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THE SCIENTIFIC BASIS OF REGULATORY MEASURES

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In this paper, we expound on the legal and moral justification of regulatory measures. These are the laws and public policy regulations that all modern societies need to protect the purity, safety and effectiveness of its drugs and foods.

Passage of laws or promulgation of public policies alone is not sufficient to ensure enforcement of regulatory measures. Enforcement needs besides the force of government, the support of social and moral mores. The ultimate justification for legal as well as social enforcement is scientific evidence.

THE LANDMARKS OF THE FDA

The history of the FDA of the United States is an example of how essential regulatory measures in a modern society have been developed, and what legal and social forces had to be marshaled in order to make them effective.

When the agency was established in 1906, it was largely concerned with the purity of foods and the protection of proprietary name brands of over the counter drugs.

Then in 1937, an "elixir of sulfanilamide" was distributed in this country which killed in a short time 107 people. An investigation revealed that the culprit was the carrier of the "elixir", diethylene glycol, which was found by a chemist named Watkins to be an excellent solvent for the rather insoluble sulfa drug. Unfortunately he was unaware that this solvent was lethal and did not test it for toxicity. In the landmark Federal Food, Drug and Cosmetic Act of 1938 subsequently enacted, all drugs and components had to pass toxicity and safety tests and the contents had to be labeled before they could be sold. Drugs had to be safe.

In the 1962 amendments to the 1938 act, an added stipulation for the licensure of a new drug was the demonstration of efficacy. In retrospect, this was revolutionary, because heretofore the practice of therapeutic medicine was not required to be based on rigorous scientific evidence.

THE PROOF OF EFFICACY

Until the mid-twentieth century, all medical practices, whether ancient, modern, eastern, or western were largely based on uncontrolled observation and experience, which eventually developed into dogma. Dogma was accepted and learned by generations of physicians without knowledge of the primary evidence of efficacy. There is no doubt important discoveries were made by uncontrolled observations and experience. Some highly effective medicines or therapeutic measures can still be established by this method. The effects of fox glove (digitalis) on dropsy, of mahuang on asthma, of quinine on malarial fever, of insulin on diabetic acidosis, and the life saving effect of penicillin on bacterial endocarditis and of streptomycin on tuberculous meningitis are dramatic therapeutic effects demonstrable without complex controlled clinical trials. But these are exceptions. Rarely are drugs so dramatically effective. Even in the case of each one of the examples cited above, while the primary effect might have been apparent without clinical trials, the precise indication, dosage and toxicity of the drug had to be worked out in subsequent, detailed, often tedious clinical trials.

The scientific basis of modern western medicine can be divided into two parts. The first is the steady accumulation of knowledge

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in the basic biomedical sciences, such as biology, anatomy, pathology, physiology and microbiology, over the course of about one to two hundred years. It has had its glorious spurts, such as the present spurt of exponential increase in the knowledge of molecular genetics. These sciences are revered by all nations now and promoted by them without reservation.

In contrast, the development of the basis of scientific proof of efficacy, the development of controlled clinical trials is only about 50 years old, and its acceptance is by no means universal. Not only is it barely known in the so-called non-western "alternative" medicines, especially traditional Chinese medicine so popular in the Pacific basin, the controlled clinical trial has even been attacked by prominent academic western physicians to this day. Why?

The basic idea of a controlled clinical trial is simple. It is the comparison of the results of a treated group of patients with an untreated control group. The first problem that arose with such trials was the nature of the controls. Before World War II, controls used in clinical trials were frequently historic controls, or patients were intentionally selected as controls. Selecting controls inevitably introduces bias and may vitiate a scientifically valid comparison. Nowadays the consensus is that truly valid controls must be random and unselected. "Blinding" both observers and patients of a trial may further reduce bias of observation, so that treated and untreated patients cannot be distinguished. Other less controversial aspects of clinical trials are that eligibility of patients and end points of the trial should be clearly defined, and that results are statistically validated.

The crux of the ethical and moral difficulty of controlled clinical trials is its basic assumptions. One assumption is true ignorance; ignorance of whether or not the drug or therapeutic measure works. It is often very difficult for physicians and scientists, particularly those intimately involved with the development of a new drug, to avow true ignorance. They often develop blind faith in its efficacy. It may be equally difficult for a patient to accept the possibility of receiving a placebo instead of the benefits of a promising new drug which is being tested.

Another assumption is the ancient but powerful basic principle of medical ethics, "primurn non nocere" (first of all, do no harm). This tenet has received powerful affirmation in the aftermath of the notoriously harmful human experiments revealed during the Nuremberg trials. It may work either way in a controlled trial. It may help advocate the introduction of a placebo controlled trial to test a new drug which might be toxic, or it may help defeat such a trial because an advocate believes that unless one uses the drug one is doing harm.

