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It is common to read in the medical news about some study suggesting a novel approach, for example to cancer or atherosclerosis. The research reported often describes important observations that suggest a powerful therapeutic or preventive approach. One recent example involves the inhibition of a certain biochemical activity in a number of processes in the body including atherosclerosis. It is called Galectin-3 and the research suggested that inhibiting it could have a very significant effect on the progression of atherosclerosis and heart failure.

There was some discussion of a natural product, modified citrus pectin (MCP), which appeared to be an effective inhibitor and could have a major impact on atherosclerosis including reversing it. However, if MCP was to be recommended by suppliers to patients as a potentially important supplement with the above benefits described, it would violate the regulations requiring a number of expensive studies to verify the efficacy and safety. High-quality MCP, the brand used in studies, is actually available by the pound from Amazon. It is rather expensive. There is little guidance concerning dose and certainly no 5-year randomized controlled studies that would quantify absolute benefit. No studies that used CT scans to follow the plaque burden were done. There is research reported concerning patentable inhibitors but regulatory approval would take at least 4-6 years and a lot of money. It looks like inhibiting Galectin-3 is not likely to go anywhere, at least not with a natural product. Business considerations win, the patient potentially loses.

Aged garlic extract seems to be the only exception where professionals are able to suggest it with lots of data and significant studies that support its beneficial action in slowing progression or reversing coronary plaque. Combined with coenzyme Q-10 it is even more effective. Many readers of IHN are aware of this. It seems safe to say that very few doctors even know about it much less recommend it. However, coronary atherosclerosis is a big deal and stopping progression or reversing it is significant.

While on the subject of MCP, some readers may be aware that there is interest in its cancer preventive and therapeutic possibilities. It is a natural product that is then modified by heat and pH to get the active form. Put the full name of MCP linked to cancer in the title and require listing only publications that were clinical studies in PubMed, the universally used search

engine for the medical literature. With no date limit you will get one study concerning it use in treating recurrent prostate cancer with recurrence after standard interventions. It was published in 2003. Drop the clinical trial filter and you will get 12 studies—suggestive of merit, but done with cell cultures or rodents. The results of the one clinical trial were quite impressive. Then silence on the research frontier for clinical studies. Why has no one picked this up and run with it. Because MCP is a natural product which is not a patent medicine, it is ignored by mainstream medicine, and there is no financial incentive.

As most readers of IHN know, Salvestrols for the treatment and prevention of cancer have the same problem. It is a mixture of four natural products (polyphenols). The biological plausibility of benefit is compelling; there are a number of studies supporting the mechanism of action, supporting literature going back several decades, and a number of case histories. Salvestrols are being use by doctors in a number of countries, mostly outside North America, with excellent reported results. However, the only allowed claim is that it is a dietary supplement. However, of course the cancer connection is anecdotal evidence and case histories are ignored by anyone dedicated to remaining faithful to evidence based medicine like it was a religion. The millions saved by penicillin can be thankful that when it was discovered, years of phase I through phase III trials were not even thought of then. It was obvious to even a child that it worked.

Wishing you and your family good health,

William R. Ware, PhD, Editor

Welcome to our 300th issue! Our beginnings go back to January 1992 when the very first issue of IHN was published. In this inaugural issue we reported, among other news, that ubiquinone (coenzyme Q10) helps prevent heart disease [*New England Journal of Medicine, September 12, 1991*].

Then in November 1994 *International Health News* became the first newsletter published on the Internet that focused on natural health and alternative medicine.

Bill Ware and I are proud to continue the IHN tradition of providing you, the reader, with current, factual, and verified information that can make a real difference to your life.

