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OBESITY – ARE PHARMACEUTICALS THE ANSWER?

Since obesity became a recognized health problem, the dream has been for a pill that produces weight loss. Drugs to fight obesity have been in the news recently and prime time ads are featuring the latest iteration with the name Wegovy. This drug is called semaglutide and Wegovy applies to a particular injection dose just being introduced. Incidentally, another weekly injection version of semaglutide is already in use (Ozempic) but with a lower dose. This is one of the new drugs principally used by diabetics to manage diabetes. However, Wegovy is intended for non-diabetics to be used specifically to assist the obese in achieving a large weight loss. Semaglutide, a hormone mimic, belongs to the class of drug termed *Glucagon-Like Peptide–1 Receptor Agonists* or GLP-1 RAs or just GLP-1 drugs. An agonist is a substance that binds to a receptor inside a cell or on its surface and causes the same action as the substance that normally binds to the receptor.

This class of diabetes drug has become popular because it is effective in lowering HbA1c and reduces the risk of heart disease including heart failure and stroke, as well as kidney disease. These benefits were accidentally discovered because of government regulations that required new diabetic drugs to be tested for adverse cardiovascular effects. The opposite was found and in addition, associated weight loss.

A BIT OF HISTORY

The idea of using a pharmaceutical to help with weight loss goes back to the 1990s and the first drugs or class of drugs were all approved and then withdrawn due to unacceptable side effects. The most famous were Fen-Phen and Redux. Included were drugs that worked by fiddling with the brain function such as acting on norepinephrine or serotonin. Currently there are only four drugs aside from the GLP-1 class which are still used*.[1]*

The GLP-1 medications mimic the action of the hormone GLP-1. When blood sugar levels start to rise after eating, these drugs stimulate the body to secrete more insulin. It is not exactly clear how the GLP-1 drugs result in weight loss. However, GLP-1s are thought to help suppress appetite. These drugs also slow the movement of food from the stomach into the small intestine with the result that the person feels full faster and longer and thus eats less. They also suppress pancreatic glucagon release*.[2]*

Side effects include nausea, vomiting, diarrhea, headache, weakness, or dizziness. Some side effects are warning signs of serious conditions. For example, nausea and vomiting with abdominal pain could indicate pancreatitis (inflammation of the pancreas). Side effects have not been a significant reason for termination of treatment.

EVIDENCE GLP-1 THERAPY WORKS

There are two key randomized controlled trials addressing the efficacy and safety of semaglutide for inducing weight loss.*[3,4]* One examined the dose dependence of daily injections for doses up to 0.4 mg/day. The other used a 2.4 g per week dose, i.e., the drug Wegovy. Both found large, significant weight loss and minimal side effects.

The protocol for the Wegovy trial included for the first 8 weeks a low-calorie diet (1000-1200 calories per day) provided as meal replacements. Participants then transitioned to a slightly higher calorie diet of 1200-1800 calories per day. During the trial an intensive behavioral therapy was used involving 30 counseling visits over the trial duration of 68 weeks. Escalating physical activity was started at randomization.

The results of the clinical trial of the weekly 2.4 mg injected dose of semaglutide were as follows (when not otherwise indicated, mean values*):[4]* body weight decrease was 16%; proportion of subjects with body weight decrease greater than 15% was 39%; BMI decrease 6.6 units; waist circumference decrease 16 cm (7 in); HbA1c decrease 0.6% points; systolic blood pressure decrease 6.2 mm Hg; triglycerides decreased by 25% and C-reactive protein by 63%. This last change represents a large decrease in inflammation and the large change in triglycerides has positive heart health implications.

This trial also compared semaglutide with another GLP-1 drug, liraglutide and demonstrated semaglutide considerably superior in terms of the endpoints of the trial. Liraglutide is also used as a weight loss drug although developed for management of diabetes.

