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CONSENSUS AMONG EXPERTS: THE UNHOLY GRAIL

LOUIS LASAGNA, M.D.*

Mr. Gordon: . . . I felt a cold coming on sometime ago and I dosed myself with a lot of vitamin C, but it did not stop the cold from coming. I must confess, however, that after I got the cold, I took some of my wife's chicken soup. It did a much better job than the vitamin C.

Dr. Katz: Well, there is no question, Mr. Gordon, that hot chicken soup is very good. Hot drinks of any sort, hot tea, hot cocoa, hot chocolate, hot milk, hot toddy, anything hot is of great value in upper respiratory infection. . . . [Hearing before the Subcommittee on Monopoly of the Select Committee on Small Business, Washington, D.C., December 5, 1972]

. . . the uncertainty, under which we still remain, in regard to the virtue of the waters of Bath. Few medicines have been more repeatedly tried under the inspection of such numerous and able judges; and yet we have had in the present age a dispute between those who by their experience and sagacity were best qualified to decide this question, in which one side asserted that paralytic patients were cured, and the other that they were killed, by the use of these waters. Such contrary decisions, so disreputable to physicians, and so perplexing to the sick, could never have happened after so long a trial, if a very small part of those, whose practice had afforded them frequent opportunities of observing the effects of Bath waters, had told the public what in their judgment was to be hoped or feared from them. It is probable that in some cases it would have been almost unanimously determined they do good: in others, that they do no harm, though it might be doubtful whether they be of much use: in a third sort they would be generally condemned: and in a fourth class of diseases, some might judge them to be beneficial, and others detrimental. [WILLIAM HEBERDEN, *Commentaries on the History and Cure of Diseases*, 1802]

A century ago the Swiss historian Burckhardt foresaw that ours would be the age of "the great simplifiers, and that the essence of tyranny was the denial of complexity. . . . It is the great corruptor, and must be resisted with purpose and with energy. [DANIEL MOYNIHAN, farewell speech to the president's cabinet, 1970]

It is not surprising that experts disagree. We are accustomed, in almost every walk of life, to hear amazingly discrepant opinions and rec-

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ommendations. Every week we read in our newspapers that the recession is over and that it is not. Economists provide little comfort for the average citizen when they make diametrically opposite judgments about why the world faces fiscal chaos.

The news media also carry abundant evidence of such disagreement among experts in the field of science and medicine. We are told that saccharine and cyclamates are carcinogenic and that they are not (and the government bars the latter but not the former); that we are an overmedicated society and that we are undermedicated; that U.S. medical care is unexcelled and that it is seriously defective when compared with other, less affluent nations; that research and training support is seriously inadequate and that it is excessive; that physicians are generally hard working and competent and that they are greedy, unfeeling, irresponsible, and therapeutically Cro-Magnon in orientation.

Two editions of a fascinating book, *Controversy in Internal Medicine*, have been built around the ease with which experts can be found to debate the pros and cons of a series of vital issues in the diagnosis and treatment of some of our most common and important ailments. The Food and Drug Administration (FDA) is taken to court simultaneously for being too lax and too strict in its regulation of drug usage. The list of examples is almost endless.

Let us, then, grant the existence of the phenomenon: experts not only *can* disagree, they can be *expected* to disagree. So what? The answer to that question is the reason for this essay. It is my purpose first to document, in data from an actual survey, the extraordinary extent of disagreement about a number of therapeutic agents and then to discuss the implications of the data. It is, further, my contention that there are increasing tendencies in our society to regulate the practice of medicine as if "*the experts*" were often unanimous in their recommendations and as if disagreement either did not exist or was trivial in extent and consequences. It will, finally, be argued that the practice of medicine and its regulation call not for dogma and authoritarian straitjackets but for a fallibilistic and pluralistic approach which is consonant with the real world.

*The Expert Judgments*¹

The investigation that follows was conducted several years ago, to solicit and compare the opinions of a group of physicians about some commonly used, well-known, and somewhat controversial drugs: Ritalin

¹The data referred to in this section were collected as part of a study of physician prescribing by Marshall Becker, Lois Sloan, Paul Stolley, and myself. My colleagues bear no blame for any opinions expressed herein.

