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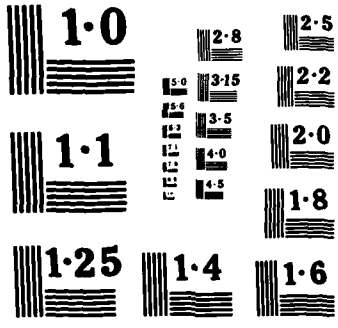

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Six criteria are propounded for judging the credibility of a reported experiment in athermal bioelectromagnetics. Following this, twelve criteria are propounded for judging the merit of the design of a reported or contemplated experiment in athermal bioelectromagnetics.

It is concluded that experimentation in athermal bioelectromagnetics would be markedly facilitated by the identification of the mechanisms underlying the observed effects.

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CRITERIA FOR THE DESIGN OR SELECTION OF A BIOELECTROMAGNETICS EXPERIMENT

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William F. Pickard
Department of Electrical Engineering
Washington University
Saint Louis, Missouri 63130

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SYNOPSIS

SUMMARY OF ALL WORK ACCOMPLISHED:

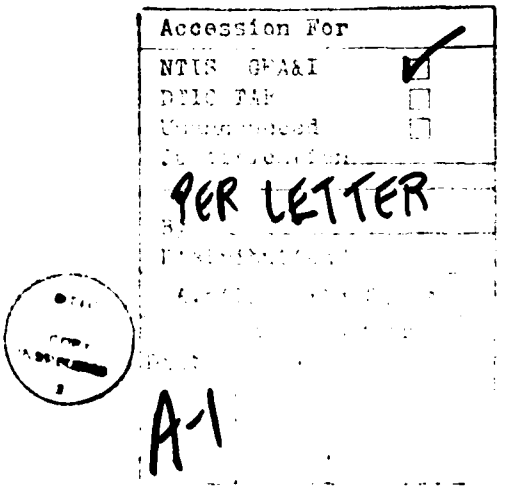
This is provided in the sections following.

INDEX OF ALL TECHNICAL REPORTS:

This final technical report is the only technical report produced on this contract.

INDEX OF ALL PUBLICATIONS:

As of the date of this submission, no manuscripts have been formally accepted for publication. However, it is anticipated that two will eventually result; and reprints thereof will be forwarded to the Scientific Officer when they become available.



PROLOGUE

The aims of this contract (N00014-84-K-0457) were (i) to examine the present state of bioelectromagnetics research and from this examination to distil a set of guidelines with which one could more effectively design prospective experiments or evaluate extant experiments, (ii) to apply these guidelines to the preparation of a major research proposal which focused on the need to understand the mechanism of action of the effects of low level electromagnetic fields, and (iii) to prepare a "criterion document" in which these guidelines were delineated. Task (i) has been carried out; and Task (ii), which was based upon it, has likewise been completed. This Final Technical Report is intended to fulfil Task (iii).

In the preparation of a document intended to assist a bioelectromagnetics professional in the design or evaluation of experimental programs, the need for concreteness might seem of paramount importance; and the reader would therefore be justified in expecting great specificity of detail, with numerous real examples of allegedly felicitous (or misbegotten) procedures being provided for each guideline listed. This, however, is bioelectromagnetics, a small field in which everybody knows everybody else; and the author is reluctant to single out in such fashions experiments whose creators are still living. To denigrate an experiment, however justified the grounds for doing so might seem, could conceivably provoke counterproductive controversy. To cite as exemplary a particular experiment could, while delighting some, leave others feeling slighted. The author has therefore opted for sparse footnoting and generally has left the reader, assumed to be knowledgeable in the field, to provide his own illustrative cases.

INTRODUCTION

Within bioelectromagnetics, it is usual to categorize a biological effect of an electromagnetic field of suboptical frequencies as either "thermal" or "athermal". The terms are loose, and their use will oftentimes provoke uncertainty in some and annoyance in others. The terms are also so familiar and so well established that to attempt to avoid them would itself be controversial.

By "thermal" one normally means an effect which (i) has been been explained in terms of the heating produced by the absorbed electromagnetic energy or (ii) is seen primarily at levels of absorption where such heating might be expected to be physiologically significant. By "athermal" one normally means an effect which (i) has been explained explicitly and unambiguously in terms of mechanisms other than increased random molecular motion (i.e., heating), or (ii) occurs at absorbed power levels so low that a thermal mechanism seems unlikely, or (iii) displays so unexpected a dependence upon some experimental variable that it is hard to see how heating could lie behind it.

