

Treating High Cholesterol by Replacing Hormones Lost to Aging

by

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Could it be that everything we think we know about cholesterol is wrong? Current conventional wisdom assumes that we obtain too much cholesterol in our diet or produce too much in our liver. A shocking finding by two Life Extension medical advisors reveals that the underlying cause of excess serum cholesterol is a multi-hormone deficiency. Since cholesterol is the precursor to steroidal hormones, when we become deficient in pregnenolone, DHEA, testosterone, progesterone, etc., our body responds by overproducing cholesterol in an attempt to restore healthy hormone balance.

To confirm their findings, Drs. Arnold Smith and Sergey Dzugan conducted a clinical study on 41 patients with high cholesterol between years 1997 and 2003. The astounding result from this study was that by properly replacing the steroidal hormones lost to normal aging, 100% of the subjects experienced a significant

reduction in blood cholesterol levels.

Today, cholesterol-lowering drugs are the most commonly prescribed medications in the United States. These drugs induce side effects and fail to address the underlying reason (hormone deficiency) for why the body is overproducing cholesterol. This article describes how a deficiency in these youth hormones (pregnenolone, DHEA, testosterone, progesterone, etc.) is the underlying cause of many disorders associated with normal aging, including hypercholesterolemia. It then goes on to discuss ways that aging humans can safely restore their hormones to healthy levels.

The findings you are about to read could radically alter the way aging humans with high cholesterol are medically treated. It also confirms previous findings showing that hormone imbalance is the culprit behind many age-related disorders.

Our article will concentrate on the 58 million Americans who represent the market of the “worried well.” The focus of this discussion is hypercholesterolemia (high blood cholesterol) and a possible novel approach to the correction of cholesterol disorder.

Coronary heart disease (CHD) is still a leading cause of mortality in developed countries.^{1,3} Numerous studies have shown that hypercholesterolemia is a major risk factor for coronary atherosclerosis and myocardial infarction (MI).^{4,5} Doctors and patients have struggled for years to find ways to lower cholesterol levels with pharmaceutical drugs and diet modifications. Most countries currently have public health strategies that attempt to lower the level of cholesterol.⁶

Despite considerable success in the treatment of hypercholesterolemia, atherosclerosis remains a serious problem in the healthcare system.

The lowering of cholesterol is the primary measure to prevent cardiovascular disease. If cholesterol-lowering drugs (CLD) could prevent the origin of hypercholesterolemia, it would be a major contribution to the health of the general population. But unfortunately, cholesterol-lowering drugs only diminish the symptoms of the disease known as hypercholesterolemia, and not its underlying cause.

The use of cholesterol-lowering drugs has risen substantially in most countries^{7,8} yet there remains intense debate about their overall efficacy. A number of studies show that although primary prevention is effective, long-term tolerability is still a matter of controversy.^{9,10} Several studies suggest that the reduction of total cholesterol in blood by CLD is accompanied by a decrease in the incidence of CHD, but not in total mortality.^{11,12} The benefits associated with cholesterol reduction may not outweigh the risks in all patients with hypercholesterolemia. Cholesterol-lowering interventions should be recommended with caution in patients with increased risk of cancer, stroke and depression.¹³

Recommendations to lower serum cholesterol are widespread, yet



low serum cholesterol is associated with poorly understood morbidity.¹⁴ Unfortunately CLD is associated with serious side effects, which were seen in 4% to 38% of patients, resulting in discontinuation or dose reduction.¹⁵⁻¹⁷ Low or reduced serum cholesterol concentration increases mortality from hemorrhagic stroke and violent deaths.¹⁸⁻²⁰ The adverse events, including poor quality of life, severe rhabdomyolysis, renal failure and death indicate the need to find better treatment regimens for cholesterol elevation.^{21,22}

The concept of quality of life adjusted survival has been developed in many areas of medicine to address an increasing awareness that survival alone, while easily measured, should not be the sole determinant of superiority in assessing interventional therapies.

Aging is a global dilemma. Due to an increase in the segment population over age 65, an increase in cardiovascular morbidity is predicted.²³ There is a correlation of decreasing production of multiple steroidal hormones (testosterone, DHEA, pregnenolone, etc.) with intercurrent life threatening lipid disorders. Different studies presented

controversial results of using estrogens, progestogens, androgens and dehydroepiandrosterone (DHEA) for lipid disorder correction.²⁴⁻²⁹ There is a lot of information about the effect of estrogen therapy with or without progestogen on the level of cholesterol in medical literature. Nonetheless, the findings about the benefit of such hormone replacement therapy (HRT) in the prevention of cardiovascular disease are still very controversial.³⁰⁻³⁴

We suggest a new hypothesis for hypercholesterolemia and in this article we will try to present the main points of this hypothesis.^{35,36} Also, we will describe a new method of cholesterol disorder correction by the rejuvenation of steroid hormonal profile.