(methylphenidate), Equagesic (a fixed-ratio combination of aspirin, ethoheptazine, and meprobamate), injectable B-12, Chloromycetin (chloramphenicol), and oral contraceptives. For all except the last, the questionnaires supplied both the trade and generic names. (By error, the aspirin ingredient was omitted from the questionnaires for Equagesic. Only one of the cooperating physicians pointed this out to me; whether others spotted the omission is an interesting question to which I have no answer.)

For all the medicaments covered, there were certain reviewers in common—five nationally eminent clinical pharmacologists and five internists in practice in Baltimore who had academic appointments at the Johns Hopkins University School of Medicine. In addition, each product was reviewed by four to six experts chosen from among the panel members who had reviewed drugs in that specific area for the Drug Efficacy Study conducted under the auspices of the National Academy of Sciences—National Research Council under contract with the FDA.

For each product, a series of conditions was listed. Each respondent was asked to check a response to the product's use in regard to each item, choosing one point on a five-point scale as follows: "strongly approve," "mildly approve," "uncertain," "mildly disapprove," and "strongly disapprove." The items chosen for such judgment were specifically listed in the product package insert at the time of the study as either an indication or a contraindication. Although several respondents complained that some of the simplistic language (taken from the official insert and used in the *Physician's Desk Reference* [PDR]) made responses difficult, only rarely did anyone fail to check a response.

RITALIN (METHYLPHENIDATE)

Pooling the response of the 16 experts who were sent the questionnaire on this drug, the following "consensus" emerges, based on the mean response for each item: it was considered (1) a drug for which few uses were considered acceptable (only narcolepsy was "mildly approved" as an indication, with childhood hyperkinesia rated partway between "uncertain" and "mildly approve"); (2) a drug whose use for "psychoneurotic or senile apathy or withdrawal," childhood stuttering, or "chronic fatigue and lethargy associated with convalescence or senility," was rated as "uncertain"; (3) a drug whose use for "fatigue," "chronic fatigue and lethargy associated with illness or concurrent ingestion of other drugs such as tranquilizers, barbiturates or anticonvulsants," "severe emotional depressive states," "appropriate indications for patients with glaucoma or pregnant or lactating women," or for any reason by patients with arthritis or rheumatism was mildly disapproved; and (4) a drug whose

use for marked anxiety, tension, or agitation, or as a placebo, or by any patients with hypertension or epilepsy (except to relieve drug-induced sedation) was strongly disapproved.

As might be expected, however, this "consensus" masks certain intergroup differences. The internists, for example, were uncertain about Ritalin's use in hyperkinetic children (presumably because of lack of knowledge about, and experience with, this syndrome), whereas the mean score for the clinical pharmacologists was halfway between "uncertain" and "mild approval," and the psychiatrists' mean was halfway between "mild" and "strong" approval. Regarding use of the drug for "fatigue" or by arthritics, the psychiatrists' mean reflected uncertainty, whereas the other two groups' means were "mildly disapproving."

The psychiatrists' mean score showed the strongest disapproval of Ritalin's use in epilepsy and severe depression, while the clinical pharmacologists were the most strongly disapproving group in regard to Ritalin's use by glaucomatous individuals and by pregnant and lactating women. In regard to hypertensive patients, the psychiatrists' mean indicated less strong disapproval than did the other two.

So much for the mean scores. Taking the *individual* responses, however, there is even more disagreement, whether one considers the individuals within a specialty subgroup or all the doctors surveyed. For none of the 22 items in the Ritalin questionnaire was exact concordance achieved by the 16 doctors. Indeed, there was no item which had a range for the 16 that was less than two scale units. For seven of the 22 items, there was either at least one doctor who checked "uncertain," while at least one other checked "strongly approve" or "strongly disapprove" or at least one physician who checked "mildly approve" while another checked "mildly disapprove." For seven other items, the 16 doctors were apart by three scale units; and, for each of five items, at least one respondent checked "strongly approve" while at least one other checked "strongly disapprove."

Since there were 22 items, there was a total of 66 occasions available for seeing how much agreement there was *within* each specialty group. Total agreement was seen on only eight of these 66 occasions. The members of the subgroups differed by three scale units on 21 items and by four scale units (the maximum) on four items. Thus, even within a given area of expertise, considerable disagreement was manifested.