Note that for BMIs of 40, 35 and 30 a 16% weight reduction takes them down to 34, 29 and 25. These changes approximately result in obesity reclassification. When defined by BMI, overweight is 25 to 29.9, obese 30-39.9 and morbidly obese 40 or greater. Furthermore, while the participants were free of type 2 diabetes, some were prediabetic judged by the range of HbA1c. The drug treatment took most back into the normal range with a large change in this metric.

Note also that the tested weight loss protocol used not only the drug but also 150 minutes of exercise per week and a diet with a deficit of about 500 calories. The diet was 30% from fat, 20% from protein and 50% from carbohydrates.

Bariatric surgery generally produces a much larger weight loss than 15% but is normally restricted to those with morbid obesity (BMI over 40). The prevalence of morbid obesity in US adults is about 10%. For all obesity it is about 40% and has increased by 26% since 2008.

WEIGHT LOSS THAT CAN'T BE MAINTAINED SEEMS POINTLESS

Some readers probably wonder why this weight loss, while impressive, has any meaning since the natural history of weight loss interventions is that the weight lost is with high probability regained even if efforts are made to prevent this. Thus, a strategy is needed to fight the natural compensatory changes in levels of weight regulating hormones such as leptin and ghrelin that invariably occur when there is a significant weight loss. It is common for patients with obesity who experience weight loss with drugs such as GLP-1 to regain weight when the treatment is finished.*[5]* One of the common features of weight loss protocols is that the weight rapidly declines and then levels off in a plateau, which is generally regarded as due to metabolic adaptation.

However, the consensus appears to be that for many individuals, maintaining the weight loss will realistically require medications, perhaps even continuing with GLP-1 drugs. In fact, clinical evidence supports the notion of using GLP-1 therapy for maintenance.*[5]* Based on the failure of diet and lifestyle to maintain weight loss for many, this view is probably realistic.

An approach to successful weight loss maintenance has been developed.[6] The protocol involved 20 obese non-diabetic individuals who underwent an 8-week weight loss program on 800 calories supplied by prepared meals. This resulted in a 13% mean weight loss. The maintenance program involved calorie restriction based on an estimated daily energy requirement including that needed for physical activity minus 600 calories to yield a mean 1400-calorie intake. Weight gain was combated by additional calorie restriction and counselling. Biomarkers were measured before and after the weight loss diet and during the maintenance phase. During the maintenance phase, biomarkers associated with appetite inhibition retained increases gained in the weight loss diet. The decrease in appetite stimulating mechanisms which occurred during the weight loss phase continued to contribute to successful long-term weight loss maintenance. Thus, physiological changes during weight loss important to success were sufficiently preserved by the protocol to enable successful weight loss maintenance.*[6]*

Finally, a study is ongoing that addresses the question of whether once weekly semaglutide 2.4 mg injections will reduce the risk of cardiovascular events in patients overweight or obese with prior cardiovascular disease (secondary prevention),

LATE DEVELOPMENTS

A perspective article in the June 23 issue of *The Journal of the American Medical Associ*ation carried the *title Semaglutide's Success Could Usher in a "New Dawn" for Obesity Treatment.* It was suggested that physicians should welcome this new approach to obesity since the **eat less and move more** advice no longer inspires confidence in many patients. In fact, it is an admission of not understanding the disease of obesity which is not adequately explained by character weakness or lack of willpower.*[7]*

In addition, a letter just published online in *Annals of Pharmacotherapy* describes a case history of the use of oral semaglutide to treat obesity.*[8]* The patient without

diabetes was a 35-year old male who at the time of starting treatment weighed 107 kg (to get pounds, multiply by 2.2) with a BMI of 31.4. He was given daily doses of increasing amount from 3 mg to 14 mg. The protocol included exercise, intermittent fasting and avoiding unhealthy snacking. There was no calorie restriction. After 84 days, he weighed 86.8 kg. Maintenance 7 mg daily semaglutide was started and after 25 days his weight was 84.1 kg for a 21% weight loss and a BMI of 24.8. Thus, the change was from moderate obesity to not overweight. Typical weight loss protocols do not achieve anything like this weight loss. A 21% weight loss takes a BMI of 37 to 29, i.e., from being close to morbid obesity to being simply overweight.

