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SUMMARY

Chronic diseases are in many ways more complex than acute diseases. In chronic diseases, response times to environmental effects are long, and confounding variables are numerous and may fluctuate with time. Treatment schedules are complicated and may be unique to the individual patient. Controlled trials deal with rigid hypotheses and permit control of error rates; prospective registries permit access to homogeneous subgroups. There is now a need for a new methodology for the study of the treatment of chronic diseases, which combines the merits of both approaches.

The purpose of a clinical investigation is twofold: to develop an understanding of a disease process and to aid the physician in developing a treatment strategy. When the etiology of the disease is known, these two issues are frequently coupled through an intervention aimed at disrupting the disease-initiating process. The bulk of acute disease fits this characterization while chronic disease for the most part does not. Etiology is frequently not understood, and therefore the basing of treatment on etiology is difficult at best. In fact, there is now mounting evidence in the biomedical literature to suggest that experimental methodologies are deficient when applied to the investigation of chronic disease. These deficiencies are particularly apparent to the doctor treating an individual patient.

Chronic disease appears to be substantially more complex than acute disease in several respects. Thus, before we discuss methodologies for supporting clincal decisions, it is important to enumerate the differences between acute and chronic processes.

Chronic disease is dynamic. It represents the long-term cumulative effects of interactions between a host biological system and the surrounding environment. The environmental influences are not static, so chronic disease acquires a time-varying characteristic. Many physicians recall hypertension of 20 years ago to be quite different from hypertension as seen today.

In contrast to acute disease, chronic disease is characterized by the slow time response of a biological host interacting with the surrounding environment. This interaction can be forced by the use of a specific treatment, or it may just happen in the course of the patient's daily life. The response time can be as long as several decades, as evidenced by hypertension, atherosclerosis and diabetes. Such a long resonse time provides a setting where many uncontrollable events may occur, confounding the interaction between host and surrounding environment. Acute disease, however, occurs over a short time (days to weeks). Thus, the 'influence' of an acute disease process is usually localized, producing a relatively homogeneous setting within which one can investigate interventions. With

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chronic disease, many loosely coupled organ systems have an opportunity to interact with the environment, thus producing a setting in which patients with the same illness form a remarkably heterogeneous group. Compare, for instance, the chief complaints and physiological responses of patients with an acute bacterial or viral infection with those given by patients with coronary artery disease.

Adding to the complexity of studying a chronic disease is the role played by the patient in the intervention. Study or treatment of an acute disease process requires little initiative by the patient. The patient's role is more or less passive, involving little or no cooperation. Interventions or treatments are limited to simple injections where the patient is quite passive (until the moment of injection) or to a short period (1–30 days) of self-administered tablets. Since treatment is directed toward cure, patients need little motivation. The response to the intervention occurs soon (within a matter of days) and is usually quite noticeable, indicating that cure is occurring.

Treatment of a chronic illness is usually quite different. First of all, the treatment is generally directed toward management of the patient and containment of the disease process, not toward a cure. More importantly, the patient now is an active participant in the treatment. Current clinical investigative practice of simply noting the intervention, while ignoring the patient–environment interaction, assumes that any such interaction is negligible. Such an assumption is often unwarranted. Diet, exercise, stress and working conditions frequently are confounding factors acting to modify the setting within which a treatment is being evaluated.

The practising doctor is confronted daily by patients with chronic illness, who are seeking any means of remaining productive members of society. The doctor is motivated to treat each patient on an individual basis because he/she is aware that no single treatment exists for a single chronic disease entity. To date, clinical investigations are unable to aid the physician with this task. Clinical trial results, where a trial has been performed, are reported in global terms based on average responses in groups of patients. Where the disease is studied within a homogeneous group, such results can be applied to individuals. For studies of chronic disease, however, this is not the case. The data derived from a clinical trial supporting 'treatment of choice' are so voluminous that many details remain unpublished.

To date, the literature reflects limited activity in the development of investigative strategies capable of dealing with slow response-time systems, heterogeneous experimental preparations and the treatment of choice. There are two fundamentally different but complementary approaches in use for dealing with the study of chronic disease: the controlled clinical trial and the prospective patient registry.

The controlled clinical trial is a well-known investigative tool and need not be described here. The prospective registry as an aid to patient care and clinical investigation, however, may be unfamiliar to many. Briefly, the prospective registry, in our hands, is a tool developed to provide the physician with an accurate representation of our local experience. There are three integral components: baseline data capture, intervention or treatment data capture and repetitive (yearly) follow-up data capture. Data are stored in a time-shared database computer that allows timely access to arbitrarily-defined subsets of patients. Past experience derived from the subset is presented in tabular form, with subdivision by treatment strategy and time course of follow-up events. Because of the time course involved with many chronic illnesses, this tabulation can be viewed as a time-lapse photograph, providing the doctor with an easily grasped view of a decade of experience.

Clinical decisions are individualized by the doctor and represent compromises among

patient goals, the expected time course of the illness, and available treatments. Biostatistically, decision making can be viewed as an informal 'play-the-winner' rule, with deviations based on the 'context' of the patient and the 'winner' determined by recent past experience.

Both methodologies have limitations and are subject to misuse and misinterpretation. So far, supporters of either approach have been satisfied with throwing darts at the limitations of the other methodology instead of developing tools appropriate to the study of chronic disease. The time, we believe, has come to recognize that chronic disease is a tough nut to crack and such dart throwing does little to help.

The primary issue can be simply stated. Can a biostatistically sound basis, financially realizable, be constructed to support clinical decisions and investigations in the setting of chronic disease? Controlled clinical trials give us bounded error rates supporting specific, temporally static hypotheses. Prospective registries give us a temporally continuous nonsampled representation of clinical experiences, making possible ready access to homogeneous subgroups. The doctor would like the best of both worlds: bounded error rates, access to homogeneous subgroups, and data dealing with the temporal variations of a disease.

Inexpensive computing and bulk storage, now available, are new tools of potential value for dealing with clinical-decision support systems. Large amounts of data can be readily accessible, and complex analyses can be performed conveniently. The time has come to review our toolbox of investigative tools, to restate the problem and to develop new methodologies capable of dealing with the complexities of chronic disease and treatment of choice.

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Résumé

Les maladies chroniques sont de beaucoup de manières plus complexes que les maladies aigues. Dans les maladies chroniques, les temps de réponse aux effets du milieu sont longs et les variables confondues sont nombreuses et peuvent varier avec le temps. Les plans de traitement sont compliqués et peuvent être particuliers à chaque patient. Les essais contrôlés traitent d'hypothèses rigides et permettent le contrôle des vitesses d'erreur; les enregistrements prospectifs permettent l'accès à des sous-groupes homogènes. Se ressent actuellement le besoin d'une nouvelle méthodologie pour l'étude du traitement des maladies chroniques, combinant les mérites des deux approches.

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