EQUAGESIC

The questionnaire for Equagesic was the shortest and did not solicit opinion about the drug's major approved indication, uncomplicated painful muscle spasm associated with anxiety or tension. Hence the results were bound to be negativistic. The most strongly disapproved items

by the total of 14 physicians (including four analgesic experts) were those pertaining to the drug's use by patients with known intolerance or allergy to the combination's ingredients and to its use by patients operating dangerous machinery or for pain associated with skeletal-muscle spasm, anxiety, and tension in pregnant or lactating woman. Mildly disapproved was Equagesic's use in the treatment of alcoholics or former drug addicts or of pain associated with skeletal-muscle spasm *without* anxiety or anxiety and tension *without* skeletal-muscle-spasm pain.

Despite the relatively straightforward questions, however, the 14 experts did not agree exactly on any item, and on only two of the 18 possible occasions did all the members of a given specialist subgroup agree exactly with each other. The 14 doctors were apart by two scale intervals on three of the six items and by three scale units on the other three.

CHLOROMYCETIN (CHLORAMPHENICOL)

Enormous publicity has been given to this antibiotic's capability of inducing (very rarely, to be sure) fatal aplastic anemia, and for many years now the PDR and the drug's package insert and advertising have carried dramatic warnings. In contrast to the two products discussed above, some amazing unanimity was seen on at least some of the items on the questionnaire for this drug.

There was, for example, unanimous disapproval among the 15 infectious-disease experts, internists, and clinical pharmacologists of the drug's use for sore throats, colds, and influenzas and for chemoprophylaxis. All but one of the 15 strongly endorsed the drug's use to treat typhoid fever or severe infections resistant to other antibiotics but susceptible to chloramphenicol.

Using the entire group's mean scores as a basis for judgment, the survey elicited mild disapproval of the use of chloramphenicol in cystic fibrosis regimens and in treatment of *Salmonella* gastroenteritis and "uncertainty" about its use for *Hemophilus influenzae* meningitis in infants, meningitis due to gram-negative organisms, lymphogranuloma venereum, psittacosis and rickettsial infections, and for elimination of the typhoid-carrier state.

A look at the mean scores for the specialist subgroups reveals considerable heterogeneity of response. For pediatric *H. influenzae* and other gram-negative meningitis and gram-negative sepsis, for example, the three subgroups' mean responses ranged from mild approval to mild disapproval, with the clinical pharmacologists being the most negativistic. For *Salmonella* gastroenteritis, the subgroup means ranged from strong disapproval (the infectious-disease experts) to uncertainty (the internists) and, for treatment of the typhoid-carrier state, from mild

disapproval (infectious disease experts) to uncertainty (clinical pharmacologists).

Taking the total sample of 15 physicians, the individual respondents disagreed markedly on six of the 14 questionnaire items, with at least one doctor voting strong approval and at least one voting strong disapproval on each of these.

B-12 INJECTIONS

As might be expected concerning a drug with both impeccable indications and highly unorthodox ones, the 15 respondents (including five hematologists) voted strong approval or disapproval of different items on this questionnaire. The group strongly endorsed B-12 as treatment for pernicious anemia and gave only slightly less strong endorsement for its use as a "flushing dose" of vitamin in performing the diagnostic Schilling test. The group's mean constituted only mild approval for B-12's use in treating "other macrocytic anemias (sprue, gastrectomy, fish tapeworm, blind gut loop, etc.)," uncertainty about its use for nutritional anemia due to poor diet, mild disapproval of its use for nonspecific neuropathies and neuralgias, and stronger disapproval of its use to stimulate growth rate in infants, as a placebo, or as a "tonic."

Taking the mean scores for the three expert subgroups, however, one finds that the judgments on the indication "other macrocytic anemias" ranged from uncertainty to approval midway between mild and strong, on nutritional macrocytic anemia from uncertainty to mild approval, and on B-12 use in the Schilling test from mild approval (internists) to strong approval (hematologists, the group with the most experience and expertise here).

For all 15 individuals, exact agreement was obtained for one item and disagreement by one or two scale intervals for two items, by three scale intervals for four items, and by four scale intervals (the maximum) for two items. Even within the three specialist subgroups, the five members of the group were apart by three scale intervals on six occasions and by four scale intervals on two occasions.

ORAL CONTRACEPTIVES

The oral-contraceptive questionnaire contained 32 items, all related to possible contraindications. It was completed by the same clinical pharmacologists and internists who answered the other questionnaires, plus four specialists in obstetrics or endocrinology.

