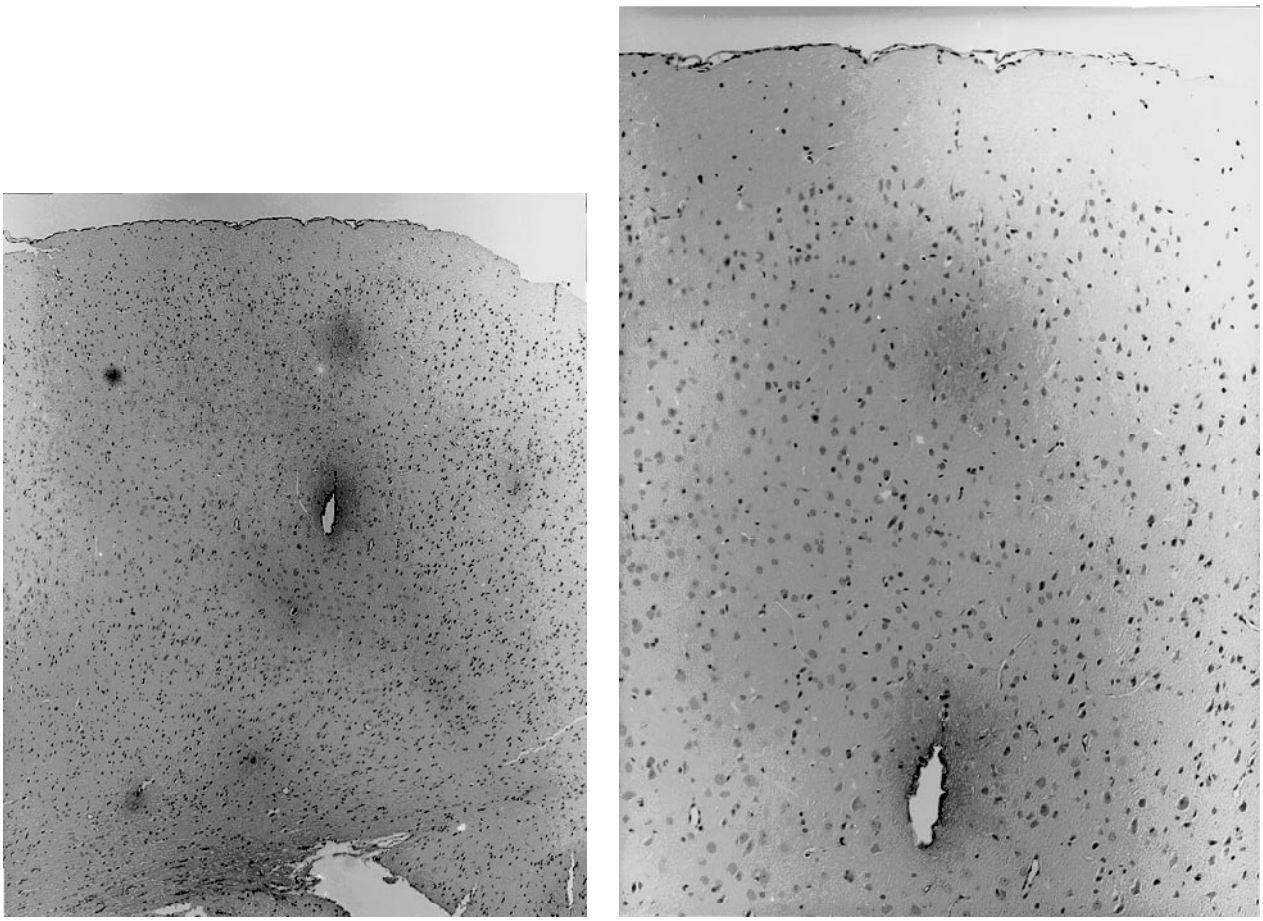
2.3. Statistics

The frequency of occurrence of albumin extravasation in exposed and control animals were compared with chi-square or Fisher's exact probability test.

