

the blood brain barrier as a selective filter rather than a barrier. Investigations have shown that permeability increases when there is an increase in the body's temperature and when there is an increase in function. An increase in the brain's temperature while using a mobile phone hardly ever occurs. Concerning this, after the test person had been using the telephone for a quarter of an hour at maximum power, the temperature under the cranial calotte was increased by 0.1°K. During a warm bath, hard physical labour or being exposed to the sun for a longer period of time all lead to an greater increase in temperature. How the blood brain barrier reacts in these situations or how the body tolerates such changes is yet to be investigated.

Since the extent of permeability returns to its original state after an increase in temperature, experiments should be done investigating these effects shortly after the influential factors produce an effect. If changes are discovered weeks after exposure, as described in the Salford (5) study, it can not be ruled out that in the duration there were other effects which could have affected the test animals and gave rise to changes affecting the filter function of the blood brain barrier.

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Developments in research concerning this subject

Is the blood brain barrier effected by mobile radio fields?

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Again and again the public is alarmed by reports stating that telephoning with a mobile phone will cause the blood brain barrier BBB to open and nerve damage will result or even brain tumours may develop. How serious are these warnings and how protected are we by the current limit values?

Firstly, it must be established that the blood brain barrier is not an anatomically localized organ but is a special feature of the blood capillaries located in most areas of the brain. In order to protect the brain, which is the most sensitive organ in the human body, from toxic substances the capillary endothelial cells are joined by tight junctions, a sealing mechanism that makes it difficult or impossible for certain substances to permeate the BBB. Only soluble gases required for cell respiration, oxygen and carbon dioxide, as well as nutrients such as D-glucose, D-hexose, L-amino acids and lipid soluble molecules are able to permeate this barrier. In stress situations, cranial trauma and with various illnesses a malfunction of the barrier

can occur, these malfunctions are usually quickly repaired. (Blasberg et al. 79).

Quite early on one thought that high frequency fields could cause an increase in temperature and quasi induce an artificial fever and this in turn would lead to the BBB being affected. This unwanted side-effect had been observed in conjunction with the so-called short-wave therapy. However on the other hand, it was used to administer medication directly to the brain (Lin et al. 98). Therefore, this effect has been investigated for more than three decades.

The first animal experiments in connection with possible harmful effects to the BBB caused by radio and radar fields were done in the 1970s by Frey et al., at first they thought that this would also promote cancerostatica in the brain (Frey et al. 75, Frey 79). Sutton and Carroll (79) have pointed out that when the temperature of rats' brains is increased to 45° C induced by a 2450 MHz-field there is an increase in protein absorption.

Oscar and Hawkins (77) examined in rats the absorption of ¹⁴C marked sugar molecules of various molecular weights, while they were being exposed to different power densities of continuous and pulsing fields of 1.3 GHz. While dextrin with a molecular weight (MG) of 60.000-75.000 was not absorbed at all, they discovered that mannitol (MG = 182.2) and inulin (MG = 5.000-5.500) had an absorption intensity as a function of the applied power flow density, which showed the maximum to be at about 10 W/m². Pulses of the same average power flow density but of differ-

ent lengths and frequencies showed differences in absorption intensities. These results could not be confirmed later (Meritt et al. 78, Preston et al. 79, Gruenau et al. 82, Ward et al. 82, 85).

How can this contradiction evident in different investigation be explained? Obviously there is a series of methodological difficulties which are easily open to misinterpretations (Rapopor et al. 79, Williams, Hoss, et al. 84, Williams, Plattner et al. 84). So for example, a change in capillary perfusion could slightly increase the permeability of substances, without a change in normal permeability taking place. However, artefacts are to be seriously considered, which can occur during the dissection of the brain and during its histological processing. If the fixation process or the freezing of the tissue which follows is not done properly, the substances being investigated could during this process permeate the BBB. During the storage of preserved brains the diffusion of these substances can enter into areas of the brain that are not protected by the BBB. What can also occur is that the indicator substances can smear during dissection and this can especially happen when histological slides are being prepared. Since the BBB is without a doubt permeable for larger molecules when there is a clear rise in temperature, an exact dosimetry is all the more necessary. An erroneous assessment of local SAR-values in the brain with the application of HF-fields can easily lead to such an effect being produced by warming.

In various studies Salford et al. (92, 93, 94) as well as Persson, Salford et al. (92) have shown with histochemical techniques that pulsing as well as continual 915 MHz-fields are able to temporarily make the BBB permeable to plasma-albumin. Unfortunately, in these studies there is no reliable data on the power density and SAR-values. In spite of this the results received a lot of attention and different attempts have been made to verify the re-