Cholesterol and your body

We will evaluate the problem with hypercholesterolemia from a non-traditional point of view. We know that the plasma cholesterol levels increase with age, as does the incidence of CHD.^{37,38} The mechanism responsible for the age-related hypercholesterolemia is not well understood. Conventional

medicine understands the reason for the elevation of cholesterol only partially. Genetic risk and a high fat diet are the two main reasons shown in most medical textbooks. Although much is known about hypercholesterolemia and the associated risk for the development of atherosclerosis, very few researchers have focused on cholesterol metabolism.^{14,39}

There is an enormous level of confusion about the whole area of cholesterol, so we will provide the information in a simple concise manner.

Cholesterol is an important part of the story of blocked arteries (but it's not the whole story!).

Cholesterol has an extraordinarily important function in an organism; it is the critical compound for life. It is the basic component of the cell membrane, bile acids, steroid hormones, and, in conjunction with sunlight, vitamin D3.

Neither cholesterol nor triglycerides can be dissolved in blood. They have to be wrapped up in a sphere known as a lipoprotein in order to transport them out of the intestine. In short, lipoproteins are the transport for insoluble cholesterol and triglycerides.

Low-density lipoproteins (LDL) carry cholesterol from the liver to different organs. Cholesterol is then absorbed by the cells around the body. Excess cholesterol is reabsorbed by the liver and reused or excreted into bile. LDL is known as "bad cholesterol" (even though "LDL" is not "cholesterol").

High-density lipoproteins (HDL) are made in the intestine and the liver. They help to remove cholesterol from artery wall. HDL acts as a cholesterol mop, scavenging loose cholesterol and transporting it back to the liver. HDL is known as "good cholesterol" (even though "HDL" is not "cholesterol").

The human organism is in a state of dynamic equilibrium, known as homeostasis. One of the main roles in normal homeostasis belongs to multiple feedback loop mechanisms. Cholesterol is the precursor or the building block for the basic hormones: pregnenolone, DHEA, progesterone, estrogen, testosterone (Fig.1). Deterioration of the reproductive function, one of the most striking endocrine alterations

occurring in aging, is related to a complex interplay of factors. Target organs may become less sensitive to their controlling hormone or may break them down at a slower rate. Hormone levels may change; some increasing, some decreasing and some remaining unchanged. Many of the diseases that middle-aged persons begin experiencing including depression, abdominal weight gain, prostate, breast and heart disease, are directly related to hormone imbalances. Conventional doctors are prescribing drugs to treat depression, elevated cholesterol, angina and other diseases that may be caused by hormone imbalance.

A few years ago we found out that some patients who had high cholesterol levels before hormone restorative therapy (HT) were free of cholesterol problems during therapy. We started pondering as to why this had happened?

In our opinion, when the production of hormones starts to decline our body tries to correct this problem by increasing the production of cholesterol. A similar situation happens to women during pregnancy. When a female's body needs more hormones for herself and her baby, cholesterol levels are elevated significantly.⁴⁰⁻⁴² If a woman's body is unable to increase the production of cholesterol the risk of an abortion and miscarriages

is increased.⁴³

Another situation is a low level of cholesterol. If your total cholesterol is less than 160, you have nothing to worry about. Wrong opinion! A low level of cholesterol means a low production of basic hormones (because of a limited amount of building blocks). Patients with a low level of hormones have life problems that include suicides, criminal behavior, depression, attention deficit disorder, cancer at young age, etc.⁴⁴⁻⁴⁹ Low cholesterol is a marker for poor underlying health.

When patients take cholesterol-lowering drugs (CLD) we can surmise that hormonal production will decrease. That's why many patients on CLD have severe fatigue, fibromyalgia-like pain, depression, high risk of cancer, suicides, weight gain and impotency.⁵⁰⁻⁵²

Normally our body tries to keep a normal ratio between different hormones: DHEA/cortisol, estrogen/progesterone, female/male hormones. When we have a malfunction in a feedback loop mechanism we start to have the problems related to the imbalance of hormones (for example: male or female dominance, estrogen dominance, etc.).