This study also indicates the potential for oral semaglutide for weight loss maintenance. Optimum frequency and dose would need to be determined.

The patient's copay was $20/month but not all insurance companies would cover the treatment in the absence of diabetes. The 30-day cost depends on the vendor but is around $800-900, independent of dose from 3 to 14 mg. Thus, the cost issue will depend on the frequency and duration of medicated maintenance. The cost of Wegovy, the 2.4 mg injectable has of this writing not been announced but it has been suggested that it will be around twice the oral dose per month.

CAUTIONS: GLP-1 drugs are not recommended for anyone with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia. In addition, they are not recommended for anyone who has had pancreatitis. While dangerous hypoglycemia is a documented side effect (10% prevalence)*[4],* medical supervision of the use of GLP-1 drugs for weight loss should minimize this risk.

CONCLUSION

The constant increase worldwide in the incidence of obesity and the associated impact on health and for many but not all, coupled with the history of diet and exercise as a failed solution, justifies the search for permanent weight loss methods that meet the requirements of being adequately effective in terms of weight loss and adherence and as well meet the requirements of weight loss maintenance in order that the protocol has real life meaning. We appear to be on the threshold of success, but the use of drugs will go against the views of many who deplore the notion of a pill for everything.

RADIOPHARMACEUTICALS
A NOVEL PROSTATE CANCER THERAPY CREATES ENTHUSIASM

A novel prostate cancer therapy has received mainstream news media coverage recently due to positive results. It is described as potentially ground-breaking, a therapy that specifically targets a protein on cancer cells. It has also been described as like sending a tactical nuclear warhead into cancer cells. The "warhead" is a molecule containing a radioactive atom which attaches to the prostate-specific membrane antigen. The warhead is an organic molecule to which is attached a radioactive element, in this case lutetium-177, which decays by electron emission (beta emission).

Most readers have probably never heard of Lutetium. It is an element in the rare earth family. The range in tissue of the high-energy electron is very short (670 micrometers) confining the damaging energy deposition (200-400 million electron volts) mostly in the cancer cell. Because the radioactive molecules collect mostly on the prostate cancer cells, there is minimum but not zero risk to other cells. The decay is finalized by gamma-ray (like X-ray) emission which allows detecting the location and concentration of the bound molecules. The final decay product is a stable (non-radioactive) isotope of Hafnium. Lu-177 has a half-life of 6.7 days. It is generally made by neutron bombardment of Lutetium in a nuclear reactor.*[9]* The half-life is long enough to allow shipment after bombardment to laboratories which introduce the isotope into a carrier molecule and distribute the product for therapeutic use. In Canada, the Bruce nuclear power station in Ontario is active in medical isotope production including Lu-177.

Novartis, the large pharmaceutical company, has now conducted both phase II and Phase III trials of this "drug*",[10]* and the phase III trial (VISION), while still ongoing, has just reported at the annual meeting of the American Society of Clinical Oncology.

Participants were restricted to those previously treated with chemotherapy and hormone therapy and neither was effective. They had progressive metastatic castration-resistant (resistant to androgen suppression therapy) prostate cancer, i.e., patients with poor prognosis. Furthermore, the cancer is now not localized, and therapy involves seeking out and killing cancer cells that are potentially in several sites. The trials compare the Lu-177 therapy with standard therapy as a control. The drug was delivered by IV every 6 weeks for up to 6 cycles. The mean overall survival was found to be 15.3 months vs. 11.3 months for the standard of care. However, there is a wide range of overall survival with some having no recurrence over more than a year. The mean recurrent progression free survival benefit was 8.7 months vs. 3.4 months for the control. There were no serious side effects or treatment-related deaths, but anemia was more prevalent in the Lu-177 group than in the standard of care group, suggesting radiation damage outside of the cancer cells was perhaps present. The treatment cost in Europe where the treatment is available is about US $10,000 for the full treatment.
https://www.urologytimes.com/view/177lu-psma-617-significantly-improves-survival-in-mcrpc