The mean scores for the entire group of 14 physicians showed strong disapproval of the use of oral contraceptives by women with thrombophlebitis, thromboembolism, cerebrovascular accident (CVA), papil-

ledema, a past history of thromboembolism, CVA or retinal thrombosis, and suspected breast cancer. Only slightly less strongly disapproved was their use by women with a past history of thrombophlebitis, migraine headache, or jaundice during pregnancy, serious liver disease, cancer of the breast or of the uterine corpus, diplopia, sudden loss of or decrease in vision, or migraine. There was only mild disapproval of their continued use by women with two consecutive missed periods while on the Pill, by patients with epilepsy, heart or kidney failure, diabetes mellitus, hypertension, optic neuritis (or history of same), uterine fibromatosis, ovarian cancer, or a history of emotional depression, and by young girls with open epiphyses.

Midway between mild disapproval and uncertainty was scored the use of oral contraceptives by women with cervical cancer, benign ovarian tumor, and abnormal vaginal bleeding.

The three subgroups of experts varied significantly on some of the questionnaire items. Optic neuritis, for example, was considered a strong contraindication by the internists and an uncertain one by the obstetrician-endocrinologists. The use of oral contraceptives by women with uterine fibromatosis or abnormal vaginal bleeding received subgroup ratings ranging from mild disapproval to mild approval. Their use in cases of migraine received mean subgroup ratings from uncertain to mild disapproval, and, by women with a history of two missed periods, ratings from strong disapproval (clinical pharmacologists) to uncertain (obstetrician-endocrinologists). Heart failure, hypertension, and the presence of open epiphyses in young girls were considered strong to mild contraindications by the internists and clinical pharmacologists but uncertain ones by the obstetrician-endocrinologists.

Of the 32 items, on only one (thromboembolism) did all 14 respondents agree exactly. The entire respondent population was one scale unit apart on six other items, two apart on 10, three apart on 10, and four apart on five items.

Looking at intragroup agreement, the picture is substantially better: on 26 occasions, the subgroup members were in total agreement and only one scale unit apart on 25 other occasions. On 34 occasions, however, subgroup members were apart by two scale units. They were three apart on nine occasions and the maximal four units apart on two occasions.

Discussion

Given professionals of good will and expertise, how can one explain these kinds of disagreement?

To begin with, experts may be speaking from different data bases. Academic physicians, for example, often have a clinical exposure differ-

ent from that of the man in practice not only numerically but in the mix of patients seen as well. The university medical center is often a place where problem cases are referred—complex problems in diagnosis or treatment that have often failed to be handled satisfactorily outside the hospital. Inpatients certainly differ from outpatients in important ways. Furthermore, specialty practice will confer a data base that is also idiosyncratic: internists are faced with patients who differ considerably from those who go to psychiatrists or obstetricians. (A special occupational hazard for the expert is the Irwin Corey [“the world’s greatest expert”] phenomenon, which is referred to by Alvan Feinstein as the “Mickey Mantle phenomenon” [in which a great baseball player is hired to teach tennis].)

Furthermore, one’s personal data base includes information gleaned from one’s colleagues, from one’s reading of the literature, and from meetings attended. In these respects as well there is the possible genesis of disagreement.

But there is another major source of disagreement: *different value judgments, given the same data base*. The first quotation at the head of this article illustrates this nicely. Scientists who can be extremely critical and demanding about one therapeutic maneuver can be permissive about another, despite a comparable lack of evidence for both remedies. This is typified by the Chicken Soup Dogma. There are, to my knowledge, no controlled clinical trials that document the putative merits of chicken soup (or any other hot drink) in the treatment of infections. Thus everyone has the same experimental data base, that is, none. Yet one finds such critics as Senator Gaylord Nelson, his influential staff man Benjamin Gordon, and a number of distinguished clinicians blissfully content to agree at a Senate hearing on the remarkable benefits to be obtained from chicken soup. Why? The answer is at least in part attributable to personal bias and background, to the nontoxic character of most generic and brand-name versions of this remedy (so far as it has been tested, i.e., not at all), and to the fact that it is generally considered a food and not a drug. One does not have to deny the possibility of therapeutic merit in chicken soup to acknowledge these other sources of input to the individual value judgment. One could certainly find at least a few physicians who would scoff at the merits of chicken soup in the absence of a controlled trial.