Once again, when the production of hormones starts to decline, our body tries to correct the deficiency of hormones by the extra production of cholesterol. It looks like the elevation of total cholesterol serves as

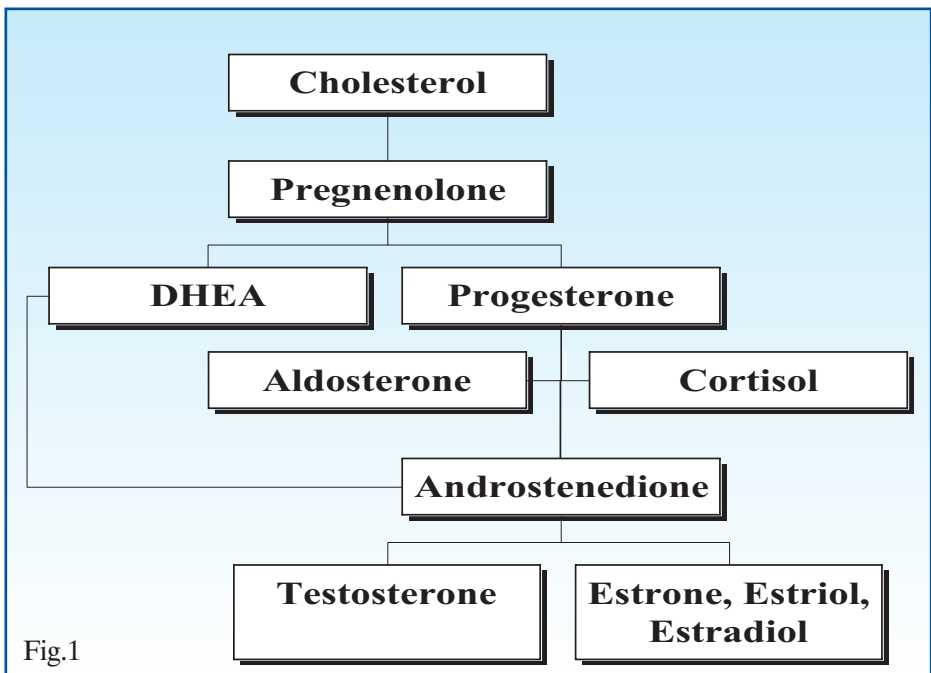


Fig.1

a compensatory mechanism for hormonal deficiency. Considering this, if we restore a youthful level of hormones there is no reason for the extra production of cholesterol. Hormonorestorative therapy may play a key role in “resetting” the various endocrine loops.

Formulation of new hypothesis

We suggested a new hypothesis, which we call the *hormonodeficit hypothesis of hypercholesterolemia*. This hypothesis implies that hypercholesterolemia is the reactive consequence of the age-related, enzyme-dependent down regulation of steroid hormone biosynthesis and their interconversion. In short, hypercholesterolemia is the compensatory mechanism for age-related decline of steroidal hormone production.

Basic understanding of our cholesterol metabolism can help with the process of restoring our body’s natural synchronization. Hormone supplementation can help bring our bodies back into balance.

Testing of the hypothesis

Forty-one patients ages 25 to 81 with hypercholesterolemia were treated between July 1997 and April 2003. Male to female ratio was 1:1.6 (16 to 25). All patients were treated by hormonorestorative therapy (HT) using anthropo (human)-identical hormones. This included a combination of several agents: oral pregnenolone and DHEA capsules and topical triestrogen, progesterone and testosterone gels. HT includes chemically identical molecules to human hormones and is administered in physiologic ratios with dose schedules intended to simulate natural human production cyclicly. We prefer to use the topical gels because they contain highly lipophilic molecules with low molecular weight, are very well absorbed through the skin, may use adipose tissue as a reservoir, and facilitate individualized dose prescription. Dose recommendations to patients during HT were individualized and were determined

by serum hormonal levels during serial testing. That is why we did not use standard dose, rigid protocol or traditional design for this study. Doses were individually modified during HT to produce youthful physiologic (not “normal”) serum levels. We titrated doses to reach the laboratory defined hormonal blood levels of young adults between the age of 20 and 30 for both genders at which time a good level of all steroid hormones naturally occurs.

There are a few rules for HT: anthropo-identical structure of hormones, individually modified doses, cyclical manner and larger dose in the morning. *Mono- or bi-hormonal* therapy is usually inadequate. *Poly (multi)-hormonal* therapy is optimal. What we mean here is that all steroidal hormones should be properly replaced at the appropriate time of the day. If even one steroidal hormone is left out, then the body may respond to this deficiency by synthesizing more steroidal hormonal precursor, i.e. cholesterol.

