Late in 1974 some human clinical experiments were conducted just around the corner from here by Dr. James Chan at the George Washington University Hospital. Because of prior research, most of which had been performed on chickens, rats, and dogs, Dr. Chan and his associates felt there was ample justification for small scale, tightly controlled tests on human subjects.

The experiments called for the use of a newly developed pharmaceutical agent. Naturally, in cases such as this the Hospital's Human Rights Committee must first give their official approval. Then each patient is advised of the experimental nature of his/her treatment and given an "informed consent" release to sign.

The Patients, all suffering some form of renal dysfunction (kidney disease), were experiencing varying degrees of renal osteodystrophy, a disease ~~of the bones~~ in which newly available calcium is not readily absorbed by the bones of the body. Over time this disease permits calcium to leach out of the skeletal structure leaving it brittle and weakened. Eventually, if not effectively treated, the victim of renal osteodystrophy becomes near totally handicapped, unable to walk without the assistance of prosthetic devices.

The experimental compound used by Dr. Chan was a metabolite of vitamin D-3, known as "1,25 Dihydroxycholecalciferol". This compound is identical with vitamin D-3 with the simple addition of 2 hydroxyl radicals (-OH) at the 1st and 25th carbon atom sites. One of these OH groups is added to the vitamin by action of the kidney (to be more precise the mitochondria of the renal cortex) in the normal, healthy human being. Consequently, in the patient with kidney failure, who must undergo regular hemodyalysis to escape uremic poisoning, the metabolism of vitamin D is interrupted in such a way that it can't perform the functions it must if good health is to be maintained.

To return to Dr. Chan and his associates at GWU Hospital, his patients were adolescents who had already been on the kidney machine for an extended period. The calcium was leaching out of their bones making them brittle, weak, prone to breaking. If this condition could not be corrected, they would eventually suffer permanent damage.

In the USA, there are approximately 50,000 victims of this renal osteodystrophy condition each year. Ten percent of these are children. Anyone who is kidney machine dependent for 6 months or longer is subject to the disease to some degree, but most frequently it inflicts the greatest damage on children whose bones

are in a stage of ~~normally~~ rapid growth.

Dr. Chan's patients were mostly in their teens and already owed their lives to twice weekly treatment on the GWU hemodyalysis unit, the apparatus that filters the blood of impurties that are normally excreted by the kidneys. But his patients were slowly losing their rescued existence to deteriorating bones. Beginning in April 1974, the experimental compound was administered to the patients at the same time as their machine treatments.

Over a period of months, X-Ray evidence showed conclusively that the compound performed the same way when administered orally as when produced naturally by action of the kidney and liver. In short, the calcium leaching stopped and the bone lesions healed. The treatment was dramatically successful. This would be a happy ending except for a few technicalities. If you, a relative, or close friend of yours were unfortunate enough to become one of this year's 50,000 victims, you wouldn't be able to go around the corner to GWU Hospital for treatment. No, if you needed treatment with 1,25 Dihydroxy vitamin D-3, a substance which every human body produces to maintain itself, you would have to go to France or some other country where it is licensed for general use. It's general use is illegal in the United States. A chemical which is present in the blood plasma of everyone of us here today, always has been and always will be if we are lucky enough to stay healthy, has not been sufficiently tested to be deemed safe by the U.S. Government. This state of affairs is the direct result of statutory law, passed by Congress in its wisdom and administered by FDA, the same folks who brought you the recent ban on saccaharine and the cyclamate scare of a few years ago. But before I get too deeply into the conflicts of Executive Agencies, or the far wider debate on whether our Government regulates too much or too little, or even into the realm of one of our society's paramount political issues, "centralization of power vs individual rights". before I digress to these topics, let me address the notion of ethics in the conduct of scientific public policy.

Ethics is one of those words that can have a slippery meaning. Too often "ethical" is something we feel is right, while ~~and~~ unethical is something our enemies feel is right. If we can just say that an ethical judgement is one based on a system of moral values governing commonly held notions of right and wrong, then that slippery essence begins to come clear.

The problem is "commonly held" notions of right and wrong." History has seldom witnessed a society as seethingly pleuralistic as our own. In such a society, plowing as it is through the surf of the 20th century's closing decades, figuring out what those commonly held notions are isn't as easy as it once was. a public law which regulates the introduction of new pharmaceutical agents onto the market and administered by FDA represents a notion, held in common by the majority of the U.S. Congress, on what is "right" for the American people. Yet in the case of individuals suffering from the disease treated by Dr. Chan, the unavailability of 1,25 Dihydroxy vitamin D-3 clearly does not seem to be right, proper, or just. To what extent, and under what circumstances should society withhold this treatment to those who critically need it, in order to protect the population at large from a possible or theoretical danger? This issue, which is, as you know, at the root of much debate in public policy issues concerning science, is fraught with many examples of well meaning government intervention that frequently results in denial of products or services for which there is a pressing need. The FDA requires on the average 4½ years to license a new pharmaceutical agent. The basic patents for the vitamin D-3 metabolites

were issued in 1968, yet today in 1977 ~~they~~ the compounds are still generally unavailable because they are not licensed. This type of delay is not uncommon. There is an anti-convulsant, Clonozapam, used for the treatment of Petit Mal seizure, licensed overseas, and especially useful in cases where the drug of choice, Dilantin, is poorly tolerated. It took 11 years from the time the license application was made until it was granted. Another pharmaceutical, chenic acid, marketed under the name Ulmenide by Hoffman La Roche in Switzerland has been demonstrated to dissolve 60% of gall stones due to the build up of cholesterol when gaulic acid is not present in bile fluid to a sufficient degree. This drug was discovered in Nutley, New Jersey, but now almost 8 years later, it is not available to Americans who must seek relief from the only other technique available, surgery. What is the social cost over the years of the pain and expense of surgery compared to the benefits of simple pharmaceutical administration?