One can use much more dramatic examples of disagreement, given the same data base. I recently discussed coronary-bypass surgery with an old friend whose anesthesiologic experience in this area is as extensive as anyone’s in the world. It was his view, despite an operative mortality of 5 percent, that anyone with multiple-coronary-vessel disease should have such surgery, “because he’s got nothing to lose.” There are a good many

cardiologists (and perhaps even a few surgeons) who would strongly disagree with such a view, while being perfectly willing to accept such an operative risk in a patient with intractable angina pectoris.

In 25 years of teaching and research, I have come to the conclusion that physicians differ dramatically on what might be called the efficacy-risk continuum. Given a set of therapeutic options ranging from mildly effective but very safe to very effective but highly risky, physicians will select options that fit in with the degree of therapeutic derring-do with which they are comfortable.

Patients, too, will differ in their propensities for different therapeutic options. I recall a woman who telephoned me some years ago after a newspaper carried an account of a talk in which I described the thromboembolic risks of oral contraceptives (then a very disputed topic). She asked whether it was possible for a user of the Pill to suffer a stroke. I said yes, but that the risks were very slight, the benefits of the Pill considerable, and that pregnancy carried risks too. None of this made any difference—the possibility of a contraceptive technique causing a cerebrovascular accident was too painful for her to live with, and she preferred to return to other techniques which, while less “effective,” carried for her “only” the risk of pregnancy, a state not considered a disease and not associated in her mind with serious risk of any kind, let alone a stroke.

Even a hasty look at the medical literature is sufficient to pose a series of diagnostic, prophylactic, or therapeutic questions that physicians will answer differently. Here are just a few:

1. Is it proper to treat sore throats with antibiotics in the absence of a positive bacteriological culture?
2. Should small, medium, or large doses of insulin be used to treat diabetic coma? By what route should the insulin be given?
3. Is propranolol safe enough for widespread use in the treatment of angina pectoris?
4. What importance should be attributed to carcinogenicity from a medicine in one species of mouse?
5. Should flour and bread be routinely fortified with iron?
6. Does vitamin C in large doses have any impact on upper-respiratory infections? Is such treatment hazardous?
7. Is amphetamine less defensible as a treatment for obesity than for narcolepsy?
8. What kinds of diet should be advised for patients with various gastrointestinal diseases?
9. Are prophylactic antibiotics justified in certain kinds of surgery? Which ones? What about chemoprophylaxis in patients with chronic bronchitis?
10. When are anticoagulants justified in myocardial infarction? In postoperative patients?
11. What routine screening tests are useful and economically defensible?
12. How much “workup” is indicated in the “average” hypertensive?

13. Are lipid-lowering drugs useful?
14. Are opiates sufficiently indispensable to medical practice to justify the continued cultivation of opium poppies?
15. Are most advanced "solid" tumors worth treating with the available (and very toxic) oncolytic drugs?
16. Which is to be preferred in the treatment of hyperkinesis in children, amphetamines or methylphenidate?

The judgments of the experts in the survey reported on in this paper will strike different readers differently. For myself, I find it incomprehensible that anyone could doubt the appropriateness of trying methylphenidate in hyperkinetic children or seriously disapprove the selective use of chloramphenicol in such entities as *H. influenzae* meningitis or other serious infections. The risks of chloramphenicol are so low compared with those of the diseases in question that the risk-benefit analysis poses no problems for me. (Nor, it should not be forgotten, are other, alternative antibiotics free of risks.) Those curious about such matters might like to compare the expert judgments described above with either the 1970 or the 1976 approved package inserts for the drugs studied; there are interesting discrepancies that have obvious implications for medical practice and litigation. (Diazepam used to be contraindicated for epileptics; it is today the drug of choice for status epilepticus, a life-threatening ailment.)

What, then, is our society to do? It is possible that we can neither live with our experts nor live without them? Is there no right and wrong? Are not certain practices so clearly right or wrong that we can so characterize them?

The answer, in my view, is neither to legitimize (or ignore) error nor to impose a procrustean Lysenkoism on the practice of medicine. It is always tempting for the pedagogue as well as the politician, regulator, and religious leader to embrace simplicity as opposed to complexity. Many people seem to prefer simple falsehood to complicated truth. But socially such a philosophy is both reprehensible and shortsighted.

