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Editorial

Prospect of gastroenterology and hepatology in the next century *

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The task of predicting what Gastroenterology and Hepatology may look like in the coming century is a great personal challenge and at the same time an awe-inspi ring assignment. Not only have these two medical specialties become very large and diversified but there are so many new discoveries and ideas that it is a capricious undertaking to attempt fore-telling which of them may become part of the next century's medical practice. I therefore will take the personal privilege of being highly selective, choosing only topics for discussion which I believe have a distinct potential of generating novel scientific concepts, fresh approaches or new therapeutic modalities.

Over the past few decades, the biological sciences which form the basis of contemporary medicine have evolved enormously, producing an ever-increasing volume of new information and technology that is keeping Gastroenterology and Hepatology changing and advancing at an accelerating pace. Looking back half a century to the end of WWII and China's liberation, it may seem astounding how elementary gastroenterology had been at that time. Modern science hardly had touched it and most of the diagnostic and therapeutic dogmas were still those of the 19th century. But over the past 50 years, Gastroenterology and Hepatology have profoundly been remade. We have witnessed a dramatic increase of insight into the causes and mechanisms of disease and our diagnostic and therapeutic capabilities have vastly expanded and improved, for example, the discovery of the viruses causing infectious hepatitis, of transplantation of the liver, pancreas and small bowel, or of the introduction of fiberoptic endoscopy. And to top it all, recall the recent revolution in peptic ulcer disease which unceremoniously has toppled old dogmas about gastric acid and made it instead a readily curable infectious disease.

I believe with confidence that this dynamic evolution will continue and probably accelerate in the coming century. And there is no question that it will bring much novel and unanticipated clarification about currently obscure diseases. It will also greatly refine diagnostic procedures and expand therapeutic choices. What seems more difficult to predict though, is what directions this evolution will take, and how we are going to make use of the new opportunities and how we will pay for them.

Human Genome Project

The Human Genome Project is a joint enterprise that undoubtedly will have an enormous and irreversible impact on the future of Gastroenterology and Hepatology. It probably is the largest international scientific project ever undertaken. Once its ultimate goals are reached, presumably early in the next century, the entire human genome will have been sequenced and mapped and it will be possible and perhaps become routine to screen an individual's genome from a simple blood sample. Genetic mutations which result in hereditary diseases of the gastrointestinal tract or the liver will readily be identifiable. Individuals or families at risk for a hereditary disease may be screened for the genetic defect. And eventually, such screening may become available even for prenatal use. It is likely, of course, that the function of many of the new genes identified by the sequencing initially will not be known and will have to be determined stepwise, one by one. This will be a huge task which may well take several decades of painstaking investigations. But once this has been accomplished, gastroenterologists of the future will look at intestinal and liver diseases from a vastly different perspective, and they will use treatments which are far beyond today's imagination.

The sequencing of the full human genome will have far-reaching consequences in many other ways. Many genetic diseases are polygenic, i.e., there is more than one allele in the same location or the phenotypic expression of a primary gene defect is modified by one or several additional as yet unidentified genes. This probably accounts for the

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wide spectrum of clinical expression that is seen in many inherited diseases. For example, homozygous Wilson disease, copper storage disease, may clinically present as progressive cirrhosis, as a severe chronic disease of the central nervous system, or as acute hemolytic anemia. This phenotypic variability probably reflects the polygenic nature of this disease, a hypothesis which is likely to be resolved by the successful sequencing of the human genome. Another example of highly variable expression of a genetic defect is observed in α-1 antitrypsin deficiency type ZZ. Here, only 20% of the patients homozygous for the defect actually develop progressive liver disease and cirrhosis. In the majority of patients, the liver merely exhibits scattered hepatocytes bearing variable amounts of defective and hence misfolded and precipitated antitrypsin which accumulates in the cells, eventually killing them by apoptosis. The variation in phenotypic expression of this hereditary defect may reflect genetic differences in the activity of cellular metalloproteases fitted to degrade the precipitated antitrypsin. Again, the genome project is likely to resolve this puzzle.