Yours in health,
Hans R. Larsen, MSc ChE, Publisher

Highlights

GENERIC DRUGS. HIDDEN DANGERS AND A HOPELESS PROBLEM

When a drug patent expires, as they all must at some point, any company is free to copy the drug and market it as generic. The price is almost always dramatically lower than the brand name drug. The two classes of the same drug are differentiated by a brand name and another name, the latter becoming more and more difficult to pronounce as new drugs are approved. For example, Crestor, the lipid-lowering drug is the brand name, and rosuvastatin calcium, the generic name. Names like Coumadin, Imitrex, Lipitor, and Prozac and even Advil are all brand names, and are generally manufactured and marketed by the companies that developed them. However, even companies making brand name drugs are now starting to purchase the active ingredient from other companies, mostly located in Asia (especially India and China), in order to reduce costs. According to a Canadian Medical Association Journal blog by Dr. Iris Gorfinkel (March 27, 2019), currently 80% of the world's pharmaceutical active ingredients are made in China, but this must include those intended for generic drugs.

The growing popularity of generic drugs which are mostly manufactured in China and India raises obvious questions concerning actual potency, proper formulation especially for slow release drugs, chemical and other impurities, stability, and shelf-life. This is the subject of a recently published book titled *Bottle of Lies* by a well-known American investigative journalist Katherine Eban.[1] It is a 460-page exposé of generic drug manufacturing in Asia, mostly India. It is shocking, alarming, and highly disturbing. The basis is hundreds of interviews with regulators, especially the US Federal Drug Administration (FDA), employees, whistle blowers, lawyers, prosecutors, prominent physicians reporting shocking life threatening adverse effects immediately after patients switch to a generic drug, court documents and documents made available by whistle blowers and concerned ex-employees. The focus is on generic drugs that are imported from Asia and marketed in the US. The book provides a unique insight into the functioning of the regulators charged with protecting US citizens from dangerous products and the profound challenges they face dealing with companies based in distant countries but having dozens of manufacturing facilities, different languages, cultures and ethics. Major US newspapers and news magazines covered the exposé. It is surprising, considering the importance of the related public health issues, that the medical literature is essentially silent. However, the research required, I.e. complex investigations such as are required in this context, is foreign to medicine and most medical researchers.

***The regulator's problems*.** The manufacturers of patent drugs made in the US or elsewhere, destined for the US market, are periodically subjected to plant inspections by FDA personnel. Eban provides lengthy discussions of the corruption of this process,

outside the US. Since the results of these inspections can result in a temporary ban on exporting to the US, it is an important event. When done in the US, surprise inspections are the rule. However, when the FDA wanted to do the same in India where most of the generic drugs were made, the FDA yielded to pressure from the foreign affairs department to provide several days if not weeks advance notice, since otherwise relations between the two countries were deemed at risk. It turned out that this offered the companies a unique opportunity if they were so disposed, to hide data and equipment not linked to the monitoring servers, delete computer records, clean dirty facilities and then orchestrate the inspection. Some companies even went so far as to build a factory which was used only to show inspectors.

In spite of this, the largest company in India was repeatedly caught with fraudulent activities and unsafe manufacturing practices which evolved over a number of years into federal charges of fraud, the blocking of imports to the US, and the refusal to approve a critical new drug, generic Lipitor. This was a significant achievement considering the incomplete picture the FDA was able to obtain. One of the heroes of the story was a whistle blower who subsequently suffered financial and marriage problems, and constantly worried about the safety of his family. However, when the company settled with a guilty plea and huge fine, he was well compensated and all his legal bills covered, although his marriage did not survive. Incidentally, the company actually then received clearance to market their generic Lipitor. The results of this court case confirm the dreadful picture the author paints throughout the book of fraudulent, dishonest, and deceptive practices in a number of companies whose drugs were on US pharmacy shelves and used in hospitals, a picture which will appear to most readers as frightening if not unbelievable.

