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Beyond the Drosophila

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By Jeffrey W. Wilson, M. D.

Dr. Wilson took his undergraduate degree and all of his medical education at Duke University. After two years in the navy, he eventually settled in Lynchburg in 1979, practicing in his specialty of rheumatology. Jeff and his wife Sandra have two daughters and three grandchildren.

In September 2007, Dr. Wilson was presented the William Barney Award by the Lynchburg Academy of Medicine for his many contributions to the community and to organized medicine.

BEYOND THE DROSOPHILA

Jeffrey W. Wilson MD

"If it were not for the great variability among individuals, medicine might as well be a science and not an art." Sir William Osler (1892)

My sixteen year old cousin Jimmy Ray Bush was visiting his brother in Morgantown for a WVU football weekend in the fall of 1965. As they headed into the Mountaineer Pub one of the bouncers stopped Jim. "You got a ID, son?" Jimmy Ray responded: "ID? ' Bout what?" Our concerns today about our identification and ID security leave us fretting with Passwords and PIN numbers and firewalls. That's not the identity I am going to discuss. Anne Gibbons in her inaugural Sphex Club presentation January 8, 2009 entitled "Last in the Atlas; First in My Heart"told us about her home state of Wyoming. Her opening question? Where are you from? Certainly part of your identity. We're going to explore the question of : What are you from? How did you get where you are? Where are you going? In other words, what has resulted in the phenotypic expression of your genotype that you represent? Genotype is defined as a person's genetic makeup, as reflected by his or her DNA sequence. Phenotype is the clinical presentation or expression of a specific gene or genes, environmental factors, or both (from "Genomic Medicine—a Primer" by Guttmacher and Collins in **NEJM** Nov 7,2002).

In July 1989 in the Academy of Medicine newsletter I discussed the cost of chemicals making up the human body. Here is a copy of "On My Mind: Roe, Wade and Gabler" Lamlight Volume 3; #7. The combinations of carbon, hydrogen, nitrogen and trace elements had a projected cost of around $20.00. Even by today's prices (probably $200) the cost of our building materials is surprisingly low—but the construction from these raw materials is amazingly intricate following the detailed inherited blueprint of your genotype.

The night before Duke spring break 1967. The Sigma Nu premeds spent the night counting fruitflies (Drosophila) and putting the finishing touches on our Genetics lab books. Red eyed, brown eyed, crinkled wings---did it fit an autosomal dominant or recessive pattern? College rules then were as different as genetics in the 1960s compared to the molecular genetics of today. You could not miss your last class before the start of vacation and had to be present for your first class after break time ended. Notebooks turned in by 10:00 AM; classes ended and the blue Chevy Nova was loaded with 3 fellow students (Ed Weber; Chip Milspaw; and Becky Bogard) heading to Pittsburgh sharing gas costs. It was always an adventure in travel. Never a question of if we would have a flat tire or car repair; simply a matter of when. Following the traditional college "all-nighter" I was drowsy and after slipping off the road side shoulder around Sperryville a couple of times, I accepted Ed Weber's offer to drive while I dozed.

The face of genetics was already changing by the first year of med school 1968. In the spring of 1969 we began learning to take a history and conduct a physical examination. The Family History section intrigued me. Maybe that was because of my W Va heritage. The News and Advance had a front page article several years ago stating that scientists were no longer as worried about genetic defects from first cousin matings. This was comforting coming from a state of first cousins, and if you'll recall Ted Craddock's last talk—we may all be first cousins. Unfortunately, also in the same paper was an article discussing the scientists' fascination with a two headed snake. Hmmm, maybe not so comforting.