Another benefit of the genome project will be identification of the genetic factors which determine individual susceptibility to environmental assaults, such as viral, bacterial or fungal infections or exposure to toxins or poisons. Clearly, different people respond to such noxious assaults differently. For example, some experts believe that inflammatory bowel disease, such as ulcerative colitis or Crohn's disease, may be the result of a genetically determined aberration of the immune response to the trillions of microorganisms inhabiting the intestinal lumen. To date, no such genetic immune defect has been identified but the sequencing of the genome may change this. A similar differentiated response is also observed in chronic alcoholism. Surprisingly, only 25% of chronic alcoholics develop cirrhosis of the liver. Why is it that the majority escapes hepatic injury It clearly is not due to dietary factors or to a preferred alcoholic beverage. Rather, I suspect that this striking difference is caused by genetic factors which determine how the liver is reacting to the metabolic products or reactive oxygen radicals which are produced when alcohol is metabolized. Here, too, the sequencing of the genome in the next century may provide plausible answers.

The Human Genome Project is of importance also for the future of gene therapy for inherited diseases. This is because it will facilitate identification of the nature of the genetic error in a mutated gene e.g., transposition of a base pair, missense mutations, deletion of several nucleotide sequences etc. This information is crucial for construction of the new gene to be transposed. As you are aware, somatic gene therapy *in vivo* has been used successfully in many animal models and in a few highly selected genetic defects in humans. There are still problems which need to be addressed, but I am confident that they will be resolved in the not too distant future. One of these problems concerns the vehicle or vectors which are used to transport the replacing gene to the targeted cells or organ. At present, this is usually accomplished by packaging it into liposomes, adeno or retroviruses, or more recently, adeno-associated viroids. But these RNA viruses often cause immune or toxic reactions which limit their usefulness as vectors. Moreover, it is difficult to target live viruses to specific cells or tissues in which the mutation is being expressed.

As an attractive alternative a highly imaginative new approach has been proposed (Kren *et al*. Nature Medicine, March 1998) which employs a chimeric RNA/DNA oligonucleotide embedded in a short stretch of DNA. This is coated with a polycation containing a ligand that permits targeting of specific cells. And it is the cells' own DNA mismatch repair mechanism which is used for integration of the new oligonucleotide into the cells'DNA. This new technology has been tested successfully for site-specific introduction of a single base-pair mutation in rat hepatocytes in vitro and in vivo. It is very promising particularly for gene therapy of hereditary diseases expressed in the liver and it undoubtedly will play a commanding role in the next century.

A second problem with current gene therapy is that the somatic cells selected for gene repair have a limited natural life span and then undergo apoptosis. A repaired gene therefore can be expressed no longer than the life span of its cell, which may range from a few days for intestinal mucosa cells to several hundred days for hepatocytes. To overcome this major limitation, one would need to repair the genetic defect in embryonic germ cells, an approach which at present is neither possible nor ethically justifiable. A more promising design might be to target gene therapy to an organ's stem cell compartment. Stem cells are undifferentiated pluripotential progenitor cells, which can either replicate themselves or undergo differentiation to more mature cells. (Science, March 5, 1999). Such pluripotential stem cells have been identified in, or isolated from, a variety of animal and human tissues, including bone marrow, intestinal mucosal crypts and brain. In the liver, unequivocal identification of stem cells has not yet been reported, but so-called oval cells have been identified and isolated (Petersen *et al*. Hepatology, February 1998). Ovalocytes are believed to represent stem cell-derived intermediary precursor cells which are able to differentiate into hepatocytes or bile ductular cells (Matsusake *et al*. Hepatology, March 1999). They typically are found in regenerating liver under experimental conditions in

which replication of mature hepatocytes has been blocked. Since ovalocytes' differentiation potential is limited, identification of the authentic hepatic stem cell compartment currently is a top research priority. Once this has been accomplished, it should be feasible to transpose new genetic information into the stem cells' genome thereby making it available indefinitely to daughter cells. I am confident that in the coming century, such technology will become available which would represent a true breakthrough in gene therapy of a large number of hereditary diseases. At present, of course, permanent cure of hereditary diseases of the liver, such as Crigler-Najjar disease, OTC deficiency and hereditary analbuminemia, can be accomplished only by orthotopic liver transplantation.