Furthermore, there is often no *need* for yes-no verdicts. The practice of medicine is different from a court case, or a contest, or an election. It is said that some years ago a World Health Organization (WHO) group, asked to judge whether oral contraceptives had thrombogenic potential, voted seven no and six yes, but that, because WHO regulations insisted on unanimous recommendations, the report represented the decision as unanimous. Whether the story is true or apocryphal makes no difference—it is typical of what all too often happens in regard to public display of "what the experts say."

Ingelfinger, commenting on "medical Delphination," has aptly observed, "Committee decisions, whether reached by face-to-face discussion or by mailed iteration and feedback, are bound to be compromises,

with extreme ideas discarded. . . . The several rounds of the Delphi routine tend to silence mavericks injudicious enough to stand up for their position in spite of the panel's majority" [1, pp. 158-159].

Anyone who has worked in academic circles has seen one persuasive committee member carry the day in regard to a given faculty appointment, grant approval, or curricular change. This is increasingly a problem in governmental-committee deliberations, both because of the desire of government for a decision by vote and because of the tendency to have representation of social groups (consumers, general practitioners, women, blacks, etc.) as well as more traditionally chosen "experts." It is an ancient truism that a committee can be devised to come up with any decision desired, if it is constituted with such Machiavellian purposes in mind. The current tendency carries other risks, however, including those of majority decisions made by groups whose members do not speak the same language, who differ in their ability to comprehend the problems or data, whose priorities and value judgments are irreconcilable, and in which vigor of stand need bear no relation to scientific defensibility.

Such conflicts are not necessarily harmful. Indeed, one could argue that committees should be so constituted as to *ensure* heterodoxy. It is not disagreement that is bad but the false semblance of orthodoxy that results from yes-no decisions. Why not, instead, aim for a procedure which takes account of the two characteristics almost always applicable to the practice of medicine: pluralism and fallibilism?

Since it is more often true than not that doctors and patients will disagree on what is "best" or "proper" and since individual judgments are both necessary and desirable in most of medicine, the appropriate goal should be a clear exposition of the facts (such as they may be, including what is *not* known) to doctors and patients, with the probabilities (where they exist and updated as necessary) of benefit and harm for the various options available. Then the individual can make his own judgment.

An example of this approach would be in the field of contraception. There are many available techniques: abstinence, rhythm, oral contraceptives (of several types), injectable contraceptives, the condom, the diaphragm, the IUD, etc. Each has a reasonably well documented list of advantages and disadvantages. Factors affecting choice will include convenience, cost, comfort, aesthetics, religion, personality, and sexual habits. Since there is no "right" or "wrong" way for all women, each candidate for contraception deserves a fair exposure to the contraceptive smorgasbord before making a choice.

This recommended approach does not rule out certain "large" decisions being made by regulatory agencies or professional groups. A given drug or device may be so dangerous or minimally effective that it de-

serves to be banned or its use severely restricted. So be it, provided that we can be sure that such large decisions are being wisely made. (Of necessity, they will be of the yes-no type.) The majority opinion—even of the experts—is often wrong. Indeed, much scientific progress can be equated with proving the expert majority to have been wrong. It was “the experts” who told us that the Pill was “safe,” that strict and prolonged bed rest was required for all patients with myocardial infarction, that calcium carbonate was the antacid of choice, that all digoxins or tetracyclines were alike, and that major tranquilizers could not possibly be antidepressants. In most of these cases, it was the poor, benighted practitioner who was ahead of the experts and whose wisdom was eventually acknowledged. Our society wants to rely on experts, knowing (forgetting?) that they have been wrong in the past or that they may change their minds, or that they often disagree.

It is not easy for experts to be humble or to accept fallibilism as a philosophy. An expert is by definition more knowledgeable (in some way) than a nonexpert, and his opinion should (in some way) carry more weight than that of the nonexpert. Yet the expert should appreciate better than most the disagreements and errors of the past as well as the honest controversy of the present.

The expert might well hang up on his wall the following quotations:

I beseech you, in the bowels of Christ, think it possible you may be mistaken. [OLIVER CROMWELL]

My own suspicion is that the universe is not only queerer than we suppose, but queerer than we can suppose. [J. B. S. HALDANE]

REFERENCE

1. F. J. INGELFINGER. *New Engl. J. Med.*, **292**:158, 1975.