Diabetes, hypertension, cancer, heart disease, strokes---"That runs in my family" the patient would say. We learned to draw the family tree (family pedigree) depicting members of various generations preceding, accompanying, and following the patient. Our general attitude was "You can't beat the genes." But are the die cast with the inherited genome? Believe me, just as we medical students were susceptible to imagined cases of all the diseases we studied in Pathology, likewise, we were aware of our personal family maladies especially those presenting with early morbidity or mortality. Since that time we have mainly concentrated on altering the manifestations of the genetics—meds to lower the cholesterol and decrease the incidence of heart attacks; meds to lower BP, control sugar, uric acid, etc. Now with studies of molecular genetics and the human genome can we actually alter the genotype or alter its expression rather than tend to the phenotype?

JAMA—the Journal of the American Medical Association , the Mayo Clinic in their journal Mayo Clinic Proceedings ("Primer on Medical Genomics"), and the American College of Physicians newsletter The Observer have run series of articles on modern genetics over the past several years to prepare us for new attacks on disease and a better understanding of personalized medicine (inherited predisposition to diseases; immunogenetics; pharmacogenetics). Genomics may be defined as the study of the functions and interactions of all the genes in the genome, including their interactions with environmental factors.

After many articles in the series one author reemphasized the importance of the traditional family history. Dr.W.Gregory Feero is a family physician with a PhD in human genetics who serves as a senior adviser for genomic medicine in the Office of the Director at the NIH National Human Genome Research Institute. There is even available online the U.S. Surgeon General's family history tool, My Family Health Portrait (https://familyhistory.hhs.gov). What could that possibly provide of importance beyond this modern sophisticated analysis of the patient's genome? Answer: Exposures and possible triggers that might affect the expression of the inherited genetic makeup.

An article by John Carey in Business Week Nov 3, 2008 "Gene Tests: Behind the Hype" discusses the limitations of the commercial human genome information and quotes Dr. Greg Lennon, a PhD geneticist and entrepreneur: "Most people can save themselves $1000 just by asking Aunt Clara what runs in the family." Why is that? The human genome consists of about 3 billion pairs of chemicals that make up DNA. The majority (99.7%) of the base pairs are identical in all individuals (first cousins? Or maybe a monkey's uncle or more precisely a monkey's niece or nephew? Scientific American May 2009 article "What Makes Us Human?"by K. Pollard, PhD found that 99% of the human and chimpanzee DNA blueprint are nearly identical—do we hear Darwin chuckling as he celebrates the 200th anniversary of his birth?). An estimated 10 million show variations. These differences are called SNPs (single nucleotide polymorphisms). A gene-test company may look at 1 million SNP variations, which means they are missing at least 90% of the total variation. Even whole genes aren't perfect predictors. Dr. Eric Topol, a genomics professor at Scripps Research Institute, looks at the "wellderly", older people who have always been healthy. Surprisingly, these people have as many "bad" genes for Alzheimer's, heart disease, or various cancers as average individuals. Are there other gene interactions that cancel out or control the bad ones? Micro RNA is being recognized as such a regulator of gene expression probably by inhibition of messenger RNA expression.

In rheumatology we have found that 90% of people with RA have a particular genetic marker (HLA DR4) or SNP (single nucleotide polymorphism—a common variant in the genome sequence; the human genome contains about 10 million SNPs). In twin studies what would you expect the incidence of RA to be in identical twins with the SNP? If one twin has RA the likelihood of the other is only 10 to 15%. If a non-twin sibling, parent, or child had rheumatoid arthritis the likelihood of another family member

developing the illness is three times the normal incidence of the disease. If the incidence of RA is 1 in 1000 in the general population, the chances are 3 in 1000 among relatives of the RA patient. Significant, but not like the inheritance of blue eyes or brown eyes. Another important paper appeared in the March 2009 issue of **A&R**—"Familial Associations of RA with Autoimmune Diseases and Related Conditions". When we talk about collagen vascular diseases or connective tissue diseases we consider a spectrum of disorders with RA at one end and Lupus at the other. In between are Scleroderma, Sjogren's Syndrome, Dermatomyositis, Polymyositis, and Mixed Connective Tissue Disease. It is no surprise that family members of a patient with RA would have a greater likelihood to have one of these "cousin" disorders. What this study showed, however, is that all autoimmune disorders appear more frequently—Addison's disease (autoimmune adrenal insufficiency); pernicious anemia (B12 deficiency); the most common cause of hypothyroidism (Hashimoto's thyroiditis); myasthenia gravis; MS, etc. The lesson to be learned is that family members of the patient with RA should be considered at greater risk for these diseases—they have an inherited tendency to develop these autoimmune disorders. Be vigilant in following your RA patient and his or her relatives for the development of these associated autoimmune disorders. With the DNA sequence, states Dr .J. David Sweatt of U. Alabama you have only half the information; a tentative plan. What determines how you execute it?