Other new and promising applications of gene therapy recently have been described for the treatment of malignant tumors or cancer metastases in the liver. The trick here obviously is to package the genetic information to be transposed in a vehicle that is able to recognize specific molecular features of cancer cells, particularly cell membrane receptors or membrane-bound antigens. The majority of malignant tumor cells exhibits mutations in genes expressing so-called cancer repressor proteins, such as p53, p16 and others, which act primarily by controlling the cells'mitotic cycle. When these genes are mutated or lost, the result is unregulated cell replication and tumor growth. In animal models, gene therapy targeted specifically to surface receptors of malignant cells was able to successfully reconstitute functioning p53 or p16 genes, resulting in sustained tumor shrinkage and prolonged survival. In an alternative approach, the DNA sequence to be transposed into tumor cells was coupled to a monoclonal antibody which recognized a glycoprotein abundantly expressed in hepatocellular carcinomas (Mohr *et al. Hepatology*, January 1999). Although to date, these and other novel techniques of gene therapy have been tested only in experimental animals or in cell cultures, they obviously have great promise for cancer therapy of the future and eventually may substitute for surgery, radiation or chemotherapy.

I have discussed the Human Genome Project and particularly gene therapy in some detail because within their frame of reference both will have an epochal impact on the future practice of Gastroenterology and Hepatology. But the enormous advances in the basic biomedical sciences, particularly in molecular and cell biology and in molecular virology and genetics, will literally revolutionize the way physicians of the future will think about mechanisms of disease. And the next generation of gastroenterologists and hepatologists will be handed a staggering array of new therapeutic modalities, most of which have not yet been invented. To illustrate what I mean, I arbitrarily have chosen for discussion three recent major scientific contributions which I believe have the potential to make an immense impact on clinical medicine of the future.

The first scientific break-through is the so-called nucleic acid or naked DNA vaccine.As you know, most of the currently available antiviral vaccines consist of attenuated live DNA or RNA viruses which have lost most of their virulence but retained their antigenic potential. Examples are vaccines against viral hepatitis, poliomyelitis, measles, varicella, yellow fever, etc. All of these, of course, are modeled, as it were, after Edward Jenner's classic experiment with cowpox as protection against the deadly smallpox. Although most of these live vaccines are highly protective, reservations often are expressed whether avirulent viruses could spontaneously undergo back mutation to a more virulent form; or whether attenuated live viruses could cause unsuspected morbidity decades after they had been used in a vaccine. The advent of recombinant DNA technology now has made it possible to design novel vaccines which provide strong and sustained antigen expression but exclude these lingering doubts about live-vaccines' safety.

The principle of this new approach is relatively simple. A gene from a pathogenic microbe encoding a microbial antigen, is spliced into a bacterial plasmid. The vaccine consisting of the plasmid bearing the spliced gene, is injected into muscle tissue where it directs the muscle cells to manufacture microbial antigen.The latter evokes a sustained immune response, involving both,antibody formation and a T-cell response. Although, to date, this new naked DNA vaccine has been tested only in experimental animals, persistent high titers of circulating antibodies have been obtained and the animals were protected against infection. It is thus evident that this new approach to vaccination has great promise and is likely to be a relatively inexpensive procedure. Indeed, naked DNA vaccine looks like the vaccine of the 21st century.

TRANSPLANTATION OF ISOLATED SYNGENEIC HEPATOCYTES

The second subject I have selected for discussion is still in its experimental phase but its great potential for future medical applications already is unmistakable. It concerns the transplantation of isolated syngeneic hepatocytes into a recipient's liver *in vivo*. Development of such a technique for clinical use obviously would open new avenues not only for correction of genetic defects, but also for the management of acute hepatic failure. It eventually may contend with, if not substitute for, orthotopic liver transplantation which in view of the scar city of available organs might be a solace.

The first satisfactory technique for isolation of intact and functioning hepatocytes from

experimental animals was developed by Berry and Friend in 1969 (J Cell Biol, vol. 43). It stimulated a profusion of attempts to culture such isolated cells in vitro or to introduce them into various organs of congeneic rec ipients *in vivo*, but with few exceptions, the cells failed to survive, let alone to proliferate. In 1982, Mito *et al* in Japan (Gastroenterology, Vol. 82) reported the exciting finding that in rats, syngeneic hepatocytes transferred into a recipient's spleen not only survived and retained their characteristic physiologic functions, but also proliferated. In fact, partial hepatectomy of the recipient a few days after transfer of hepatocytes into its spleen greatly magnified the number of mitotic figures in the transplanted cell population. And then, in 1991, Gupta *et al* (Proc Natl Acad Sci USA, Vol. 88) announced the surprising observation that a major fraction of the hepatocytes extant in the spleen eventually migrated to the host's liver where they were fully integrated into existing liver cell plates, properly functioning and apparently surviving indefinitely (*Hepatology*, February 1999).