3. Results and discussions

Example of pathological leakage around small vessels is demonstrated in figure 1. The number of pathological rat brains among all control rats is 62 out of 372 (ratio: 0.17 ± 0.02). These findings are occasional and rare and are probably due to normal minor disturbances. The frequency of pathological rats among controls in the various groups is not significantly different ($p < 0.4$).

In the present investigation we exposed male and female Fischer 344 rats in a TEM-chamber to microwaves of 915 MHz as continuous wave (CW) and pulse-modulated



(a) (b)

Figure 1. Example of pathological leakage around small vessels demonstrated through immunostaining against albumin. Hematoxylin eosin staining. (a) Section through frontal lobe with cortex and white matter, magnification $\times 5$. (b) Part of (a) with vessel, magnification $\times 10$.

with different pulse power and at various time intervals. The CW-pulse power varied from 0.001 W to 10 W and the exposure time from 2 min to 960 min. In each experiment we exposed 4 rats with 4 controls randomly placed in excited and non-excited TEM-cells, respectively.

We have in total investigated 630 exposed rats at various modulation frequencies and 372 controls. The frequency of pathological rats is significantly increased ($p < 0.0001$) from $62/372$ (ratio: 0.17 ± 0.02) for control rats to $244/630$ (ratio: 0.39 ± 0.03) in all exposed rats. Grouping the animals according to the level of specific absorbed energy (J/kg) that is normally referred to as "Specific Absorption" (SA), give significant difference ($p < 0.0001$) in all levels of absorbed energy above 1.5 J/kg compared to controls. (see table 1).

The exposure was 915 MHz microwaves either pulse modulated (PW) at 217 Hz with 0.57 ms pulse width, at 50 Hz with 6.6 ms pulse width or continuous wave (CW). The frequency of pathological rats (< 0.2) among controls in the various groups is not significantly different ($p < 0.4$). The frequency of pathological rats was $170/481$ (0.35 ± 0.03) among rats exposed to pulse modulated (PW) and $74/149$ (0.50 ± 0.07) among rats exposed to continuous wave exposure (CW). These results are both highly significantly different to their corresponding controls ($p < 0.0001$) and the frequency of pathological rats after exposure to pulsed radiation (PW) is significantly less ($p < 0.002$) than after exposure to continuos radiation (CW) (table 2). The degree of pathological leakage in exposed animals is more severe and more frequent per animal compared to the controls.

The results of BBB-permeability of albumin in rats exposed to 915 MHz microwaves with different modulation frequencies for groups exposed to similar SAR values are displayed in figures 2–5. In figure 2 are displayed the results at SAR values 4×10^{-4}–8×10^{-3} W/kg. Although the SAR values are very low, around 1 mW/kg, this group indicates the highest fraction of pathological findings recorded in the entire investigation. There seems to be a maximum effect around 8–50 Hz modulation frequency. In figure 3 is given the results at SAR values (2–8) $\times 10^{-2}$ W/kg. In this group the effect of CW and 50 Hz modulation is the same but the effect of 16 Hz and 8.3 & 217 Hz GSM modulation is very low and not significant. The overall effect of pulse modulated exposure is, however, significant. Figure 4 shows the results at SAR values 0.11–0.95 W/kg. The effect of CW exposure is about the same as in previous group but the effect of 217 Hz pulse modulation shows

Table 1
BBB-permeability of rat brain after 915 MHz RF-exposure at various intervals of specific absorption SA (J/kg).