Thus, in spite of the enthusiasm and "big breakthrough" description, this novel treatment is not for most a cure. The researchers suggest that the synthetic molecule may not be able to reach enough cancers cells to be completely effective. This therapeutic approach has also been successfully used to treat pancreatic cancer.*[11]* If the site concentration problem can be solved, this could be a very effective treatment.

There is another similar agent called Xofigo, a dichloride salt of radium 223, which decays by alpha particle emission (helium nuclei). This high-energy particle is very efficient in damaging cells. Xofigo binds with minerals in bone to deliver radiation directly to bone tumors. It has been administered to patients also having castration-resistant metastatic prostate cancer and achieved increased overall survival of 15

months vs. 11 for the placebo.*[12]* Its first use for metastatic prostate cancer was reported in 2013. The use of radium for cancer therapy goes all the way back to Marie and Pierre Currie in Paris. This was in about 1910. At that time, the risks of radiation exposure were not recognized, and Madam Curie died of radiation-induced cancer in 1934. She was the recipient of two Noble prizes, one in physics and one in chemistry. While the first women to become a professor at the University of Paris, she was never invited to join the French Academy of Science which accepted its first female member in 1962, ironically a student of Marie Curie.

Related to the use of molecules carrying radioactive isotopes to provide *in situ* radiotherapy is brachytherapy. However, this approach requires that the cancer be localized in the prostate and that no metastasis is evident or suspected. It involves placing radioactive pellets or removable radioactive rods in the prostate. Brachytherapy is also an alternative to external beam radiation therapy. Neither are alternatives to the use of radiopharmaceuticals which are appropriate for metastatic cancer and designed for a seek-and-destroy mission. It is like conventional chemotherapy and immunotherapy. i.e., a systemic approach required by disseminated cancer. Thus, it is not surprising that the results, while perhaps superior to other systemic therapy, also do not yet yield a permanent remission. To call it “game changing” as some have is perhaps an exaggeration.

The targeting philosophy for using a molecule that binds specifically to the prostate specific membrane antigen is similar to that associated with the utility of Salvestrols which only interact with the P450 CYP1B1 enzyme expressed as the protein in the cancer cell cytoplasm. For the radiopharmaceuticals, the cancer cell is destroyed by the radiation. For Salvestrols the enzyme acts on polyphenols taken orally which end up in the cancer cell cytoplasm and are converted into anticancer drugs. Both approaches leave normal cells alone and thus there is no or little toxicity. Case histories of successful treatment to achieve permanent remission of prostate cancer with Salvestrols have been described, one with a Gleason score of 6.*[13]*

THE NEWCASTLE DIET
IMPROVEMENT IN HEART HEALTH WITH DIET INDUCED REMISSION OF TYPE 2 DIABETES

A just published study from Dr. Roy Taylor’s group at Newcastle University addresses the issue of the cardiometabolic benefits of the Newcastle diet.*[14]* The study is based on data from the randomized controlled (DiRECT) study using the Newcastle short-term rapid weight loss intervention.*[15]* It was designed to answer the obvious question, does the weight loss induced remission of diabetes reduce the cardiovascular risks associated with the disease?

Cardio-metabolic parameters were used to determine changes. The QRISK-3 10-year absolute risk calculator was used to determine the effect of the diet on the risk of a heart attack or stroke. This study used the following QRISK factors: age, sex, ethnicity,

height, weight, systolic blood pressure, smoking status, diabetes status, HDL/total cholesterol ratio, and the use of anti-hypertension medication. This calculator was developed specifically for the UK population. The calculator also evaluates the theoretical heart age. The 10-year risk is for fatal or non-fatal heart attack or stroke.