Since the spleen is a relatively small organ, only a limited number of donor hepatocytes can be transferred to the liver with this procedure. Nonetheless, in rats and mice, it was able to at least partially correct genetic defects such as analbuminemia and unconjugated hyperbilirubinemia. Fortunately, a complementary experimental stratagem has been developed (Laconi *et al*. Am J Pathol, Vol. 153, 1998) which allows for a significant increase of the number of donor hepatocytes which can be delivered to the liver via the spleen. This consists of preparatory treatment of the designated recipient animal with the pyrrolizidine alkaloid retrorsine which is taken up selectively by the liver. It blocks the resident hepatocytes' cell cycle and therefore suppresses their proliferative potential. When combined with a subsequent two-third hepatectomy, the proliferative thrust generated by this resection is lost on the blocked resident hepatocytes thereby greatly favoring the transplanted cells. In preliminary studies with this approach, one to two months after the procedure, up to 80 percent of the recipient liver's cells consisted of transplanted hepatocytes and their progeny.

Although these are unusually exciting experimental findings, in its present form, this technology clearly is far from being applicable to clinical medicine. Nonetheless, I believe that on the basis of the new scientific information and technical expertise gained from these experiments, it will only be a question of time until a clinically acceptable and promising version of this approach will be developed. Given the rapid progress in research on inducible immune tolerance, it even may become possible to use allogeneic hepatocytes for transplantation instead of being limited to syngeneic donor cells. To start with, I can think of two important groups of liver diseases in which hepatocyte transplantation via the spleen may be the therapeutic approach of choice. One is fulminant hepatic failure of variable etiology, including potentially fatal tylenol poisoning, in which the number and/or condition of surviving liver cells during the acute phase may be insufficient to sustain life and eventual recovery. The other consists of genetic defects expressed in the liver for which conventional gene therapy may be unavailable or lacking promise. These include α-1 antitrypsin deficiency type ZZ, Wilson disease, analbuminemia, Crigler-Najjar disease and several others. Two different technical approaches are possible. One is to transplant hepatocytes obtained from a syngeneic donor; the other is to use the patients'own hepatocytes after the genetic defect had been corrected ex vivo with DNA supplied by an unrelated donor. Either approach would seem attractive and technically feasible.I am confident that in the next century, this cellular approach to liver transpl antation will become a very important and frequently used procedure.

ACTIVE BIDIRECTIONAL EXCHANGE OF NUCLEATED BLOOD CELLS BETWEEN FETUS AND MOTHER

The third scientific issue that I wish to discuss is really a working hypothesis, but one that is supported by powerful, though indirect, evidence. It concerns the recent demonstration that in pregnancy there often an active bidirectional exchange of nucleated blood cells between fetus and mother, producing what has been called microchimerism. In the maternal circulation, immune-competent fetal cells are detectable not only during pregnancy but often for several decades thereafter (Bianchi *et al*. Proc Natl Acad Sci USA, Vol. 93, 1996). It is unknown, of course, how these immunologically foreign cells are able to survive and proliferate in the mother and what consequences, if any, this may have for her own immune system.

The original discovery in maternal blood of cyncytial trophoblasts derived from fetal placenta was recorded in 1959 (Lewis Thomas *et al*. Trans Assoc Am Phys, Vol. 72). At that time, identification of these giant multinucleated cells was possible only by morphological means. But in the last decade, much more refined technology has become available for cell identification and isolation, such as polymerase chain reaction and fluorescence-activated cell sorters. With these new methods, forty middle-aged women were studied, all of whom had given birth to at least one son over the past three decades. The DNA of the Y chromosome was used for identification of male fetal cells in the mother's blood. Quantitative results were expressed in terms of the number of male fetal-cell DNA equivalents identified in a

specified sample of maternal blood (Nelson *et al*. The Lancet, Vol. 351, 1998). In the blood of healthy women aged 35.61, the range of male cell DNA equivalents was found to be very low (range 0.2, mean 0.38). But surprisingly, in women with established systemic sclerosis, a presumably autoimmune disease, the values were 30 times higher (range 0.61, mean 11.1, *P value* = 0.0007). In a comparable albeit less carefully controlled study of a larger group of women suffering from systemic sclerosis, male DNA sequences were identified in maternal blood in 46 percent, but only in 4 percent of healthy controls (Artlett *et al*. N Engl J Med, Vol. 338, 1998). These striking findings demonstrate not only a much higher incidence of fetal microchimerism in women with systemic sclerosis, but also a much more elevated level of fetal-cell DNA equivalents in the patients as compared to healthy controls.