The Cleveland Clinic experience*.* Eban devotes an entire chapter to the experiences of Dr. Harry Lever, a Cleveland Clinic cardiologist who specialized in treating hypertrophic cardiomyopathy (HCM). Lever depended on a variety of medications such as beta blockers, calcium channel blockers, and diuretics. After hearing about the pathetic record the government has had in keeping bad, dangerous or even counterfeit food out of the country, he began to wonder about generic drugs. It was not long before he encountered several cases which all had one thing in common, patients had just switched to different generic drug. The onset of adverse symptoms or the failure of the medication he had been regularly prescribing seemed striking. A bit of research indicated that the generic drugs came from one of a small number of firms manufacturing in India, one of which was the firm mentioned above that was successfully prosecuted for federal fraud. However, this was after joining the dots. The switch to a different generic eliminated the new problem. The book provides 5 case histories. In addition, a physician in the clinic heart transplant section found problems with a generic antirejection drug that was resolved simply by changing drug manufacturer. He started demanding that his patients take only brand name antirejection drugs.

These examples were just canaries in the mine or tips of icebergs. These were only the experiences of two clinicians, but highly reliable sources. Surely similar problems were

popping up all over the US, uncounted with even the significance not comprehended. The conventional wisdom simply indicated that the approved generics were bio-identical and met strict safety, released design, and contamination standards.

Another example*.* When drugs are developed, their metabolism is of course studied and in some cases there is great merit in having a slow-release version. To get this right so that the generic is identical to the brand name drug can be tricky. Failure can lead to disaster. The book describes a problem with a slow release antidepressant. The generic manufacturer got it really wrong and the slow release was actually a rapid release version. In fact, it delivered a strong overdose. Patients went wild, wanted to climb walls and most importantly, were flooded with suicidal thoughts. It took some time before someone tested the release rate and discovered the problem. Note this is why one should never cut an extended release tablet to obtain half the dose.

China**.** China is becoming very important in the manufacture of generics and especially active ingredients. Eban tells us that there are 400 factories, many hundreds of miles apart. Some are joint ventures with large US or international pharmaceutical giants. There is also a huge language barrier for anyone examining quality control data. Combine just these factors and it appears that informative inspections are generally hopeless. There is already a history of adulterated heparin generics.

In 2015 the FDA had one inspector in residence, Peter Baker, but he was probably the best in the business. He had only a rudimentary knowledge of Mandarin learned in college but it was enough. While the FDA had been carrying out inspections, the prevalent view was that the US inspectors were easy to fool. He started by inspecting 35 plants. He found numerous violations. The list looks like the one presented above summarizing the problems in India, including “show plants.” Fraud was endemic. Earlier inspectors were apparently not up to date regarding computer technology, did not know the language, and were not provided with translators. Baker’s reports were met with concerns at the FDA which appeared to regard some companies as “too big to fail.” Cracking down severely would not only impact drug supplies, but cut approvals which would potentially decrease the FDA’s income. When Baker’s reports caused import restrictions for one large company, shortages quickly developed, and some restrictions were lifted. Baker’s view that these drugs were not good enough was ignored. A very soft, lenient approach was taken by the regulators. Baker left China in 2018 to relocate to Chile, but resigned a year later.

The valsartan saga. In the epilogue of Eban’s book, she discusses the well-publicized discovery and subsequent recalls of this drug used to control hypertension. The brand name is Diovan, the generic valsartan hydrochloride. In 2018 a carcinogenic impurity known as NDMA was discovered by regulators in Europe. The generic had been made with materials from by a Chinese company, the world’s largest manufacturer of valsartan active ingredients. The presence of the impurity may go back to 2012 when the company altered the production process to increase yields to maximize profits. The change was given an OK by the FDA. In May 2017, a FDA inspector found the company was failing to investigate potential impurities in its own drugs and designated it “Official

Action Indicated" (OAI) which has serious consequences, but the agency subsequently downgraded this to "Voluntary Action Indicated", a slap on the wrist compared to OAI. Thus it is possible that the carcinogen exposure had gone on for over 6 years before the first warning. The FDA in their internet website assures the public that the levels present no danger but set an upper limit for acceptability, 9.82 ppm (note the absurd three significant figures). However, it is beyond belief that human dose, age and gender dependent toxicity studies had been conducted. Who would volunteer? The FDA implies they are able to extrapolate the risk of exposure to 70 years! Later, a second carcinogenic impurity was identified. The latest FDA update (6/12/19) available on the interned lists three drugs in this class, valsartan, losartan and irbesartan and provides the recall history. Valsartan is widely used, judging by the number of companies selling it.