At the present state of development of the field, our knowledge of thermal phenomena significantly exceeds that of athermal phenomena, but interest is skewed toward the athermal. This is not to say that thermal phenomena are no longer of any deep scientific interest: there is still a lot to be learned about hyperthermia therapy for cancer or microwave assisted room heating. Nor is it to state categorically that athermal phenomena of biological and/or environmental significance do in fact exist: while many believe that they do, others would assert that (subject to certain reservations outlined below) few if any reported low level athermal effects have ever been successfully converted from the status of "claimed" to that of "well established" and "well understood".

This distinction between thermal and athermal effects works fairly well from low radio frequencies to the infrared, say from 30 kHz to 30 THz (10 km to 10 μm). Below 30 kHz classical electrophysiological effects (including extremely low frequency biomagnetic phenomena) can begin to appear. Although electrophysiological phenomena are primarily athermal by the definition provided above, they are normally considered separately in practice; and the definition of athermal is normally restricted to exclude them.

Thus, the term athermal refers to those phenomena which remain when the set of all suboptical bioelectromagnetic phenomena has had subtracted from it both thermal and classical electrophysiological effects. The principal debate in bioelectromagnetics today is between those who suspect that the athermal category is rich in subtle and unexplained phenomena

and those who suspect that, for practical purposes, it is a null set. The principal question of athermal bioelectromagnetics today is that of the mechanism(s) by which putatively athermal effects might be produced. The principal challenge of athermal bioelectromagnetics today is that of moving reported effects from the category of "claimed" to the categories of "well established" and "well understood".

For an effect to be categorized as "well established" there must be substantial agreement within the scientific community both about the conditions under which it can be observed and about its characteristics when observed. It must have been subjected to enough independent confirmation to have become reproducible on demand; and this in turn implies (i) that it be a real phenomenon which is reproducible in principle and (ii) that several groups, distinct from the one which discovered it, have cared enough and had resources enough to reproduce it in actuality. When an effect has been tied down to this extent, exploratory experiments can be superseded by experiments in the hypothesis-test paradigm and an explicit search for mechanism undertaken. Only when a mechanism for an effect has been identified and has achieved marked ascendency over its rivals, can the effect be said to be "well understood".

The aim of this report is to discuss guidelines by which an experiment directed toward the discovery or elucidation of an athermal effect might be designed or evaluated. It will consist of three main sections.

First, the "great commandment" of athermal bioelectromagnetics will be discussed: that any reported, putatively athermal bioeffect be robustly reproducible.

Second, six criteria for estimating the credibility of a claimed effect will be given.

Third, twelve criteria for designing an ideal experiment will be given.

In each case, the criterion itself will probably elicit but little controversy. Where controversy can arise is in the application of a criterion (which may not always be easy to quantify) to real life situations (which are seldom free of confounding factors).

THE GREAT COMMANDMENT

Within athermal bioelectromagnetics there is a problem with once-reported effects which either have not or can not be reproduced. The "have not" carries with it a connotation of volition and the sense that, if a competent investigator cared enough and had the requisite resources, it could be reproduced or at least given substantial indirect validation. The "can not" implies that respected workers have tried and failed to reproduce the effect. The latter situation is manifestly undesirable because its basis is not understood and could be explained variously:

(i) The positive findings were simply wrong. In the absence of clearly identified blunders, this is a hard judgement to sustain.

(ii) The positive findings were the result of experimental artifacts. Again, unless the artifacts can be unequivocally pinpointed, this is a hard judgement to sustain.

(iii) The positive findings were due to unlikely stochastic excursions of the experimental variables. This source of confusion seems especially troublesome for multiparameter exploratory studies because it is not at all unlikely that one parameter in fifty will prove to be altered significantly ($p<0.05$) and because the annoyances of repeating such a study can be considerable.

(iv) The positive findings may have required a particular conjunction of circumstances which simply are not apparent to the concerned experimenters. Phenomena in this category are sometimes termed Cheshire-Cats.

Something obvious can be done about a reported effect in the "have not" category: a concerned governmental agency can motivate suitable research groups to attempt replications. The "can not" category is more troublesome because in most instances only subset (iv) can ever be positively established, and repeated failures to establish it serve only to elevate the likelihood of a non-(iv) explanation.