Blood tests measuring serum levels of total cholesterol with or without lipid profile, pregnenolone, dehydroepiandrosterone sulfate (DHEA), progesterone, estrogens and total testosterone levels were done. The follow-up period ranged from 2 to 68 months.

All patients responded to HT (Fig.2). Mean serum total cholesterol dropped by 25.6%—from 254.6

mg/dL before to 188.8 mg/dL after treatment (Fig.3). Serum HDL level (nl >35 mg/dL) decreased from 59.7 mg/dL to 48.0 mg/dL, (19.6% drop), but remained much higher than undesirable levels in all cases (Fig.4).

We believe that a decreasing level of HDL is a very good sign of correct therapy. If we normalize the level of total cholesterol, what reason exists for the extra production of HDL? If there is nothing to transport back to the liver, why produce the extra carrier? HDL, by this logic, should decrease, but in most cholesterol studies (except ours) an HDL increase is reported. Why should the elevation of HDL be a good sign during cholesterol-lowering therapy?

(Editor’s note: While the authors make a rational point to explain the decline in HDL using their program, there are numerous studies showing it desirable to maintain the highest possible level of HDL. Those seeking ultimate protection against cardiovascular disease should take steps to maintain high HDL such as moderate intake of niacin, aerobic exercise, consumption of monounsaturated fats (olive and canola oils), reducing excess body fat, avoiding cigarette smoking and even moderate alcohol consumption).

Serum LDL decreased by 23.9%—from 158.2 mg/dL before to 120.4 mg/dL after treatment (Fig.5). During the follow up period no complica-

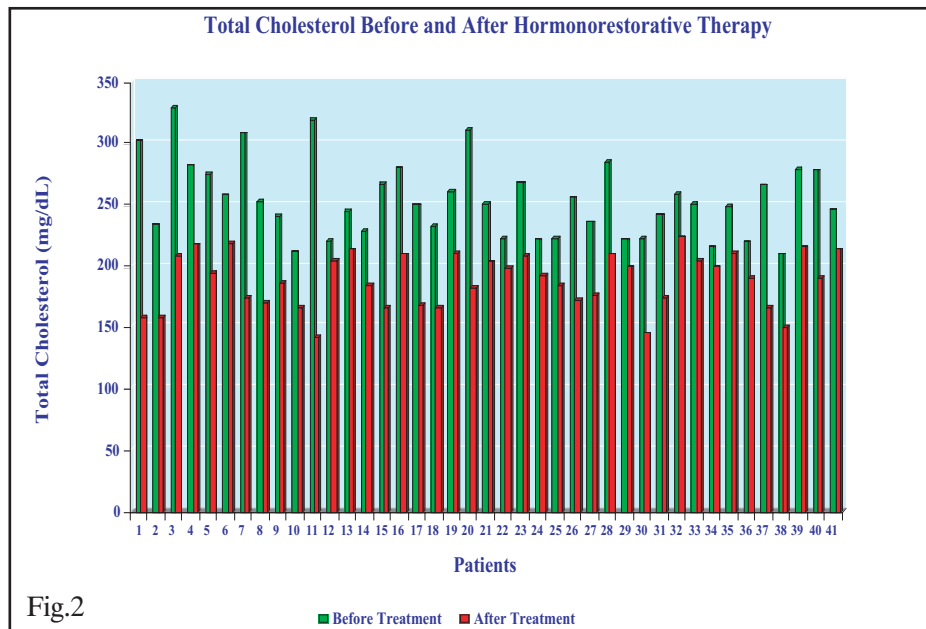
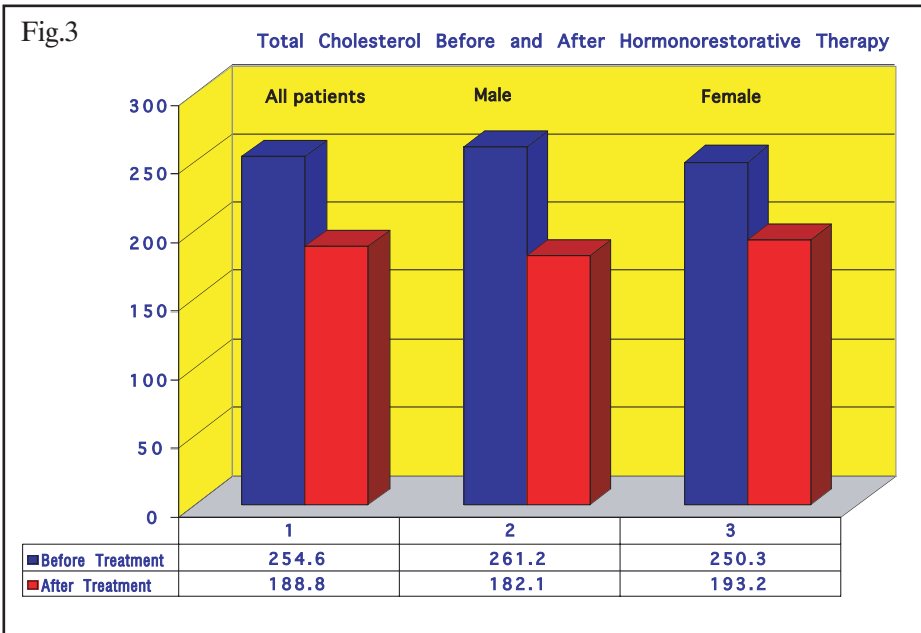