Conclusions. Most of the individuals close to these investigations will not take generic drugs unless it is critically necessary. Most of the general public and many physicians are not aware of the problem at all. The problem is especially important for those on polypharmacy which includes a vast number of the older or elderly. Many agencies and companies funding health care want only the cheaper genetics covered and the difference of cost if one is on the traditional 10 prescription drugs for life is very great indeed. No wonder we do not hear about huge forensic laboratories with expensive state of the art equipment springing up around the country to spot-check generics from every country when they enter the country or are randomly taken off the shelves for testing. The contaminated or improperly formulated generics will cause manifold strange and mysterious symptoms that almost no one will be able to figure out. The safety of brand name drugs has been impressive because of tight controls on everything. The reputation of the company is at risk. Failures and recalls are perhaps sensational, but somewhat rare. Now the stage is set for the opposite but the need for recalls and import bans unlikely to even be identified. The system appears overwhelmed and politicized.

According to information acquired by Katherine Eban, one of the sad facts appears to be that at some firms, generics are graded by the degree of potency or impurities, and the worst are sent to the poorest countries.

Read this fascinating book to get the full story and check out your prescriptions with the help of your pharmacist and the internet. However, you will probably never be able to determine where the active ingredient originated. The book allows one to make a list of the bad companies, but one must realize that many generics have ingredients sourced from a variety of sources and countries. There is no answer to where does a drug come from. Brand name drugs probably still have to pass rigorous testing by the final seller, especially if the active ingredients come from Asia.

Recently, the FDA dropped an experimental program in India where inspections were unannounced and went back to the old system of giving plenty of warning.

GLYPHOSATES FROM ROUNDUP AND RISK OF CHRONIC KIDNEY DISEASE

Glyphosate, the active ingredient in the herbicide Roundup, dominates the agricultural herbicide market. This is partly due to its being paired with crops that have a resistance to this chemical built in by genetically modification and will thus kill only weeds in the fields of resistant crops. Thus the result is genetically modified foods (GMO). In the US, corn and soy are the principal GMO crops. The obvious and critical question of human risk both associated with the herbicide and its presence and toxicity in foods is highly controversial.

Obviously human toxicological studies are impossible. No one, unless under extreme pressure (e.g. some prisoners), would agree to being subjects in such studies. Furthermore, such studies would not be politically welcome and results difficult to publish in even medium impact journals, yet thousands of tons of glyphosate are used yearly in agriculture and the amount grows annually worldwide. Monsanto developed the chemical and recently Bayer acquired Monsanto and thus the rights to produce and market it.

In the period between August 2018 and June 2019, successful lawsuits In California resulted in jury awards of over 2 billion US dollars. The claims involved the causal link between glyphosate and non-Hodgkin's lymphoma. Expert consensus based mostly on animal studies is that glyphosate is safe in the context of human exposure. However, the International Agency for Research on Cancer in 2015 labeled glyphosate as a "probable carcinogen" and California then agreed and required appropriate labeling. In 2019, Austria became the first European country to ban the herbicide for all uses. A large number of countries now have restrictions on specified uses. These actions have had little impact on use and produced much criticism as would be expected from such a financially successful chemical, in fact one that is promoted as increasing food supplies and helping satisfy he growing need for more food as he world population grows and more regions become less favorable for agriculture.

Glyphosate is found in foods, water, air, breastmilk, and in humans as judged by its presence in urine in many populations. The impossibility, immense cost, and complexity of realistic human toxicological studies prevent even the collection of data useful in interpreting such results. Rodent studies are easily dismissed no matter what the results. One is left with involuntary exposure and a recent study published in *Environmental Research and Public Health* addressing the possible association between glyphosate exposure and chronic kidney disease of unknown origin (CKDu) in Sri Lanka is thus of considerable interest.[2] One of the authors, Dr. Sarath Gunatilake from California State University Long Beach published a paper in 2014 discussing proposed toxins as the explanation for the epidemic of CKDu in Sri Lanka.[3] The author received the 2019 Scientific Freedom and Responsibility Award from the American Association for the Advancement of Science. Another author, Stephanie Seneff from Massachusetts Institute of Technology, has lead the toxicology-based campaign to show that glyphosate indeed appears significantly dangerous to human health based on

a number of studies, a campaign which the supporters of glyphosate and GMO foods actively combat by any means at their disposal.