No one can question the motives of those who call for strict regulation of pharmaceuticals by the government, yet there is a clear danger that the needs of those disease victims who must wait that space of time between innovation

and regulated application are not being paid fair heed ~~to~~. After all, it is their safety that is in danger, not the safety of the general public. If there is a choice between disease and the possible ill effect of treatment, shouldn't the patient ~~have that decision~~ choose? This question becomes even more acute in the case of a drug known as Laetrile, not because of its ill effect, but because of its nil effect. Although licensed for cancer treatment overseas, it has been found to have no detectable effect on cancer. Yet, what of the psychological effect of withholding a treatment from a terminally ill person? Is the government protecting citizens from being ripped off or denying hope to the dying who know that there is something available to foreigners that they can't have? One of the "on the air" calls to President Carter on the radio last month dealt with this exact question.

There is a tragic irony in the fact that with drugs so frequently, "apparently" "ethical judgements" made to avert potential harm or injustice end up permitting very real suffering ~~which is all too real~~. ~~In~~ addition to the past examples, let me relate one more example, ~~and~~ perhaps the most famous. A noble gesture made by Sir Alexander Flemming in the late 1920's was a cause

for this same man's most bitter regret in subsequent years. Without filing a patent application, Dr. Flemming published his historic discovery, and in doing so voided his rights to sole ownership of the commercial possibilities of Penicillin. He did this out of a feeling that the discovery belonged to the world. He did not want the immense ~~politieal~~ income. Financial reward did not interest him. However, the loss of exclusive rights due to publication had an effect he hadn't counted on. Since no pharmaceutical firm could be certain of a period of proprietary rights of production, the risk of investing large sums for the necessary capital equipment ~~for production~~ could not be justified. For 11 years the miracle of Penicillin languished. It was only resurrected due to perhaps the most immoral, unethical event of the century, WWII. It has been estimated that 5 million people a year died who might have lived with administration of the wonder drug. 55 million people between 1930 and 1941 whose mortality rested on Alexander Flemming's conscience, and a short-sighted, "ethical judgement". In this case Flemming's ignorance of an economic reality, his failure to understand the market system, cost a heavy price. He might easily have used his income to support charity, education, science, medicine, or any number of worthy causes,

but by destroying the opportunity for profit itself, he put an enormous barrier between Penicillin and the public. Barriers between innovation and public availability are becoming increasingly more prevalent.

In the case of Penicillin the barrier was clearly a bad thing, but in the most obvious counterexample, the Thalidomide tragedy, a more stringent barrier might have prevented a modern nightmare. In these two premier cases of a miscalculation in ethical judgement, the barrier to innovation troubled the lives of many millions more individuals than the lack of a barrier did. Perhaps assessing human damage in so empirical or quantifiable a manner is itself unethical, yet without it we are left totally to the subjective impression. The objectivity of an empirical analysis of cost, risk, benefit, or effectiveness of one course of action compared to an alternative is almost the only defense there is against a purely partisan viewpoint. When the official in public service is confronted with a choice of assisting implementation of a new product or opening up an avenue of new research vs hindering the introduction of scientific technological effort, she/he must balance the benefits vs the costs or in the case of

research, risks of cost. When the results of human endeavor backfire, and there is a price to pay in human lives or misery, then there is turmoil until blame is assessed and precautions are laid to insure no similar future error. But think for a moment, what happens when a beneficial course of action, product or servide is not implemented or is greatly delayed? Lack of helpful change is somehow less galvanizing than the commission of hurtful change. Likewise, in the case of potential risks and benefits that must be envisioned when one considers basic research, it is the risk of failure or accident, and not the known or potential rewards which most preoccupy the public mind. How many people here knew the facts behind Thalidomide, but had not heard the story of Penicillin's almost none existent journey to market? How many of you realized some pharmaceuticals are cleared for use after periods of time that average 4½ years but frequently take 8,9, 10 years or even longer?

I think it is safe to say that there have been errors in ethical judgement made both through commission and by omission, yet it seems to be only the committed mistakes which enflame the passions in most people. Curiously, where

scientific innovation is concerned this phenomena has made some people work toward conservative ends that are designed to hinder or stifle scientific progress. Yet these same people will most often claim to be liberal or progressively inclined, while they work to put up barriers to innovation. In our decisions which balance (compare) costs to benefits at time 1 with other costs and benefits at time 2 we cannot afford to lose sight of either source of error. We may do something wrong, but we may also not do something right.