To interpret these startling novel observations, Nelson in 1996 proposed the bold but attractive hypothesis that many chronic diseases of supposedly autoimmune nature in fact may be the result of allogeneic fetal cells which during pregnancy had gained access to the maternal blood and subsequently had engrafted and are surviving in the mother for decades (Arthritis Rheum, Vol. 39, 1996). This almost heretic hypothesis is bolstered by a number of supporting observations, such as the following:

① Many diseases of supposedly autoimmune etiology have a strong female predilection, particularly those affecting the liver, such as autoimmune hepatitis, primary sclerosing cholangitis, systemic sclerosis and primary biliary cirrhosis; the last has a female-to-male ratio of almost 10:1.

② All of these presumably autoimmune diseases exhibit morphological, immunological and chemical features characteristic of graft-versus-host disease which is a chimeric condition observed in recipients of allogeneic stem cell or bone marrow transplantations.

③ Moreover, in most of these supposedly autoimmune diseases and in graft versus host disease, intrahepatic bile ducts are a principal target of the pathological process. Furthermore, all of the above diseases tend to be associated with accessory "aut oimmune" phenomena, such a Sj-gren's syndrome, systemic sclerosis, the CREST syndrome, thyroid dysfunction and others.

Although these diverse clinical observations persuasively imply a common pathogenic mechanism for this group of diseases, by themselves they of course do not prove this novel hypothesis. But I believe that in the coming century, this issue will receive great attention and will emerge as one of immunology's leading scientific problems. And when all the scientific information is in, I would not be surprised if Nelson's hypothesis would turn out to be correct.

The three novel scientific contributions which I have discussed above are examples of work that has passed through most of its experimental phase and whose exci ting potential for clinical application is quite obvious. It seems just a matter of time until it will be ready for testing in humans. But we should realize that there still are countless obscure diseases for whose full exploration we currently lack the required intellectual basis and experimental tools. It is in these areas that I expect molecular and cell biology, virology and genetics of the future to provide the necessary conceptual framework and methodology to make progress and achieve scientific breakthroughs.

One of these areas is the vast field of viral hepatitis, particularly of the types B and C which world-wide are causing immense morbidity and mortality. Despite recent remarkable advances, we still do not understand how these viruses are surviving indefinitely and how they are causing chronic liver injury nor do we have effective, reliable and safe therapies to arrest their progression, let alone to achieve permanent cure. Some of us are old enough to recall the complete failure of steroid treatment of chronic active hepatitis B which only a few decades ago had been flaunted as the ultimate therapy for this chronic liver disease. Against this background, the current hyperbole about interferon treatment of chronic viral hepatitis appears somewhat uncritical, if not misleading. I hope and actually anticipate that early in the next century, new scientific information and technology will become available which will allow development of a definitive therapy for chronic viral hepatitis which causes no more than minor side effects to the patient and whose costs are affordable.

MOLECULAR DIAGNOSTICS

And finally, the rapid evolution of molecular biology has created a new discipli ne, molecular diagnostics, which is offering an ever-increasing number of tests of previously unthinkable variety, sophistication and sensitivity. For example, molecular techniques already are used to quantitate viral loads in viral hepatitis. But one of molecular diagnostics' most promising applications will be in the search for new infectious agents which to date have escaped detection by available staining or immunological methods. As you are aware, several gastrointestinal diseases, previously of unknown etiology, have recently been found to be caused by newly discovered microorganisms. These include, of course, peptic ulcer, but also Whipple's disease, bacillary angiomatosis and most recently, nanobacteria which cause connective tissue calcification in systemic sclerosis, sclerosing cholangitis and the CREST syndrome associated with primary biliary cirrhosis (Kajander, *et al*.