Chronic kidney disease of otherwise unknown origin (CKDu) is generally silent during the initial stages and when it becomes symptomatic the unknown origin rules out many standard treatments based on dealing with the cause. Frequently there is no cure although measures are available to manage symptoms, reduce complications and slow progression. End stage disease appears to have only two solutions, dialysis, more properly termed hemodialysis, or a kidney transplant. Dialysis significantly impairs the quality of life due to the time involved, and potential long travel times to a center. Dialysis may be associated with any of a large number of associated health problems for which the attending physician will be on the lookout. Transplants can involve a considerable wait for a suitable match. It is significant that toxicity studies have shown that the formulation of glyphosate contains additional substances which are considerably more acutely toxic than glyphosate. This complicates the interpretation of connecting Roundup with an active ingredient.

The study focused on Sri Lanka where 25% of the total imports consist of glyphosate. Starting in the 1990s an epidemic of CKDu has been identified in this country and currently has a case doubling rate of 4 to 5 years and a prevalence of 15% - 23% in some districts. Similar epidemics have occurred in districts in Mexico, India, El Salvador Guatemala, Costa Rica, Honduras, and Egypt.[2] In El Salvador, it is the second leading cause of death at 30 percent over the ten-year period ending in 2017. The most important feature of CKDu is that common causes such as diabetes, hypertension, and glomerular nephritis (inflammation of tiny blood vessels in the kidney) are not implicated raising the question as to the causative factors. In the paper, the authors develop and justify the hypothesis that CKDu in Sri Lanka is a consequence of the synergistic toxicity of glyphosate and a number of different toxic agents including the herbicide parquet, excessive fluoride and phosphate exposure, heavy metals, surfactants pathogenic toxins and dehydration. We will concentrate on Glyphosate alone due to the complexity of the suggested synergism.

The occurrence of CKDu over the past 30 years has almost always been in agricultural communities which help identify likely factors. The case for glyphosate being a significant causative factor can be summarized as follows.

- Children in the regions where CKDu is endemic are also shown to have early kidney damage.
- Farmers, especially those using or spraying pesticides without protective gear, drinking well water at home or in the field, and having a family member with kidney dysfunction are prone to CKDu.
- Evidence is accumulating that drinking water in areas of heavy use of pesticides is responsible for part of the exposure due to run off into ground water and shallow wells subject to contamination. The risk extends to family members.
- Paddy irrigation also involves contaminated water going onto contaminated soil.

- A study found that among 200 members of agricultural settlements, showed that the vast majority of villagers viewed their kidney disease as coming from drinking water from dug wells which was confirmed by examining the evidence of early kidney damage in children. Examination of both abandoned and currently used wells showed elevated levels of glyphosate.
- A study found that in addition to high toxin levels in drinking water and in particular high levels of glyphosate, cadmium, arsenic and lead were also found in urine samples. These metals act synergistically with glyphosate in terms of toxicity. Fertilizer was found to be a source of these heavy metals.
- Pesticides also act synergistically with glyphosate and one study found that one third of vegetable samples were contaminated with pesticide residues but they did not test for glyphosate.
- One study found high levels well above safe drinking water levels of glyphosate in lakes in CKDu prevalent areas as well as in sediment samples from affected areas.
- Locally grown food is contaminated with glyphosates which also contributes to the population intake and body burden.
- Ingestion of heavy metals along with glyphosates has also been shown important due to the combination interfering with detoxification processes.