sults. Fritze et al. (97) exposed rats during the course of 4 hours with these frequencies, where different SAR-values were applied, from 0.3-7.5 W/kg. Only with extreme irradiation, 7.5 W/kg, could these authors produce with certainty an increase in brain temperature and consequently a significant cross over of albumin into the brain. Even this effect was rather slight when compared to the effects produced in the positive controls where the animal had to undergo a cold shock. Recently two articles on this subject were published by Finnie et al. (01, 02). In the first publication, the Australian team reported on experiments where rats were irradiated for one hour at SAR-values of 4 W/kg (898,4 MHz, 217 Hz pulsed). In contrast to the positive controls after applying clostridium toxin, no difference could be found between the irradiated rats and the rats which were not irradiated. In the second publication they attempted to find an answer to the question as to whether or not during long-term exposure albumin could permeate into the brain. During the course of 104 weeks, mice were exposed to a 900 MHz far-field, five days a week for one

hour per day, which corresponds to SAR-values ranging from 0.25 to 4 W/kg. In this long-term experiment in an extreme case there were some negligible traces of albumin detected in the brain. However, these can be ignored when compared to the effects the toxin produced.

Even experiments testing the BBB permeability to other substances while under the influence of high frequency fields with intensities below the limit values showed no results (Lange et al. 91, Lin et al. 98, Masuda et al. 01, 02). The work of a Japanese study by Tsurita et al. (2000) has to be mentioned in this context. In this experiment rats were irradiated with fields according to the Japanese TDMA-standard for two hours a day for 2 to 4 weeks (1439 MHz, SAR for the head: 2W/kg, the entire body SAR 0.25 W/kg). In this carefully conducted experiment neither the absorption of the vital staining substance Evans-blue nor morphological changes in the cerebellum nor could Purkinje cells be detected. On the other hand, clear effects were shown in the positive controls, where head temperature was increased for a short time or where they were under cooled. In



an analysis of the work done by the Salford group, Tsurita et al. criticized it in this publication for their faulty irradiation and dosimetric techniques.

If one were to sum up the current developments in research regarding this area, one could come to the conclusion that no effects to the BBB can be verified stemming from weak mobile radio fields. Only concerning flow densities which have a thermal effect on the brain, is the BBB temporally permeable to proteins and other large molecules.

A short while ago, after a 10-year break, an report by Leif G. Salford's working group on new experiments involving the effects of mobile radio fields on the brains of rats appeared. In contrast to the first experiments, which were published in a journal that uses a referee system, this report was published in the National Institute of Environmental Health Sciences own journal. (Salford et al. 2003).

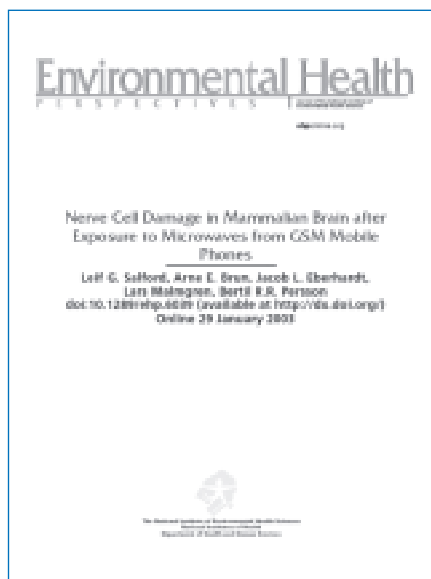
The article pertains to an experiment conducted on 32 rats of both sexes, which were divided into 4 groups each containing 8 rats. The rats from 3 of these groups were irradiated individually and only once for 2 hours in a TEM cell at a power flow density of 0.24; 2.4 and at 24 W/m². The rats in the fourth group were the control group. Calculations resulted in entire body SAR-values of 2; 20 and 200 mW/kg. After a course of 50 days the rats were finally examined, they were sacrificed being anaesthetized and the brains were fixated with a formol-perfusion. Histological examinations revealed that the irradiated rats had albumin-positive staining near the smaller blood capillaries and there was further albumin spreading between nearby cells and neurons. Moreover, with regard to the irradiated rats it was demonstrated with Kresyl-violet staining techniques that there were scattered dark and obviously shrivelled and degenerated cells. The evaluation of the histological tests blindly ensued according to a half-quantitative evaluation system in three steps: 0

= no or very few dark neurons, 1= moderate occurrence, 2 = frequent occurrence. When these figures are applied to the intensity of the exposure, a correlation can be made despite the heavy scattering effect. The authors gave a significance effect of $p < 0.002$.

The authors concluded from this experiment that through a non thermal effect, (the experimental set-up was located in a room with a thermostat), resulting from HF-irradiation an increase in BBB permeability occurred. As the authors had already hypothesized in an earlier study, when albumin penetrates the brain from the blood it could lead to a degeneration of nerve cells.

Since the experimental animals were young rats, 12-14 weeks old, the authors considered the results especially relevant concerning the question as to whether or not teenagers are exposing themselves to any risks while using mobile phones. However, it has been conceded that the effects which were observed here are in principle repairable and therefore not an immediate health risk. Nevertheless, in the long-run they can accumulate, or damage could occur in conjunction with other negative effects. The authors failed to mention that the low depth of penetration from these fields affected the entire brain of the rats, however with regard to humans only the surface layer is affected.