This approach was used in the absence of a long-term (5-10-year) follow-up study with heart attack and stroke as the primary endpoints. The study had available data on responders and non-responders, the former achieving remission, duration of the disease post diagnosis, and biomarkers and other metrics at baseline, 2 months, and 6 months after the end of the intervention. The only significant limitation appears to be the necessary use of surrogate markers.

For responders, the baseline 10-year QRISK calculated risk of heart attack or stroke was 15.3%. It decreased to 5.2% at 2 months after the end of the diet and to 5.8% at 6 months after. These are absolute risks and thus the absolute risk reduction was 10.1% and 9.5% respectively. This was primary prevention. For comparison, statin treatment yields around 1% absolute risk reduction. See IHN June 2021 issue for a detailed discussion of reducing heart disease and stroke risk.

For the responders, the heart age based on the biomarkers used in the above QRISK calculation decreased from 67.8 years at baseline to 51.8 and 52.7 years at 2- and 6-months post intervention. In fact, these reductions resulted in the heart age approaching the actual age. This 16-year decrease of course has significant implications regarding longevity. For the non-responders (still had diabetes) the 10-year QRISK risk was unchanged.

An interesting question concerns the effect of rapid weight loss and coronary artery calcification, A study based on bariatric patient results found that after 6 years, those with successful weight loss had a significantly high probability of having lower calcium scores including zero.*[16]*

NEWCASTLE DIET EFFECT ON BLOOD PRESSURE

High blood pressure frequently accompanies type 2 diabetes and it thought to be partly responsible for the reduced life expectancy of people with this disease despite blood glucose management with “good control.” Over half of all people with type 2 diabetes require treatment for hypertension aimed at reducing vascular complications. In a study from Dr. Taylor’s group that also recently appeared, the issue of the impact of the Newcastle diet on blood pressure was examined.*[17]* This was also based on data collected during the DiRECT study.

At the beginning the DiRECT trial, participants with treated hypertension were taken off medication and a protocol was in place to determine if and when medication was needed to be reinstated. All subjects experienced a decrease in blood pressure associated with weight loss. Of the 143 hypertensive participants on the diet, at 12 months (end of diet) 21 remained off blood pressure medications and at 24 months it

was 19. At 20 months, all participants had experienced a decline of systolic blood pressure of about 10 mmHg.

It was concluded that replacing antihypertensive medications with the DiRECT diet to induce weight loss reduced blood pressure substantially and may increase mild dizziness. However, Taylor points out that it is initially safe to stop antihypertension medication, but blood pressure should be monitored regularly, particularly for those on two medications, as over two-thirds will require reintroduction of some medications.

SAGA OF THE NEW ALZHEIMER'S DRUG

The source of most of the information in this discussion is from a commentary by Drs. Joseph S. Ross, MD, professor of general medicine and public health and Reshma Ramachandran, MD a physician-fellow, both at Yale University School of Medicine.
https://www.cnn.com/2021/06/17/opinions/biogen-alzheimers-drug-opinion-ramachandra-ross/index.html

The issue is the approval by the US FDA on June 7 to give fast-track-breakthrough-therapy status for aducanumab (Aduhelm), a drug developed by the US firm Biogen. This was a big event since Alzheimer's patients have waited a long time for a drug. The history of this drug approval is remarkable.

Clinical trials for this drug were stopped in 2019. The studies were halted early because the developers considered it unlikely that they would meet the primary endpoint of clinically significant reversal of Alzheimer's disease.