Fig.2

Fig.3



tions or side effects related to HT were a cause for concern. All patients described a significant improvement of quality of life.

In our study we use the term HT (hormonorestorative) with anthropo-identical hormones for treatment of hypercholesterolemia as a name for our regimen. We use this term because there is a lot of confusion with terminology. This term more clearly defines what we are doing during therapy than “HRT.” HRT was compromised because it was mainly used in the context of estrogen or estrogen/progestin replacement therapy. Problems with HRT: the majority of studies were performed with only one or two agents, no physiological cyclicality, “one-size-fits-all” (standard dose), no anthropo-identical restoration was attempted, serum hormonal levels were not used clinically and there was a mostly oral route of administration.

The term “natural” HRT is not clear because it is unknown if it is natural for humans or natural for nature, because natural means not human-made, and it may refer to phytoestrogens or equine estrogens.

The term “bio-identical to the human hormones” is unambiguous. However, “bio-identical hormones” by itself is confusing (“bios” in Greek is life). In other words, we used hormones that are identical to what humans make and utilize as opposed to what are used in other natural

arenas (such as in the bodies of horses).

We use the term “anthropo-identical restoration” because it is a more restrictive term than bio-identical (“anthropos” in Greek is human). HT with anthropo-identical hormones means that the chemical structure of the hormones employed is identical to human hormones and the normal ratios between hormones inside of each hormonal group are maintained.

Now we will try to explain some problems from the point of view of our hypothesis. You have heard that if you keep your cholesterol under 200 mg/dl you will be safe against CHD. Right? This is the “conventional wisdom.” But it is not necessarily so. We have to remember that a significant proportion of individuals with ischemic heart disease have desirable cholesterol concentration. We know that hypercholesterolemia was observed in 40% to 70% of patients with CAD.^{53,54} How can we explain that up to 60% of patients with MI have documented “normal” level of cholesterol?

We will now observe the change of cholesterol in two patients. As you can

Age	25	40
<i>Patient 1</i>		
Total Cholesterol	130	190
<i>Patient 2</i>		
Total Cholesterol	180	240

see, life cycle related elevation of total cholesterol is 60 mg/dl in both cases. We hypothesize that total cholesterol elevation over time is a critical determinant of risk for CHD or MI, not just an absolute number. In our opinion, the risk of heart attack in both cases was equal despite a normal level of cholesterol in the first case.

If we are right and our hypothesis is correct, the normal level of cholesterol during HT must decrease. We made an analysis with five patients with normocholesterolemia (so-called “relative hypercholesterolemia”) and the results are given below.

	Sex	Age	Total cholesterol (nl <200 mg/dl)	
			Baseline	Follow-up
1.	F	55	198	168
2.	M	73	202	162
3.	M	63	195	150
4.	M	56	96	113
5.	F	55	189	153

It looks like our hypothesis is substantial.

Now we can try to explain why patients with a high level of total cholesterol often have a low level of HDL. In our opinion there exists a so-called “Total cholesterol/HDL paradox.” When a patient has a high level of cholesterol that can damage arteries, the body must produce more HDL for the clearing of arteries, but in fact it decreases (a paradox). In this case another mechanism is probably working. It appears that there is no need for an increased production of HDL because there is no excess of cholesterol that must be returned to the liver, barring the fact that there is a high concentration of total cholesterol in the blood. This happens in the case where the body needs more raw materials for the production of hormones, reconstruction of cell membranes (because of a higher risk of aging damage), etc. This sequence represents the working of a self maintaining system.

The following case study presents a typical case of a patient with hypercholesterolemia during HT. This case highlights valuable information about the importance of the relationship between cholesterol and steroidal hormones.

Case study

Patient H. 66 yr, female.