Finally, the authors display three graphs that show the very strong correlation between the death rate from end-stage kidney disease over the period starting around 1995 and continuing until 2010 and the amount of glyphosate applied to corn in soy and corn crops. The same strong correlation is shown for acute kidney failure and even urinary/bladder cancer incidence, and as well the authors point out that multiple chronic diseases are rising in incidence in the US over the past two decades in step with glyphosate use in core crops.

An obvious question is why is glyphosate so toxic? Central to their arguments involves glyphosate as a glycine analogue. The authors hypothesize, with considerable justifying evidence from the research literature, that the reason for its toxicity is that glyphosate mimics the simple amino acid glycine, having only the addition of a phosphate group. It interferes with enzymes that have glycine as a substrate and these include enzymes that catalyze critical protein synthesis. It has been shown that glyphosate can compete with glycine in interacting with receptors in the brain causing neurotoxicity. This ability to substitute for glycine in a number of important biochemical processes is proposed to explain part of the toxicity of this herbicide. The authors even cite early work by Monsanto concerning this. They also identify an enzyme and a critical associated pathway where glyphosate suppresses the action of a critical enzyme and this is believed to be the main mechanism for the toxicity to weeds. Some plants are naturally immune to the effects of glyphosate due to an engineered mutation which formed the basis for the GMO resistant crops. They present other examples to support this hypothesis and point out that serious diseases with a long latency can result through disruption of protein function of a diverse number of proteins.

The paper also explores the complex issue of the synergy between glyphosate and toxic elements such as heavy metals and as well the herbicide paraquat. In addition they describe how the herbicide can interfere with the natural detoxification processes that involve the family of P450 CYP enzymes. The details are beyond the scope of this review.

The authors conclude that the causality they have demonstrated indicates that the most important steps to take to reduce the burden of CKDu in Sri Lanka would be to stop the commercial sale of glyphosate and in addition, paraquat and end the black-market availability of these agricultural chemicals. Furthermore, research is sorely needed to discover viable alternatives that provide low cost weed control while minimizing the use of GMO toxin resistance.

The issue of human toxicity associated with synthetic chemicals is one that is loaded with conflict, especially between some academics and other skeptics of the safety of glyphosate and the powerful forces represented by Big Agriculture and Big Chemical which together can marshal vast amounts of money to devote to lobbying and other endeavors to control the research and the interpretation of the outcomes and the reaction of regulatory bodies. Guess who is likely to win.

Finally, the authors point out that agricultural methods and practices to increase crop productivity without putting agricultural ecosystems and human health at risk already exist. They include enhanced soil health, recycling of biomass, utilization of cover crops, and biodiversity. Many of these were common practices before agriculture became dominated by chemicals. Skeptics would no doubt point out that we have already gone too far down the wrong road and the forces against change are too powerful to combat.

An interesting footnote concerns Dr. Gunatilake, coauthor of the above cited 2014 paper. He was subject to death threats at work and 12 scientists who obtained industry-funded grants filed a research misconduct against him. Perspective on the commercial importance of glyphosate—since 1974 1.6 billion kg of this herbicide have been used in the US alone.

DEPRESCRIBING

This is obviously a somewhat infrequently used word. It just appeared in the title of a study concerning the risk of dementia through exposure to what are called anticholinergic drugs.[4] Cholinergic drugs inhibit, enhance, or mimic the action of acetylcholine, the principal transmitter of nerve impulses. Included are antihistamines, antidepressants, antiepileptic drugs, antipsychotic drugs, those that treat overactive bladder, muscle relaxants, and gastrointestinal antispasmodics. Deprescribing is a therapeutic approach to test a hypothesis as the cause of the dementia.

The study compared 284,000 cases of dementia with 180,000 controls in order to look for an association of dementia with the intake of any drug in the above classes, and used standardized daily doses to judge the dose burden. The strongest associations

were observed for antidepressants, antipsychotics, and anti-overactive bladder drugs. The associations were stronger in patents with vascular dementia (dementia related to impaired blood supply) rather than Alzheimer's disease. Doses equivalent to 3 years of daily use of a single strong anticholinergic drug increased the odds of dementia by 50%. The authors comment that the more pronounced association with vascular dementia is novel and not understood and should prompt future research since it might help discover mechanisms of drug-induced dementia.