One study showed no benefit for patients. The other study suggested there *may be* some benefit. The safety concerns found for the high dose approved by the FDA included brain swelling (35%) with recurrent episodes (10%), and multiple small brain bleeds (20%). In November 2020, the FDA Independent Advisory Committee by a vote of 10 to 11 took the position that the data did not offer convincing evidence that the drug was effective. After this vote the FDA changed the endpoint, something that the 2008 government mandated clinical study registry tried to prevent by having all trials state at the start what the endpoints were, and this could not be changed. The FDA decided to use as the new endpoint, MRI findings of beta amyloid plaque regression, not a clinical but a surrogate endpoint.

Beta amyloid cerebral plaque targeting has been the basis of much of the unsuccessful Alzheimer's research over a number of years (flogging a dead horse?). Ross and Ramachandran point out that a review in the journal *Nature* reported finding that in more than 24 studies this surrogate endpoint was not related to the clinical endpoint of reversing of Alzheimer's disease. Even the FDA had announced earlier that they were not recognizing beta amyloid changes as a surrogate for efficacy.

The granted approval requires the drug maker to conduct a new study to confirm clinical benefit. Biogen was allowed nine years to complete the study, suggesting that the FDA recognized no urgency in the efficacy issue.

The drug was only tested on patients with early disease, but the approval allows use of the drug at any stage of the disease. This is significant since a huge demand is expected for this "breakthrough therapy" Alzheimer's sufferers have been desperately waiting for. Furthermore, the company has priced the drug at $56,000 per year. Not included are costs of treatment and the imaging to detect serious side effects. The financial consequences for patients (copayment requirements), Medicare, Medicaid, taxpayers, and private insurance premiums could be immense. Will there be a threshold of clinical efficacy imposed which will limit reimbursement and coverage?

After FDA approval it was widely reported that three members of the Advisory Committee resigned in protest. The committee had voted against approval. It can be expected that there will be a storm of letters to the editors of major journals regarding this unprecedented saga, especially the dangerous precedent it creates.

Drs. Ross and Ramachandran suggest that physicians and hospitals should stand together and agree to provide this drug only in the context of a new trial designed with endpoints that are clinically meaningful. The American Geriatrics Society which represents physicians specializing in the care of older adults and develops guidelines for diseases such as Alzheimer's have already advocated against the drug's approval.

There are almost 6 million Alzheimer's sufferers in the US. If only 3 million went on the drug, this would cost $168 billion. This is about 6% of the annual estimated total health care costs in the US.

The media has focused on the approval and the resignations. Alzheimer's sufferers need to know the full story outlined above. If FDA approval in their minds translates to a safe and effective drug, an answer to their prayers, then a huge demand will no doubt occur. Will the information provided to patients in the context of informed consent include what is disclosed above? Physicians now have an ethical problem involving adequate informed consent.

LATE DEVELOPMENT: A study just appeared in *EClinicalMedicine (*published by *Lancet)* found that Alzheimer's symptoms depend on the depletion of normal soluble protein rather than the aggregates (plaques) and that relevant future therapeutic approaches will replenish these soluble proteins to their normal levels. The authors point out that their findings are consistent with the fact that by age 85, 60% of people have plaques but only 10% develop dementia.
https://www.sciencedaily.com/releases/2021/06/210628170605.htm

IN SEARCH OF INSIGHT
SUMMER 2021 RECOMMENDED READING

- ***THE PRICE WE PAY. WHAT BROKE AMERICAN HEALTH CARE AND HOW TO FIX IT.*** **2019.** Marty Makary. MD. This book is so important that it heads the list. Dr. Makary is a surgeon at Johns Hopkins University specializing in pancreatic problems. His area of research however is public health, especially in the US and in this area he has an international reputation. Unfortunately, the principal message is very simple. Money corrupts and the major problems of the US health care system involve the impact of income and profit maximization by shocking practices which harm patients both physically and financially. This book provides a definitive discussion of why the US is at the top among its peers in health care expenditures and at the bottom in health care success. Where the money goes will shock most readers.