First visit 10/10/02

Complaints: hypercholesterolemia, fatigue, depression, insomnia, migraine, hot flashes, vaginal dryness, no libido, poor sex drive, leg cramps, short-term memory problems, constipation, colitis, etc (in total 25 complaints).

Follow up 01/09/03

Complaints: minimal problems with colitis

Blood tests at baseline and after HT treatment:

	DHEAS	Pregnenolone	Estr(total)	Progesterone	Testosterone
10/10/02	<30	<10	122	0.3	58
01/09/03	213	86	172	3.6	73
	Total Cholesterol	Triglycerides	HDL	LDL	
10/10/02	266	211	65	158	
01/09/03	166	168	41	91	

Conclusion

In patients characterized by hypercholesterolemia and sub-youthful serum steroidal hormones, broadband steroid hormone restoration was typically associated with a substantial drop in serum total cholesterol. HT is an effective intervention for hypercholesterolemia and could be a physiologic and inexpensive resource for the healthcare system.

Elevation of cholesterol is an excellent aging marker, which can be used to define the time when patients need to begin HT.

Our body is a very smart self-regulated

system. These reasons are always for the elevation of cholesterol. It can be that the age-related decline in production of steroid hormones, pregnancy, or some problems with enzymes. But hypercholesterolemia is in most cases a consequence of some reason, not a reason in itself. That's why it is not very important what method you are using for suppressing the production of cholesterol—drugs, diet or supplements. You can always correct a consequence (hypercholesterolemia)! On the contrary, we attempt to eliminate the reason for total cholesterol elevation by restoring a youthful hormonal profile. The main difference

between traditional medicine and our treatment policy is that traditional methods direct against normal physiology. During our therapy we try to model a normal, healthy physiology.

More research will be needed to determine the full clinical potential of such an approach to the management of hypercholesterolemia.

Some additional comments by Life Extension

The purpose of this six-year study was to ascertain the effects of steroidal hormone restoration (HT) on cholesterol blood levels and to assess the effects of this therapy on the overall health of patients. This study showed that total and LDL cholesterol levels declined and all patients described a significant improvement in quality of life (even though they were aging during this period).

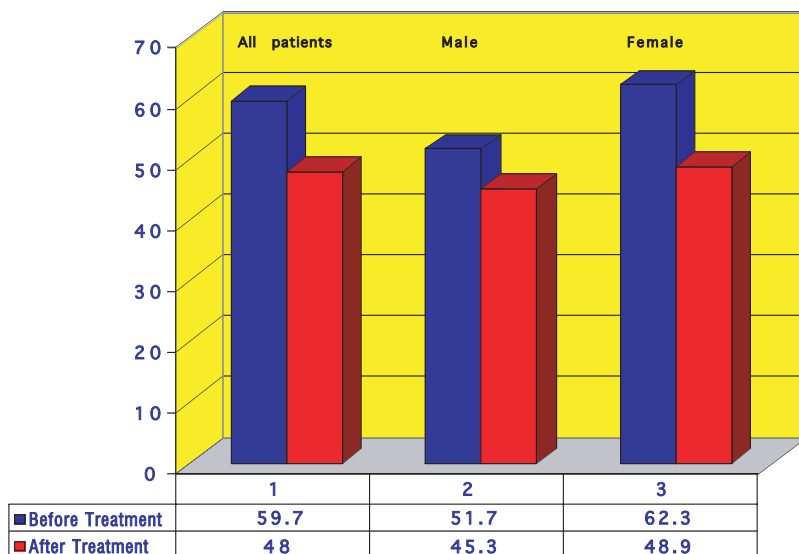
A “non-steroidal” hormone that also causes elevated cholesterol when deficient is thyroid. The authors of the study commented to Life Extension that some patients were already taking thyroid hormones before their program, but the level of total cholesterol and LDL remained high. They also mentioned that symptoms of hypofunction of thyroid hormones were improved after the start of their HT treatment. This can be explained by the restoration of sensitivity of cell membranes to the impulses of thyroid hormones.

This study showed that serum LDL decreased on average from 158.2 mg/dL before to 120.4 mg/dL after treatment. Optimal LDL levels, however, may be below 100 mg/dL. For those with chronically high LDL, the addition of thyroid restoration therapy (if tests reveal thyroid deficiency) could reduce LDL to optimal levels.

