low-quality olive oil, other vegetable oils, and animal fat. Rapeseed oil that had been treated with aniline to render it unfit for human consumption was found to have been included in some batches of case-associated oil. This finding drew the immediate attention of investigators, since it was an obvious break in acceptable food-preparation technique. Aniline in free and combined forms was found in some, but not all, specimens of oil taken from case households. However, clinical findings in TOS are not those of aniline poisoning. Moreover, anilides of fatty acids, the principal compounds of aniline found in the oil, appear not to have caused the epidemic. Erucic acid, a toxic constituent of some rapeseed oils, has also been ruled out as the etiologic agent. Contaminants associated with oil constituents other than rapeseed oil have received relatively little attention.

Toxicologic study of TOS has been hindered by the lack of an animal model. Several species of rodents and primates have been exposed to case-associated oils—by ingestion and by other routes—but so far, investigators have been unable to produce TOS in laboratory animals. This lack of disease in animals has been cited as evidence that the oil did not actually contain the etiologic agent of TOS, but this explanation is unlikely. The available epidemiologic data strongly support the oil-illness association. Studies that have compared TOS patients with control subjects have shown no other exposure to be as strongly and consistently associated with illness as the suspect oil. The few persons with clear-cut TOS who have no history of oil ingestion may have unwittingly eaten it in combination with some other food. The possibility that the etiologic agent of TOS can produce illness in humans but not in any of the species of laboratory animals tested to date deserves consideration, but the human testing required to validate this theory would be clearly unethical.

The etiologic agent in the oil may have become inactive over time. This hypothesis could explain not only the lack of illness in exposed laboratory animals, but certain epidemiologic aspects of the TOS epidemic as well. In some locations, the incidence of TOS may have begun to decline even before the oil-illness association was recognized and potentially toxic oil was collected by the authorities. Persons whose cases of TOS occurred early in the outbreak had more severe illnesses during the acute phase of TOS than persons with later onset. In addition, persons with a relatively early onset were more likely to be affected by the late sequelae of TOS. These observations are consistent with what one might see when a toxin with a limited life-span declines in concentration over time.

Research into TOS must now proceed along two lines. First, manifestations of illness should be followed over time in the large group of persons affected by the illness. This effort should include studies of the effects of TOS on specific organ systems, such as the study of De la Cruz and coworkers reported elsewhere in this issue (see page 398). Second, further study is required to elucidate the nature of the etiologic agent of TOS. Recent data suggest that case-associated oils contain greater quantities of potentially toxic lipid peroxidation products than other oils sold in Spain under similar circumstances. This and other leads regarding the nature of the causative agent require follow-up. The agent must be identified to assure that unintentional exposure to it does not recur.

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REFERENCES


Patients, Clinicians, and the Science of Investigation

A department entitled, “Clinical Investigations,” was inaugurated in the July 1968 issue of this journal.

CHEST / 88 / 3 / SEPTEMBER, 1985 325
That section contained reports of clinical trials structured to evaluate efficacy of diagnostic and therapeutic modalities. As the new editor of *Chest* then, I was delighted to receive a gracious letter from the distinguished scientist, Dr. Alvan R. Feinstein, who commented about my choice of title. Dr. Feinstein wrote that he was pleased to see that at least one editorial board believed science could be applied to the study of man and that critical scientific methodology need not be limited to laboratory and animal research.

In that same year, (1968), Dr. Feinstein introduced the phrase “clinical epidemiology” into the medical literature and noted that many investigative clinicians had begun doing the kind of research which is described under that title. A discipline of “clinical investigation” began to develop its own scientific principles and methodologic standards. Dr. Feinstein continued his pioneering efforts, and his observations after nearly two decades of scientific leadership have now been incorporated into a superb text entitled *Clinical Epidemiology*.1

Dr. Feinstein notes that the “architecture of clinical research” was considered by him as an alternative title for his new book. Both titles indicate that one of the author’s main goals is to discuss the structure and function of research published in the medical literature. Feinstein notes, despite all the instruction aimed at preparing students for their future careers in clinical practice, medical education today contains no specific courses on how to think critically about the research results that are constantly encountered by clinicians at private meetings, conferences and in public journals. Because of this omission, future clinicians are taught a great deal about how to practice medicine, but very little about how to evaluate the published evidence on which medical practice depends.1

As a result of this startling omission in our medical school curriculum, a shockingly large number of clinicians do not have the ability to differentiate between explanatory and descriptive research. Without knowledge of fundamentals of clinical investigation, the clinician is fair game for the blandishments of anecdotal observations or distorted collections of data that are presented under the guise of scientific studies. The clinician who is not a critical reader and who places as much credence on unsophisticated studies as on excellent ones cannot practice optimal medicine, and indeed may be responsible for the initiation or perpetuation of medical myths.

Feinstein’s new text, *Clinical Epidemiology*,1 will, I hope, assist in correcting some of these grave current deficiencies in medical education. This volume contains a comprehensive and authoritative curriculum which can offer masterful guidance in both undergraduate and graduate medical teaching. The book should also be “an eye-opener” for nurses, statisticians, sociologists, economists, hospital administrators and many non-physicians in other disciplines. Among the subjects considered in this volume are: “An Overview of Research Architecture;” “An Outline of Statistical Strategies;” “Additional Principles of Cause-Effect Research;” “Structure, Science, and Statistics in Cross-Sectional Research;” “Non-chorot Structures in Cause-Effect Research;” and “Evaluation of Processes.” The text also provides a modest background in biostatistics which may be desirable for maximum understanding and utilization.

I fervently hope that *Clinical Epidemiology* will be read not only by investigators, but also by clinical practitioners and other readers of medical journals. It should be required reading in medical schools and in postgraduate training years so that “the architecture of clinical research” may be understood by younger physicians.

Iatroepidemic is a term coined by Eugene D. Robin and described in his recent book, *Matters of Life and Death: Risks versus Benefits of Medical Care.*2 Iatroepidemic denotes an epidemic caused by physicians which occurs when a practice is introduced into medicine on the basis of a fundamentally unsound idea or poorly interpreted experience. Such a practice may take hold without adequate studies to establish its efficacy and then develops a life of its own. Iatroepidemics in recent years include superficial femoral vein ligation for pulmonary embolism, tonsillectomy in children, internal mammary artery ligation for coronary artery disease, and subtotal gastrectomy for peptic ulcers. I presume Feinstein would vigorously applaud Robin’s “prescription” for prevention of these “clinical epidemics.” Dr. Robin believes that the most effective single step in preventing future iatroepidemics would be to modify the curriculum of medical schools. He pleads for education which will teach young physicians “how to critically evaluate medical literature.”2

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REFERENCES
1 Feinstein AR. Clinical epidemiology. Philadelphia: W. B. Saunders, 1985