Group of specific absorption (J/kg)	Normal score < 1	Pathological score $\geqslant 1$	Ratio $\pm$ SD Pathological/all	Chi-square # Contr. p
Controls SA $= 0$	310	62	0.17 ± 0.02	
$1.5 \leqslant$ SA < 10	32	34	0.52 ± 0.11	< 0.00005
$10 \leqslant$ SA < 100	30	20	0.40 ± 0.11	< 0.0002
$100 \leqslant$ SA < 1000	116	61	0.34 ± 0.05	< 0.00005
$1000 \leqslant$ SA $< 10\,000$	122	78	0.39 ± 0.05	< 0.00005
$10\,000 \leqslant$ SA $< 48\,000$	90	52	0.37 ± 0.01	< 0.00005
All exposed (630)	386	244	0.39 ± 0.03	< 0.00005

Table 2
BBB-permeability of rat brain after exposure to 915 MHz microwaves either Pulsed (PW) or Continuous Wave (CW).

Group	Number of rats with normal score < 1	Number of rats with pathological score $\geqslant 1$	Ratio $\pm$ SD No. score $\geqslant 1$ to all	p Chi-square exposed versus controls	p Chi-square PW versus CW
Controls pulsed (259)	219	40	0.15 ± 0.03	0.68	0.34
Controls CW (113)	91	22	0.19 ± 0.05	0.49	
All controls (372)	310	62	0.17 ± 0.02		
All exposed pulsed (481)	311	170	0.35 ± 0.03	< 0.00005	< 0.002
All exposed CW (149)	75	74	0.50 ± 0.07	< 0.00005	
All exposed (630)	386	244	0.39 ± 0.03	< 0.00005	

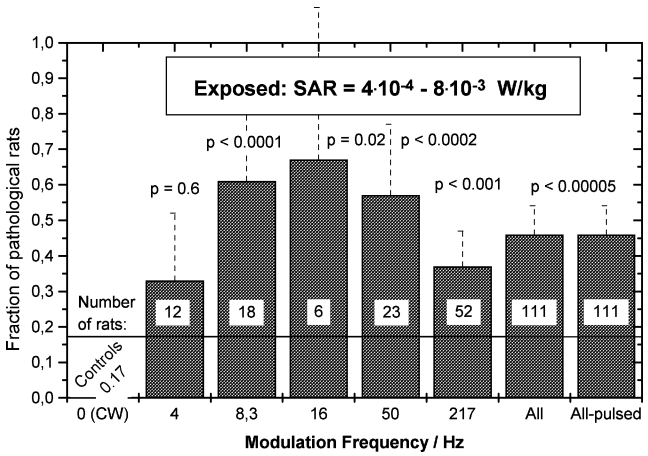


Figure 2. Blood-brain barrier permeability of albumin in rats exposed to 915 MHz microwaves with different modulation frequencies at SAR values 4×10^{-4}–8×10^{-3} W/kg. The average fraction of pathological leakage in 372 controls was 0.17 ± 0.02.

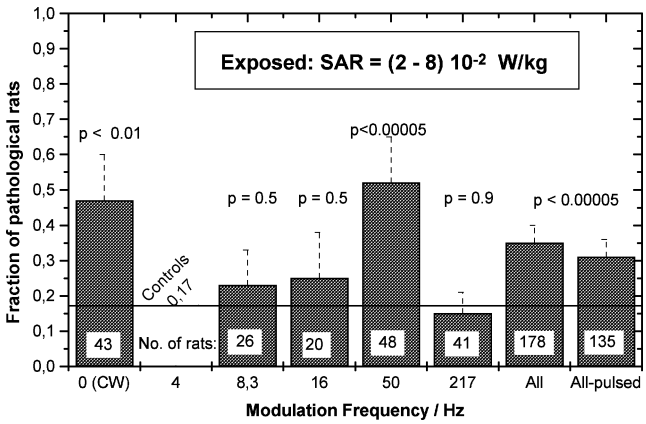


Figure 3. Blood-brain barrier permeability of albumin in rats exposed to 915 MHz microwaves with different modulation frequencies at SAR values $(2–8)\times 10^{-2}$ W/kg. The average fraction of pathological leakage in 372 controls was 0.17 ± 0.02.

a significant effect compared to controls. The effect of 8.3 and 16 Hz modulation is however not significantly different from the controls. Figure 5 displays the results at SAR values 1.7–8.3 W/kg. In this group the SAR levels approach the threshold for thermal effects and the effect of CW exposure is very pronounced with a fraction of pathological rats of 55%. Surprisingly the effect of pulse modulated exposure is not significant at this high SAR level.