Because of the confusion engendered by the report of an unreproduced effect, because virtually any report of a putatively athermal bioeffect will be greeted with a degree of scepticism, and because some claimed effects have proved evanescent upon more detailed examination, it is imperative that any effect which one proposes to report be robustly reproducible. All other characteristics of preparation and of protocol must be

subordinate to this. The great commandment is:

> Subsequent workers, following in your footsteps, must be able to approximate your results without difficulty!

Such reproducibility is the norm rather than the ideal in geology, chemistry, and physics. Why not bioelectromagnetics?

Regretably, this commandment has been (perhaps even must be) honored more in the breach than in the observance. Effects seen in lab A over a period of months (or years) do mysteriously fade away like the Cheshire-Cat; or, despite intensive cross-consultation, an effect regularly seen in lab A may never be found in lab B. Certainty is elusive, and one is therefore urged to hesitancy, reticence, and near-paranoid caution in the performance of experiments for publication.

SIX CRITERIA OF CREDIBILITY

Because exploratory experiments seeking athermal biological effects of low level electromagnetic fields tend, more often than not, to reveal no effects, a researcher seeking to understand athermal mechanisms would be far from ill-advised to select a previously reported effect for his study; but, because reproducibility can be a significant problem, the question of precisely which previously reported effect to select can often loom large. A related problem confronts the regulatory agency charged with evaluating risk in the absence of definitive data: which reported bioelectromagnetic effects should be taken seriously and which should be ignored? There are no definitive answers to these questions. Nevertheless, over his fifteen years in the field, the author has developed half a dozen rules of thumb for gauging the credibility of claimed effects. In application these guidelines could prove intensely controversial, especially if one made his assessments public; but, as private calculations and in the absence of clearly superior alternatives, they may constitute a useful heuristic.

A. Does the group reporting the effect have a good track record? This judgement is subjective to an undesirable degree. However, if their previous work has, in your opinion, not stood up well to the test of time, what reason is there to presume that this work will? Is there evidence that the group has markedly improved?

B. Has sufficient detail been given for you to proceed with certainty in a step-by-step repetition of the experiment? If the detail has not been given and can not be obtained, be suspicious. Where detail is lacking, the probability that you will end up chasing a Cheshire-Cat increases.

C. Do the identified experimental variables admit of precise control, quantification, and measurement? Independent variables which cannot be well controlled make the collection of reproducible data a virtual impossibility. Seemingly vague nominal and ordinal scales of measurement are more prone to distortion by unconscious experimenter bias than are ratio scales for which accurate measurement techniques exist.

D. Are the results at variance with rational expectation based upon previous experience? If they are, are there plausible (even though unproven) explanations for this in terms of well established mechanisms? Remember that new and unexpected biophysical principles are found but infrequently and that most of us will never be fortunate enough to stumble upon one. Less rare, but still rare, are novel applications of familiar principles to yield startling results.

E. Is the claimed effect well above the noise level of the experiment? Effects which can be resolved only when large numbers of experiments are averaged may tend to be nonrobust. At the least, they are subject to masking and distortion by normal stochastic variations in the experimental variables. Worse, in comparison with easily resolved effects, they are more readily affected by unconscious experimenter bias.

F. Finally, are the individuals who reported and who work with the claimed effect open to criticism of their exeriments? If they are unavailable for comment, or if they meet reasonable criticisms with seemingly ad hoc explanations not firmly supported by experimental data, or if they appear unperturbed by the unavoidable gaps which appear in every study, it is an inauspicious sign.

Real-world experiments are never perfect; and inflexible application of these credibility criteria will seldom prove possible if one is to retain for consideration any low level, putatively athermal bioeffects. Nevertheless, zeal in asking the six questions should serve to identify many claims which, provisionally, will fail the test of time, be relegated to the category of "unconvincing evidence", and there abide with slim chance of ultimate vindication. Most claimed effects will fail some of these guidelines: the ones to avoid are the ones whose failures are egregious.

To remove some of the abstractness from this document, these considerations will be illustrated by reference to a paper of Erich Pflomm [Arch. Klin. Chir. 166, 251-305 (1931)] in which it was reported that an isolated frog heart, exposed to a suitable electromagnetic field, would manifest a slowing of its beat rate. The subsequent history of this observation is complicated; but it does appear that fifty years of subsequent investigation have not sufficed to indentify conditions under which microwave radiation will reliably produce bradycardia in an isolated heart [cf. K. R. Foster and W. F. Pickard, manuscript submitted to New England Journal of Medicine (1985)]. The claimed effect mildly fails (A) because the Pflomm group is of unknown reputation. It grossly fails (B) because the conditions of exposure are largely undescribed and dose estimates are not possible. It meets (C) because heart rate is unambiguously quantifiable. If fails (D) because there is no obvious mechanism to account for the slowing and because heating by the field should produce a speeding up. It may fail (E) because the data presented in the report appear to be far from unambiguous. It presumably fails (F) because, more than fifty years after the fact, it seems unlikely that one could engage in a deeply informative dialogue with the investigator. Hence it would seem a less than ideal candidate to select for further investigation of putatively athermal effects; and in fact, as history shows, it violates the great commandment.