Experience has shown that these difficulties should be faced and overcome. One common way is to have an impartial monitoring board detect at the earliest possible point proven intolerable toxicity or efficacy of the drug so that the trial can be stopped.

EVIDENCE-BASED THERAPEUTIC MEDICINE

The psychological and ethical difficulties of randomized controlled trials (RCT) postponed their real entry on the medical scene until after World War II. It is an interesting sociological observation that it is in the Anglo-American democracies that this scientific method found its fertile ground and flourished. RCT was not developed or undertaken on the European continent and particularly not in Catholic or Communist countries. This suggests that a certain mind set, perhaps one less encumbered by absolutism, is needed.

The pioneer of controlled clinical trials was the British statistician, A. Bradford Hill. He undertook the first controlled trial of streptomycin on tuberculosis in 1949, and later was the first to show the causal effect of cigarette smoking on lung cancer. He did not receive the Nobel Prize, but should have for either one of these achievements.

With the development of this new methodology after World War II, the exponential increase in newly discovered therapeutic agents, and the requirement of agencies like the FDA for proof of efficacy before licensure,

the use of RCT in medicine entered its exponential phase, where it still is. The stunning elucidation of the complex antiviral therapeutics of HIV/AIDS, and the introduction of HAART (Highly active anti-retroviral therapy) from 1996 on, are all attributable to RCT. RCT is now practiced wherever western medicine holds sway. Not only are new measures being tested, but medicines and practices sanctified by past dogma are being retested. And surprising results arise. For example, it is no longer established, as it was before by dogma, that digitalis is good treatment for heart failure. While quinidine is effective for certain arrhythmias, used on a long-term basis, it shortens life and is contraindicated! Such fine points regarding therapeutic medicine would not be knowable without RCT. In fact it is no longer possible to fine-tune the use of a drug or a combination of drugs without RCT. Although we mentioned before that Bradford Hill proved the efficacy of streptomycin for tuberculosis almost 50 years ago, we are still doing RCT for anti-tuberculous therapy. There are so many questions to be asked and answered.

With all old as well as new therapies being gradually validated by RCT, the day is at hand when all therapeutic measures will have to be evidence-based. This will be demanded by the science of medicine and eventually also by laity. This is already the case with western medicine.

Eventually, I predict that the same requirement will be demanded of alternative medicine, including traditional Chinese medicine, which has always been popular in the western Pacific rim, but is even enjoying some popularity in countries like the United States.

TRADITIONAL CHINESE MEDICINE

Because RCT and evidence-based medicine is so new even in western medicine, we cannot yet expect our colleagues in alternative medicine to appreciate this new requirement. But they should prepare for it. Eventually all their therapeutic measures, from herbs to acupuncture and moxibustion, will have to be proven by RCT. First there will be a legal requirement. Then the social fabric will demand it. While this day may seem to be far off in parts of Asia, the day is nearing when only evidence-based medicine will be acceptable by society. Scientific proof of efficacy will become part of the ethics of administering therapy. Put in another way, unless a therapeutic measure is proven by RCT, it will not be ethically tolerated. This will be the moral imperative of the science of medicine.

I have been quietly propagating this message in Taiwan to our colleagues in traditional Chinese medicine (TCM). Actually the necessity of doing RCT in TCM provides an opportunity for TCM. So far attempts to put TCM on a scientific basis have failed. Its anatomical, physiological and pathological theories have remained opaque to modem scientific comprehension. On the other hand, in order to do a RCT, it is not necessary to understand or even discuss its underlying theory. RCT is an eminently empirical scientific method, and only treatment results count. RCT should be used in a systematic manner to establish the important therapeutic measures of TCM. Once established, the measure will be on solid scientific ground. Similarly useless or harmful measures can be pruned. Eventually TCM will be better medicine because of this exercise.

THE REGULATION OF TOBACCO

Tobacco is a unique substance, but its regulation, like that of other drugs and foods, must be based on scientific evidence. The accumulated weight of evidence of its harm without any known beneficial effect first swayed the government and eventually the public in favor of regulation in the United States. But the Journey has been an incredibly difficult one. And in other countries, the journey hasn't even started or it is only beginning.

While the argument about the harm of tobacco goes into antiquity, modem scientific evidence that it is a cause of lung cancer is dated to the paper published by Doll and Hill

in 1950 in the British Medical Journal. In an elegant case control study of 1357 patients and an equal number of case controls, they proved that lung cancer patients smoked more at all levels of intensity of smoking, and that mortality in these cohorts went up proportionately with numbers of cigarettes smoked.