The frequency of pathological rats was $170/481$ (0.35 ± 0.03) among rats exposed to pulse modulated (PW) and $74/149$ (0.50 ± 0.07) among rats exposed to continuous wave exposure (CW). These results are both highly significantly different from their corresponding controls ($p < 0.0001$) and the frequency of pathological rats after exposure to pulsed radiation (PW) is significantly less ($p < 0.002$) than after exposure to continuous radiation (CW) (table 2). This is a highly interesting observation as the current opinion is that pulse modulated electromagnetic fields are more potent in causing biological effects.

We have demonstrated that microwave exposure produces an unequivocal effect on the BBB in our rats. The clinical importance of this finding, however, is disputable. Our method for detection of albumin is extremely sensi-

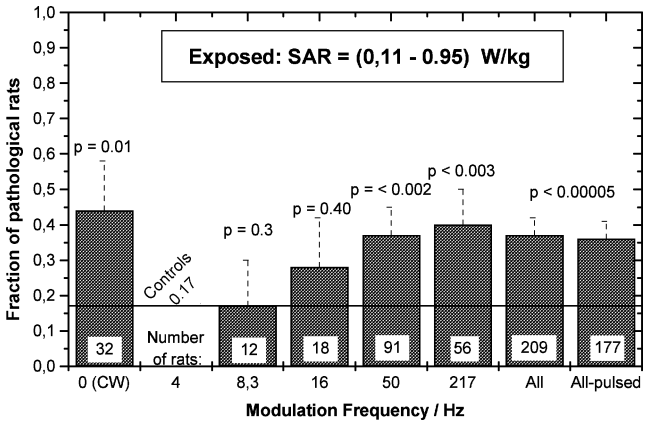


Figure 4. Blood-brain barrier permeability of albumin in rats exposed to 915 MHz microwaves with different modulation frequencies at SAR values 0.11–0.95 W/kg. The average fraction of pathological leakage in 372 controls was 0.17 ± 0.02.

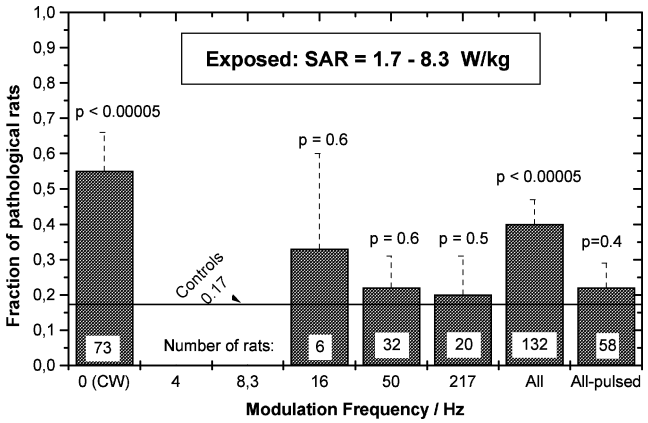


Figure 5. Blood-brain barrier permeability of albumin in rats exposed to 915 MHz microwaves with different modulation frequencies at SAR values 1.7–8.3 W/kg. The average fraction of pathological leakage in 372 controls was 0.17 ± 0.02.

tive and reveals even minute amounts of albumin leaking through the BBB, so small that they may be harmless to the brain. However, the potential health hazards of the opening the BBB during exposure to wireless communication demands further investigation.