TWELVE CRITERIA OF IDEALITY

When a claimed effect has been judged to have an acceptable prospect of robust reproducibility, it must be asked whether the effect is actually worth reproducing. This question has two components: first, is the experiment well designed; and, second, is study of the effect apt to lead anywhere? The first component is tricky because an answer in the negative normally leads to an "improved" experimental design which may in fact improve the effect out of existence, either by removing an unsuspected artifact or by inadvertently perturbing a Cheshire-Cat; and one seldom knows which. The second component is dangerously provocative but must be faced if one's interest is in the mechanism of a claimed effect: the principal question relating to athermal bioeffects is the mechanism(s) by which they might occur; and an experiment which reveals such an effect while yielding no clue to its provenance is somehow unsatisfying.

No one experiment is apt to meet all the constraints which one might place upon an ideal experiment; but an experiment which meets most of them is more apt to "lead somewhere" in the sense that it will further progress toward the elucidation of a mechanism. In the process of witnessing the controversies of the past fifteen years in bioelectromagnetics, of attending uncounted conferences, and of participating in innumerable informal discussions, the author has identified a dozen criteria by which he would characterize an ideal experiment. Of these, the first two relate to the electromagnetic field, the next six concern the biological preparation, and the final four are more miscellaneous.

1. The fields actually present within the biological preparation should be approximately known or prescribable; alternatively, the power absorbed should be known approximately. Classically, this constraint has not always been met; and the failure to meet it has frequently been correlated with nonreproducibility. Certainly, ambiguity of dosage can only serve to inhibit the identification of underlying mechanism.
2. There should be substantial control over the frequency, waveform, intensity, and modulation of the applied field. Fixed frequency experiments have long been predominant in bioelectromagnetics, and with good reasons: the cost of changing frequency (or modulation) is often frightening, and the manpower requirements for multiple frequency replications of a labor intensive experiment no less so. Nevertheless, the unequivocal identification of an athermal causative mechanism is bound to be difficult in the absence of an action spectrum for the claimed effect.

3. The preparation should be well understood. "Well understood" in this context is both subjective and relative; but the objective of learning more about a claimed effect is markedly facilitated by not having first to learn more about the basic biology of the preparation. In particular, the principal investigator himself should be deeply versed in the natural history and practical lore of the preparation (or personally acquire such knowledge as a first step of the experimental program): trusting one's subordinates to acquire and sensibly employ such information is a chancy business.

   [At the time that the original proposal for this contract was written, it was envisioned that a select list of especially suitable preparations would be assembled from which the author at least would then choose his future experimental vehicles. This naive hope was never realized for two reasons. First, the number of preparations which are well understood in the sense that they have been the subject of at least scores of research papers is vast: cat soleus muscle is well understood, but so is the Drosophila salivary gland, or the oat coleoptile, or the Paramecium, or the characean internodal cell, or the frog neuromuscular junction; and how is one to say in advance which would prove the most advantageous for an exploratory study in bioelectromagnetics? Second, the author had not yet formulated the great commandment. He now believes that any preparation which yields a robustly reproducible athermal effect is "especially suitable" and that no preparation, however well understood, which fails to yield such an effect is suitable: the problems of athermal bioelectromagnetics can be resolved only by the elucidation of mechanism, and mechanism will never be elucidated in the absence of reproducibility.]

4. The preparation should be both robust and stable. Feeble preparations tend to divert the experimenter's attention from the experiment, and finicky ones can generate more uncertainty than they dispel. The necessity of culling experiments because of miscellaneous vagaries of the preparation is to be avoided because it is a fertile source of unintentional bias, especially if one's criteria for rejection or acceptance of data are at all subjective.

5. The preparation should encourage penetration to deeper levels of understanding. Success at one level of an experiment should bring with it a reasonable sense of what steps should next be taken in a search for mechanism.