- ***WHICH COUNTRY HAS THE WORLD'S BEST HEALTH CARE?*** **2020.** Ezekiel J. Emanuel. The author critically examines the health care systems of the US, Canada, the major European countries, and Australia, Taiwan and China. The resultant ranking reveals the best and the worst and the author attempts to generalize regarding the important features. The book is fascinating and will shock Americans when the US comes out looking very bad and given their health care system, it appears that achieving improvement is a challenging proposition. However, the author under-emphasizes the terrible systemic problems characterized by widespread gaming of the system as discussed in Marty Makary's book described above.

- ***YOUR MEDICAL MIND. HOW TO DECIDE WHAT IS RIGHT FOR YOU.*** **2012** Jerome Groopman, MD and Pamela Hartzband, MD. Two Harvard Medical School professors also on the staff of Beth Israel Deaconess Medical Center discuss the complex process of how humans make medical decisions. Based on fascinating stories about a number of patients that provide readers within insight.

- ***DIAGNOSIS. SOLVING THE MOST BAFFLING MEDICAL MYSTERIES.*** **2019.** Lisa Sanders, MD. The author is an internist on the medical faculty of Yale University and is known to many through her monthly column *Diagnosis* in the *New York Times Magazine.* This is a sequel to ***Every Patient Tells a Story****.* Both books contain about 50 true short stories of solved diagnostic problems that presented significant challenge. Sander's books are highly recommended.

- ***MALIGNANT. HOW BAD POLICY AND BAD EVIDENCE HARM PEOPLE WITH CANCER.*** **2020.** Vinayak Prasad, MD. MPH. The author is a practicing hematologist-oncologist and associate professor of medicine at the University of California San Francisco. He has also written ***Ending Medical Reversal: Improving Outcomes, Saving Lives****.* As of June 2021, he has published 114 papers indexed by PubMed. This book is a valuable handbook for navigating the minefields of cancer therapy.

- ***KEEP SHARP: BUILD A BETTER BRAIN AT ANY AGE.*** **2021.** Sanjay Gupta, MD. The author is a neurosurgeon on the faculty of Emory University Medical School. He is also well known as CNN chief medical correspondent. His experience, background, and knowledge of the worldwide state of brain research makes him eminently qualified to addresses an issue that should be top priority—maintaining brain function during ageing. He provides a handbook for orchestrating this endeavor.

- ***MALPRACTICE*** **2017.** Lawrence Schlachter, MD**.** The author is a neurosurgeon and lawyer and acts as a plaintiff's attorney in malpractice litigation. Some will find this book informative and interesting. Others will simply be frightened or worse. The problem is that the complexity of diagnosis and treatment is great and the risk of medical errors both serious and fatal far from insignificant. This book provides comprehensive information regarding the risks of entering this jungle, generally in the hospital setting. Protective personal actions based on knowledge or in addition having an advocate standing by may be inadequate. However, a strong case can be made for the advocate(s) who can compensate for inadequate staffing or supervision and pick up on actions which simply do not make sense. This is the traditional function of the special nurse. The book is more a tour guide than a practical guide for actively avoiding disaster.

- ***THE GENOME ODYSSEY.*** **2021**. Euan A. Ashley, MD, PhD. The author is a professor of medicine and genetics at Stanford University. This book provides an excellent summary of the progress and impact of the genome revolution on disease diagnosis and treatment. Of particular interest is the author's description of and role in the development of the *Undiagnosed Disease Network* which now includes a number of clinics with staffs of top specialists and access to a vast number of experts worldwide as well as small, specialized companies willing to offer their technology to help diagnose cases which have resisted attempts, frequently relying on genome analysis, or supplying a unique therapeutic agent. Fascinating case histories illustrate how sorting out the genetic issues frequently leads to the ideal and in fact only therapy, even in some cases a cheap supplement. The discussion of the development of more and more rapid and comprehensive sequencing and the rapidly expanding worldwide genome plus health record databases suggests that indeed we are on the threshold of a new and remarkable era in medical practice.

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