Since then, 50,000 studies document that tobacco causes deaths of about 90% of patients with lung cancer, 30% of all cancers, 20-25% of coronary heart disease and strokes, and 80% of patients with bronchitis and emphysema. Furthermore, nicotine, which is present in all tobacco, is addictive.

In the beginning, since much of the evidence of the harm of tobacco was epidemiological and statistical, there was room for honest differences of opinion. The U.S. tobacco industry established the "Council for Tobacco Research" to develop pseudoscientific research over the course of forty years and spend millions of dollars to counteract the negative results of earlier studies. This "scientific" effort has largely ceased, largely because it is discredited. The Wall Street Journal called it "the longest running misinformation campaign in U.S. business history." The scientific credibility of the industry was further devastated in 1994, when Jeffrey Wigand, a former tobacco executive, revealed that the industry had scientific evidence that nicotine was addictive when its executives swore to Congress that they did not.

The evolution of regulatory measures began modestly enough in 1964 when the Surgeon General announced that smoking was hazardous to health and that all packages must be so labeled. The industry accepted "self regulation" of cigarette ads, including banning them on television, and accepting the prohibition of sale of tobacco to children under 18 in all 50 states (1971). After more than twenty years of such co-existence between mild government regulation and industry, in the face rising numbers of addicted children, Kessler, commissioner of FDA, first suggested in 1996 that tobacco be regulated as an addictive drug, and Clinton produced a plan to reduce smoking of young people by half in 7 years. But the coup de graceagainst the industry came in 1997 in the wake of a crushing number of suits against the industry. In a historical meeting of the tobacco executives and state attorneys general, a deal was signed in which the companies agreed to pay $368 billion dollars and more, and accept FDA restrictions on sales and advertising to teens for protection from further law suits.

REGULATION OF TOBACCO IN THE ASIAN PACIFIC RIM

By 1997, in the United States, the government and the public have after a 50 year struggle succeeded in regulating the sale of tobacco so that a significant reduction can be expected in the near future. It is still unclear whether this will be sufficient to prevent the health hazards of tobacco. Actually it is a moot public issue as to how much health hazard is tolerable and how much tobacco should be further restricted. The answer lies in more scientific investigation and probably litigation. Still what has been achieved is lauded by all who are interested in the health of the nation, especially of the young.

But the rest of the world, especially the nations of the Asian Pacific rim, are way behind the United States in regulating the sale of tobacco. Neither the governmental determination nor the public support is there. In these countries, the situation is further exacerbated by the United States government, which in the name of free trade, allows American tobacco companies to sell tobacco in ways that are prohibited at home.

In the 1980's, the U.S. government forced open the tobacco markets of Japan, China, South Korea, Taiwan and Thailand. Following aggressive promotion and advertisements, often in ways prohibited in the U.S., the sale of American cigarettes sky rocketed. Paradoxically, increase in the rate of smoking was further abetted by the national tobacco companies of these countries, which had to intensify their own promotion to compete in the market. It is a commentary of the confidence in their foreign markets that the U.S. tobacco companies were willing to pay confiscatory sums to the U.S. government to remain in business in 1997. They intend to

recoup their losses abroad.

In the various national campaigns against smoking in the Pacific Rim, the adversary includes not only the tobacco industry, and public insouciance, but also the U.S. government. The posture of the U.S. government, which allows the industry more freedom abroad than at home, should be criticized by all interested in international health. America is a democracy, and the government will yield if sufficient pressure is applied. The health care communities of all nations should be alerted to this fact.

CONCLUSIONS

- Public policy and regulatory measures should be justified and guided by scientific evidence, not dogma, hearsay, fear or fad.
- Drugs and therapeutic measures should be non-toxic and effective. The demonstration of toxicity and efficacy relies on biomedical sciences and the controlled clinical trial.
- We must teach our medical students, health workers and the public the nature and power of scientific evidence. Medical students and fellows need to understand and appreciate the randomized controlled clinical trial.
- Because of medical advances and discoveries, the work of public regulation of food and drugs is never ending. There are constant as well as changing challenges to health from the toxic effects of foods, drugs and devices, like tobacco.
- There are vast areas of medical practice, including "alternative medicines" such as traditional Chinese medicine, whose therapies are not yet scientifically proven. We should encourage leaders of such medicines that this should be done, if for no other reason than their own survival.
- Powerful forces are aligned against health workers who wish to promote prudent regulatory measures for reasons of health. These include an uneducated or unaware public, powerful national and international companies, and national as well as foreign governments. We should organize nationally and internationally to overcome these oppositions, first by education and publicity, and then by public pressure.