6. The preparation should encourage both control and data analysis in real time. When days (or weeks) elapse between the electromagnetic exposure and the assay for the bioeffect, it is hard to rule out the presence of confounding variables and to guarantee the validity of

experimental controls. When years elapse, inferences become even more difficult and post hoc ergo propter hoc an ever more lik

7. The preparation should provide biological of the initial transduction from electroma to biological effect. Without such amplif the most sensitive instruments may detect However, biological amplification may take thus there is a tension between this crite previous one.
8. The relevant properties of the preparation precisely and unambiguously quantifiable. against unwitting experimenter bias, and i use of more powerful statistical tests.
9. The measuring apparatus should neither per perturbed by the applied field. Such pert a much dreaded source of experimental arti
10. The design of the experiment should enable experimenter to distinguish between effect classical thermal or electrophysiological those of more complicated provenance. Thi exceptionally important when one's stress identification of athermal mechanisms.
11. The experiment should be emulatable. What other merits may be, experiments with daun requirements of funding stability, of manp equipment, or of technique are not likely replicated. And, the scepticism of bioele researchers toward athermal effects being unreplicated experiment is not likely to e influence.
12. The experiment should be seminal. It shou lead somewhere. It should make a profound the field. A key ingredient here is that stunning. But stunning results alone do n it is necessary also that they be engaging to a wide audience, many of whom have the acting upon them. Murky prose in an obscu will not suffice; nor will a bizarre prepa will an arcane technique. The stunning re somehow rivet the attention of a lot of sc can put them to work - scientists who find beset by a mountainous literature and many professional pressures as well.

The experiment of Pflomm, referred to in the pr section can be cited to make these considerations m It would appear to fail (1) rather badly since the to have been to a near zone field of presumably ill characteristics. It clearly fails (2) for the freq fixed at about 75 MHz . It passes (3) because fro though complicated, is a well understood organ prep is probably in some trouble at (4) since isolated f be tricky; however, with care, it should be possibl constraint. It passes (5) because of the wide numb

pharmacological challenges which can be given the preparation to dissect out the mode of action. It excels at {6} for the effects were alleged to have had a rapid onset. It may or may not meet {7}: in the absence of a clearly understood mechanism, there is no telling. It excels at {8} since heart rate is eminently quantifiable. It may or may not meet {9}: the details of the experimental arrangement are too sparse to say. It probably passes {10} since the expected response to heating is tachycardia. It passes {11} for the measurements all seem easy to make with reasonable apparatus. It fails {12} abysmally: effects which cannot reliably be reproduced cannot reasonably be called seminal.

COMMENTS

Once a field of science has been explored well enough for its practitioners to have a clear picture of its phenomena, research therein normally develops a pronounced hypothesis/test character. The goal of this development is an understanding of the mechanisms behind the phenomena. And the goal of mechanism is prediction. One cannot possibly do all conceivable experiments. One cannot even do all the experiments for which there is a societal imperative. But if one understands the underlying mechanisms, if one has a model, then one can make some fairly shrewd guesses of the outcome of a particular course of action; and one can limit expensive and time-consuming experimentation to the validation of those guesses.

In athermal bioelectromagnetics today we have few well established effects and fewer still agreed upon mechanisms. Because reproduciblity is not yet commonplace, virtually all experiments are in some sense exploratory. And, statistically, historically, exploratory experiments in athermal bioelectromagnetics have small likelihood of turning up robustly reproducible athermal effects. This has been the situation for far too long, so long that its prolongation could conceivably divest the field (and its practitioners) of the esteem of scientists in less exploratory endeavors.

These problems, coupled with the limited supply of skilled manpower in the field and the still more limited supply of research funds, bode ill for any research strategy based upon unfocused exploration. At best such work will yield effects when mechanisms are needed. The course of minimum risk for the field is to focus all efforts upon the replication of a very few selected experiments: optimally, this will yield the long sought mechanisms; more realistically, it might yield a few more robustly replicable bioeffects; at worst, it will remove a few additional claimed effects from serious consideration. Failure to pursue such a course will probably lead to a perpetuation of the present weak correlation among the research thrusts within athermal bioelectromagnetics and to a prolongation of the currently turbid status of the field. The anticipated outcome of such a prolongation is the gradual diversion of this field's funding to other fields whose practitioners know where they are going.

The evaporation of funding for athermal bioelectromagnetics while the present confused literature persists is not a societally desirable outcome because it could well leave the regulators of our environment trapped between a morass of contradictory data and a seriously worried public; and it could result in a climate severely inhibitory to technological advances which require even minimal "electromagnetic pollution" of that environment.

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