The authors noted that complete HT was required to obtain these results. A deficiency in even one steroidal hormone could cause the liver to synthesize more cholesterol in a sometimes-futile attempt to naturally replenish the missing hormone in the body. The authors mentioned that pregnenolone was a hormone often found deficient. When pregnenolone was restored to

Fig.4

HDL Before and After Hormonorestorative Therapy

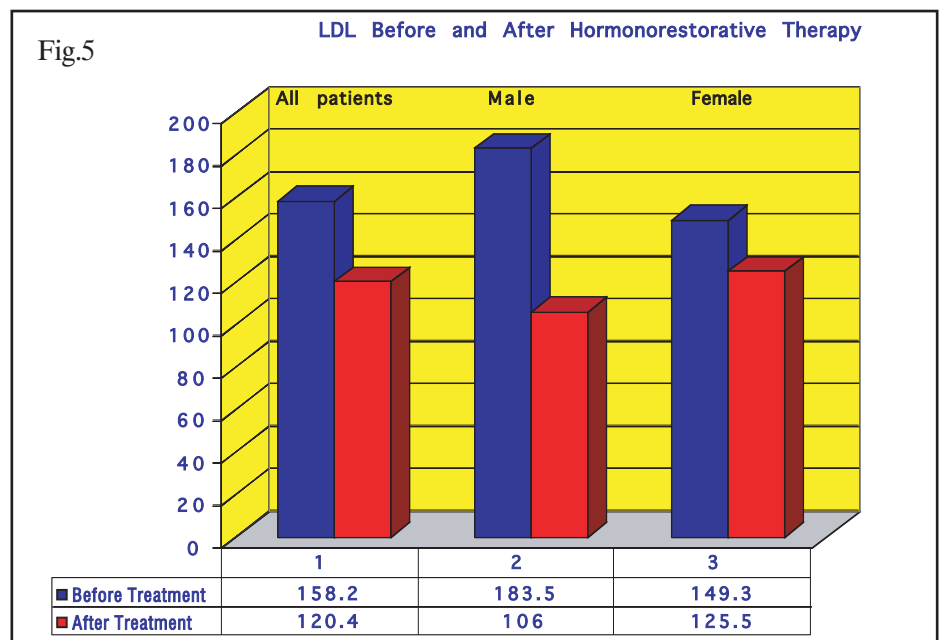
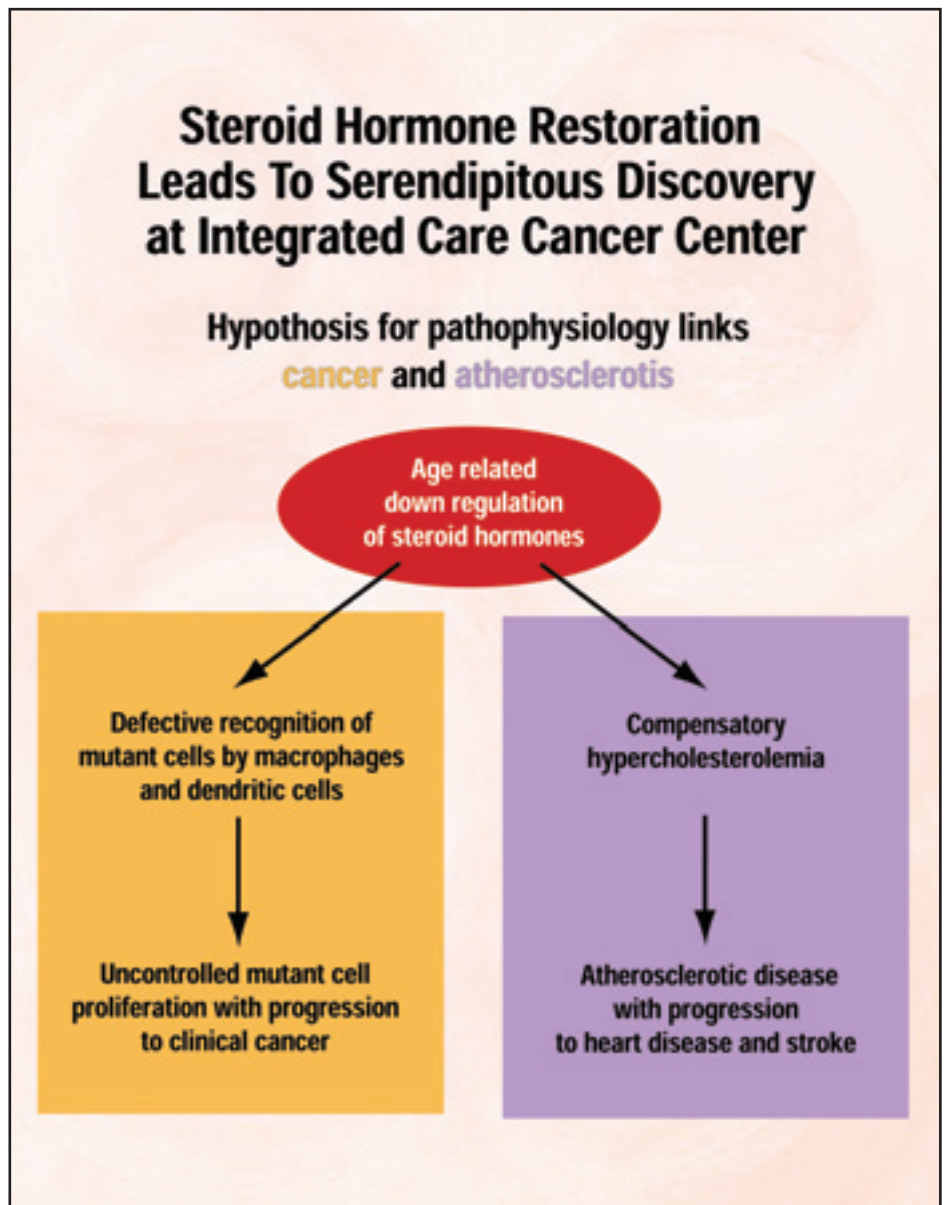