Among the classes of drugs are some with debatable value when compared to a placebo and others that may be prescribed for behavior control, an issue which may not justify the increased risk of dementia. This raises the issue of prescribing of inappropriate or marginally ineffective drugs and those with extremely weak evidence of efficacy, partly to deal with the epidemic of polypharmacy, especially in the elderly, both those living independently and those in old age care facilities. The authors conclude that more attention to risk/benefit analysis is indicated and alternative drugs or treatments should be considered including non-pharmaceutical approaches. The study also found greater increased risk associated with people diagnosed with dementia before the age of 80 indicating he need for caution prescribing the risky drugs in middle-aged as well as older individuals. With drugs where there is very little difference between the active drug and a placebo, the latter could be considered but would be considered malpractice.

The above raises the subject of deprescribing in general. It is estimated that 1 in 5 drugs commonly used in older people may be inappropriate and 1 in 3 among those living in elderly care facilities.[5] Approximately 30% of patients over 65 are prescribed 5 or more drugs and 10 is not uncommon (see April 2019 IHN for a discussion of polypharmacy). Observational studies have revealed that in at least 15% of older individuals, adverse drug reactions contribute to ill health, hospitalization, disability, and even death. The number of drugs taken daily is the single most important predicting factor for these adverse outcomes.[5] Thus the elimination of drugs that are unnecessary, marginally effective or useless should be part of the approach to patient care. In some cases the drugs have been prescribed long ago and by several physicians and simply never stopped. Some nursing homes have the house physician examine the prescription list of new residents and if appropriate, attempt to deprescribe selected drugs. However, this became difficult if the individual is emotionally "wedded" to their pills. Polypharmacy on the grand scale seen today clearly needs to be more aggressively addressed. Added to this is the problem of generic drugs which is the subject of the feature article in this issue.

It is well known that medications can interact, sometimes producing very unfortunate results. Pharmacists can pick this up, but it is not uncommon for someone to deal with several pharmacies which make the task difficult, as does polypharmacy where an additional drug is perhaps thoughtlessly added to 10 drugs taken daily, especial if it is a drug just approved, sometimes as seen on TV!

Deprescribing of course could be accomplished by simply stopping all medication to see what happens, but this is very dangerous and should probably never be attempted. Deprescribing needs to be carefully supervised by one's physician, perhaps with the additional help from a pharmacist. Psychiatric and addictive drugs are in a special class where patients generally need careful weaning over a number of months to avoid very serious problems, even suicide. Anyone questioning this should read Dr. Peter Breggin's book *Psychiatric Drug Withdrawal.*[6] Breggin is a lifelong physician-scientist and reformer in mental health whose work has brought about changes in psychiatric practice. Another problem is that physicians will have different views on the value of some drugs. Statins, antidepressants and acid reflux medications are examples. There is no simple solution to this. Furthermore, the results of deprescription of selected drugs may not produce impressive results for many individuals.[7] However well-known complementary physicians report some dramatic outcomes.

Finally, a patient may want to discontinue one or more drugs after finding out that in the clinical trials required for approval, around 98-99% who took the drug for 5 years failed to benefit and this should even cause them to question the validity of the 1-2% claimed to benefit. Requesting discontinuing may be met with strong resistance since the physician may not look at benefit in this "absolute" manner and has been recommending it for years as "lifesaving" or a "miracle" drug. It should never be forgotten that the ultimate drug for Big Pharma is one where it can be argued that lifelong use is necessary to manage some disorder or surrogate maker. Furthermore, faith in randomized clinical trials which form the basis of regulatory approval in some cases are deceptive due to unpublished negative trials, introduction of bias by subtle subject selection and prescreening, statistical manipulations, or in the worst case, data that has been fiddled with. Nor should it be forgotten that statistical significance is not the same as clinical significance or that a number of longstanding practices have been abandoned quietly when suppressed contrary results are finally published.

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