Such findings are naturally well suited for causing alarm; this could have been the reason why the authors presented their results immediately to the public, instead of submitting them to a journal with a referee system, for example "Bioelectromagnetics". On the other hand this way of doing research is deplorable because the study contains a great deal of inaccuracies and regulation violations which the international community of scientists agreed on in order to ensure the quality of such experiments. These regulations are also recommended by the WHO. The reviewers of a scientific journal would have



certainly reproached the authors about this. What is it dealing with in particular?

The authors themselves concede that the number of rats was really too small to draw any valid conclusions. Of course, this applies all the more since the study deals with half-quantitative evaluations concerning the effects, only with an absolute secure double blind evaluation while using several independent invigilators and a large number of slide preparations is it possible to make a conclusive statement. The appearance of degenerated nerve cells, proven with a Kesyl-violet staining, has been described in various neurophysiological studies without reference to the problem related to field effects. What triggers this mechanism and its cause are not fully understood. Usually it can be contributed to the phenomenon of differentiation, age or it is the result of different illness or stress factors. They occur in different regions of the brain in different intensities. Salford et al. did not go into any detail regarding this neurobiological aspect

The above-mentioned regulations which are recommended for investigations on the effects of electromagnetic fields include the so-called "positive controls". As already mentioned, they have been observed by other working groups. For example, for a malfunction of the BBB to occur temperature shock is applied (Fritze et al. 97,

Tsurita et al. 00) or certain toxins are administered (Finnue et al. 01, 02). Only through the use of such positive controls is it possible to evaluate the sensitivity and the meaningfulness of the observed effects. Only when such a comparison is made is possible to determine if the observed changes are relevant or not, or if it is merely a chance stray occurrence. In none of Salford's et al. studies, and not in his most recent study, were any positive controls done.

One poses the following question: why were the rats first examined 50 days after exposure? Did they want to report on damage occurring much later? It is well known that slight changes in the permeability of the BBB occur, for instance, with the flu accompanied by a fever, and that these changes and effects are quickly repaired by the body. Different authors have proven that the effects triggered by HF-fields of very high intensities lead to an increase in the temperature of the brain, however after a few hours it can no longer be proven. 50 days after exposure the albumin serum would be reabsorbed, wouldn't it? On the other hand, one must consider that 50 days after exposure the rats were subjected to other influences, which can not be left out of a daily control.

Despite a great deal of criticism concerning the preceding experiments, the exposure conditions of animals in this paper are very inadequately controlled. The regulations stipulate that actual energy-absorption measurements of the irradiated object or in a suitable model object must be taken. However, in this case the SAR-value was reported on theoretically without any experimental control. This can lead to serious false assessments, e.g. the body of an animal in a narrow space can destroy the field considerably. It must also be taken into account that during exposure, in a narrow cage fitted out with ventilation ducts, a possible increase in the animal's body temperature was not measured. It cannot be ruled out that the ani-

mals perspire during irradiation. This would be enough to explain why so few measured effects were produced.

It is unimaginable that the above-mentioned recommendations and criteria of the Bioelectromagnetic Society (BEMS) and the WHO for performing reliable experiments were not known to those doing this study.

There is, however, an even more general codex for scientific investigations which was not observed in case: this codex stipulates that a study's results are to be discussed in light of current developments in research. In this case this would have been especially important. We have seen above that there were negative findings even before the Salford group's first experiments. But then, triggered by the first Salford investigation, a number of unsuccessful attempts to verify their results were made. In these publications the weak points of the previous Salford study were exposed and discussed. It would correspond to scientific honesty to quote these studies and at least to explain why in Lund and nowhere else, the effects of weak fields on the BBB can be measured. Actually in the report in question only publications are quoted from acceptable authors, even if they do not really have anything to do with the subject being discussed. So in this way the impression the unbiased reader gets from the report is that the findings of the Salford-group are in complete agreement with international research.

How seriously the world took the Salford findings in 1993 became clear at the international BEMS conference in 2001 in St. Paul, Minnesota. At this conference there was a special section devoted to the problems surrounding the BBB. J. Merritt, P. Mason, J. Lin, H. Nagawa, H. Masuda showed with posters and lectures that it was not possible to verify the Salford findings or to find any other effects for that matter. Everyone was eager to hear the lecture the group from Lund (B. Persson, A. Brun, L.G. Salford) submitted for the conference. Unfortunately it turned out

that none of the authors attended the conference. Their paper was presented by a colleague who had not taken part in the study. It only contained findings from the previous publication that were already known. Unfortunately, the speaker could not answer any questions because he said he had not taken part in the experiments. It was suggested that the investigation of the Swedish group be done again in an extensive study, including the Swedish authors, but without making the same methodical mistakes. This was not however mentioned in the publication in question.

It is a pity that findings are reaching the public more often than have not undergone a voluntary scientific quality control, as it is done in peer review systems. These are findings that at the end of the day do not hold up against objective criticism. This does not help the urgent necessity to gain recognition in this area, but all it does at most is to stir up emotions.

Professor Dr. Roland Glaser was the director of the Institute for Biophysics at the Humboldt University in Berlin

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