normal levels, cholesterol reduction was observed. The significance of this is that pregnenolone is the natural precursor (mother hormone) of DHEA, testosterone, progesterone, the estrogens and other steroidal hormones. If one has healthy hormone transformation enzyme systems in place, it is theoretically possible that supplementation with pregnenolone by itself would maintain healthy levels of steroidal hormones (DHEA, progesterone, testosterone, estrogen, etc.) Unfortunately, aging people often suffer from defective hormone enzymatic transformation systems, meaning that pregnenolone does not cascade down into other critical steroidal hormones. This is why aging humans can derive so much benefit from natural DHEA, testosterone, progesterone and estrogen supplements and drugs.

The only downside to utilizing HT (hormonorestitution) in all aging people is that some have hormone sensitive cancers. Those with prostate, breast and certain reproductive cancers may not be able to enjoy the whole body benefits of HT and instead have to rely on drug therapy if their cholesterol levels are too high.

About the authors

- **R. Arnold Smith, M.D.** is a radiation oncologist who operates an integrative cancer practice in North Central Mississippi Regional Cancer Center in Greenwood, Mississippi. In addition to radiotherapy, Dr. Smith treats his cancer patients with multiple biological response modifiers that increase the percentage of cancer patients who experience long-term survival or complete response. Despite being located away from any convenient airport and doing no advertising, cancer victims who learn of Dr. Smith's aggressive approaches to treating cancer travel from far distances to become patients. Dr. Smith has been a Life Extension advisor since 1983, and has provided enormous amounts of clinical data that The Life Extension Foundation has incorporated into its cancer treatment protocols. You may wonder how a busy radiation oncologist could find the time to do



a study on the cholesterol-lowering effects of multi-hormone restorative therapy. One reason is that he has the assistance of a brilliant researcher named Sergey A. Dzugan, Ph.D. Dr. Smith has become so well known for his superior methods of treating cancer, that patients (and their families) insist that he treat other age-related diseases. As a result, Dr. Smith may be the only conventional oncologist to also practice anti-aging medicine.

• **Sergey A. Dzugan, M.D., Ph.D.**, joined Dr. Smith's practice in July 1, 1996. One of Dr. Dzugan's jobs is to search the peer-reviewed published literature in order to identify better methods for treating cancer and slowing aging. Dr. Dzugan participates in conducting studies and writing articles that are later published in scientific journals. Sergey A. Dzugan was formerly a heart surgeon and Chief of Cardiovascular Surgery at the Donetsk Regional Medical Center in Donetsk, Ukraine. His Ph.D. in cardiovascular surgery was received in 1990 and pertained to heart rhythm disorder. He was the Associate Professor of Medical University in Donetsk, Ukraine. Dr. Dzugan's current primary interest is in anti-aging and biological therapy of cancer and he participates in patient care research in Greenwood, Mississippi. Dr. Dzugan has worked with the Cancer Center for more than six years and is the author of 113 publications in medical journals and these publications include surgical, oncological, academic and anti-aging topics. While Sergey Dzugan is an accredited medical doctor, he is not currently licensed to practice in the United States.

Cancer patients who want to inquire about Dr. Arnold Smith's state-of-the-art treatment modalities may call 1-800-720-8933 for specific information.

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