Proc Natl Acad Sci USA, July 1998). But there are several other gastrointestinal diseases of unknown etiology whose clinical and pathological features seem consistent with, if not suggestive of, an infective origin. These certainly include Crohn's disease, ulcerative colitis, granulomatous hepatitis and sarcoidosis and perhaps primary biliary cirrhosis and sclerosing cholangitis. Many experts of course have postulated an immunologic origin of these diseases and a recent report, that an antibody to tumor necrosis factor α is profoundly down-regulating inflammation in Crohn's ileocolitis is supporting, but of course not proving, this hypothesis. (Baert *et al*. Gastroenterology, January 1999). Now, that highly sensitive molecular RNA and DNA probes and PCR have become available, I am confident that the hunt for elusive microorganisms will be intensified. And I would not be surprised if one or more of these diseases eventually would be discovered to have an infectious etiology.

DIAGNOSTIC AND THERAPEUTIC INSTRUMENTS AND MECHINERY

Predicting the future of Gastroenterology and Hepatology would be incomplete wit hout briefly considering what new diagnostic and therapeutic instruments and machinery may become available in the next century. Here, progress, driven by intense market competition, is so rapid that precise predictions are quite impossible. Nonetheless, some trends seem to become detectable. Radiology is likely to progress by leaps and bounds, particularly spiral computerized tomography and three-dimensional imaging. They increasingly will replace invasive diagnostic procedures, including fiberoptic endoscopy. The only exception may be fiberoptic, laser-induced fluorescence spectroscopy which uses either tissue-intrinsic or extre neously-elicited fluorescence; this is a novel procedure which appears to greatly enhance diagnostic accuracy. On the other hand, Magnetic Resonance Imaging, with its very expensive equipment, appears to be taking a back seat. And in gastrointestinal surgery, an ever-increasing proportion of invasive procedures will be performed by laparoscopy, which often makes hospitalization unnecessary and ther eby reduces costs.

ECONOMICS OF HEALTH CARE

And this brings me to a true megafactor which in a major way will shape and restrain the practice of Gastroenterology in the next century. This is the economics of health care. All over the world, per capita costs of medical care are rising steeply, far outpacing the rate of inflation. To a considerable extent, this is due to the accelerated appearance on the market of new or advanced but always more expensive machines, procedures and drugs which seem necessary to keep up with contemporary medicine. In the US, this continuing price increase has driven health care costs to a level, equaling 15% of gross domestic product (GDP), and other developed countries are not far behind. Although in the developing world, health care costs generally are lower, the cost increase in proportion is at least similar. It seems evident that if this trend should continue, health care eventually will consume a major part of the GDP. But I am afraid that as long as medical care continues to be unregulated or is remaining a competitive market commodity, it will be very difficult, if not impossible to bring quality of medical care and its costs into some sort of reasonable balance. Consider, for example, who would be qualified and publicly acceptable as decision makers. Would it fall to third party payers, that is insurance companies or health maintenance organizations. Or to employers who are funding the costs of health care Or to the medical care establishment, that is to physicians and hospitals Or perhaps to the government. However this paramount issue will be resolved, it will have an enormous impact on the future practice of Gastroenterology and Hepatology, both in the developed and in the developing world. As developing countries are striving to catch up with modern Western medicine, they rapidly are coming on mainstream, offering an almost unlimited market for aggressive pharmaceutical and medical equipment industries. This of course is further destabilizing the rapidly rising costs of adequate medical care.

CONCLUSION

In concluding, I believe that this brief glimpse into the science and practice of Gastroenterology and Hepatology in the next century is offering us a mixed perspective, one of an ever-widening disparity between rising opportunities on the one hand, and strained resources on the other. I am afraid that unless this serious imbalance will be dealt with early in the next century, the practice of Gastroenterology and the quality of health care world-wide will suffer. We need to learn how to reduce expenses by voluntarily lowering our dopendence on technical procedures and complex equipment, and by avoiding use of expensive but only marginally effective medications and surgical interventions. And last but not least, in hopelessly ill patients, we should have the courage to abstain from using every possible means at our disposal to prolong dying and suffering, as unreasonable terminal care is one of modern health system's most expensive components. These, I am afraid, will be painful adjustments for the medical establishment but they must be faced better sooner than later.

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