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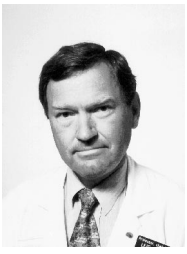
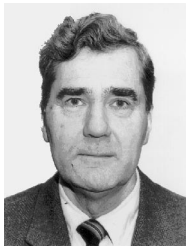
In 1977 he began to study microwave induced hyperthermia for tumour-therapy and since then this project has expanded very rapidly. He developed an equipment for local hyperthermia in patients with breast carcinoma, and recently equipment for heat treatment of benign prostate hyperplasia and menorraghia. He started already in 1982 with biomedical applications of nuclear magnetic resonance (NMR) and has developed and built a special equipment for performing in vivo NMR studies in both animal and man. In close co-operation with several other scientists he is also conducting *in vitro* studies of the NMR relaxation times in tissues of thyroid and brain, also studying the influence of paramagnetic ions and super-paramagnetic particles. He has studied extensively clinical measurements of flow, microcirculation, diffusion and perfusion with NMR. During the past years he has been deeply involved in studying the effects of electromagnetic fields on healthy brain and on brain-tumours. He was co-sponsor for the New York Academy of Science conference on the biological and health effects of clinical NMR examination held in 1991. At present he is deeply involved in studies of the effect of low power pulsed microwave fields on the blood brain barrier and other biological systems. He is also engaged in using electromagnetic fields for tumour therapy and has made a lot of progress in the use of high voltage electric fields for permeabilization of tumour cell membranes in vivo. The objective of that investigation is to study the destructive effect of electropermeabilization on tumours and its ability to introduce toxic compounds into tumour cells. He is studying the therapeutic effect of electropermeabilization on tumour cells in presence of chemotherapeutic agents (for example, Bleomycin) and radioimmunotherapeutic agents.



Leif G. Salford was born in Malmö, Sweden, in 1941. He received the MD degree from the University of Lund in 1969, and the Ph.D. degree from the same university in 1974 with the thesis "Influence of profound hypoxia on regional metabolism, blood flow and cell morphology in rat brain". During 1972–1973 he was Wrightsman scholar at the Dept. of Neurology, Cornell Medical Center, New York Hospital, NY. In 1977 he became associate professor of neurosurgery, Lund University, and in 1979 Consultant Neurosurgeon. He was Professor and Chairman, Department of Neurosurgery, Kuwait University, 1981–1983, and Professor of Neurosurgery and Director of the Departments of Clinical Neurosciences, Sahlgrenska University Hospital and Göteborg University, Sweden, 1993–1996. His actual positions are: Professor and Chairman, Dept. of Neurosurgery, Lund University Hospital, and Director of the Institute for Clinical Neuroscience, Lund University, Lund, Sweden. Dr. Salford is Chairman of the Neuro-oncology Committee of the World Federation of Neurosurgical Societies, and President of the European Association for Neuro-oncology. He is President of the Swedish Neurosurgical Society, Honorary President of the Scandinavian Neurooncology Society and Expert in the EU Information Society Forum.

Dr. Salfords' research is concentrated on the malignant primary brain tumours and on the search for efficient treatment against this hitherto incurable type of cancer. This has also resulted in his studies of opening the

blood-brain-barrier by the use of electromagnetic fields in order to reach the tumour cells with cytotoxins, and in his interest in the biophysical effects of EMF upon brain and tumour biology. Dr. Salford is Director of the Laboratory for Experimental Neurooncology, Lund University, where animal models and tissue cultures play an important role in his research in close cooperation with technological institutions such as Medical Radiation Physics. He strives to utilize the latest progress in technology in his search for solutions to medical problems. Another result of this collaboration is the introduction of electropermeabilisation *in vivo* as a tool for treatment of intraparenchymatous tumours which has proven efficient in connection with cytotoxins in the rodent brain tumour model.



Arne Brun, MD, Ph.D., is a professor of neuropathology, University Hospital, Lund, Sweden. His publications are mainly on central nervous system diseases such as dementias, especially the Alzheimers' disease and frontal dementias, also cerebrovascular incl. BBB-studies.