As some people might say "They call it a medical practice because you never get it perfect." I prefer to think that it's practice so we can continually improve. So indulge me as I share with you some observations from practice. Here is something that some of you have already experienced. At 45 to 50 years of age in spite of a better diet, exercise, and possibly weight control, your blood pressure is higher, your cholesterol is higher, and perhaps your sugar levels are higher. Why, that's about the same age that Mom's BP had to be treated; or the age that Uncle Ned's diabetes showed up. Some genes become more strongly expressed as we get older. And thank goodness they are not fully expressed at birth. It is probably why we see these problems and cancer cases presenting at older ages in general. Is there something over time that enhances the expression of these genes or causes the loss of some control (such as genetic suppressor activity) over the expression? See the epigenetics section below.

A favorite model of autoimmune disease for the rheumatologist is rheumatic fever. A strep infection—usually a pharyngitis or "strep throat" precedes the onset of an illness characterized by fever, rash, chorea—a movement disorder (St. Vitus' dance), arthritis, and carditis (inflammation of the heart). The reason patients are treated with penicillin is to prevent the development of rheumatic fever. Even without antibiotics our systems will eradicate the strep organism. But why, before antibiotics or without antibiotics, did only a few individuals develop the autoimmune disorder? We felt that this was the model of an infection triggering off an autoimmune disease in a genetically susceptible host. Most immune systems eradicated the infection, but the immune systems in some patients, once turned on by the infection, find the normal surveillance function go awry. The immune system seems to say "your skin, heart, and joints remind me of the strep infection and even though the infection is gone, I am going to react against them". Immune reaction against self is autoimmune disease. A similar disorder involves acute renal failure following a strep infection of the skin (post-streptococcal glomerulonephritis). Even though the infectious agent is gone, or eradicated, the body's immune system continues to react against itself (autoimmune disease).

Usually following shore leave when the Navy ship goes back out to sea, the medical team deals with cases of STDs (sexually transmitted diseases). In 1962, however, there was an outbreak of Shigella dysentery (a bacterial diarrhea disorder) on board a Navy cruiser described by H.R. Noer in JAMA (Journal of the American Medical Association 198:693-698, 1966). 602 of 1276 crew members

developed shigella dysentery. As expected, the diarrheal illness cleared quickly with or without antibiotics. However, 10 sailors developed a persistent arthritis condition called Reiter's Syndrome (with clinical features of arthritis, conjunctivitis, and urethritis—"can't see, can't pee, can't climb a tree" with inflammation of joints, eyes, and the urinary tract).

Over the next decade we became interested in histocompatability and its importance in organ transplantation. Dr Bernard Amos spearheaded this research at Duke and we knew that histocompatability locus (on chromosome 6) or HLA (Human Leukocyte Antigen) profile predicted successful organ transplantation. If someone was HLA A2, B27, D4, C3; he could most successfully donate or accept an organ from someone of similar HLA genetic pattern. As data collected, in Rheumatology we became especially interested in the HLA B27 story. This is present in 4 to 8% of the normal population. However, in the inflammatory arthritic disorder Ankylosing Spondylitis it is present in 96% of the patients. In patients with Reiter's syndrome usually 95% are HLA B27 positive. An interesting feature of Navy medicine is the tendency to keep records on everyone. In 1976 Drs. Andrei Calin and Jim Fries wrote a landmark article in rheumatology entitled "An Experimental Epidemic of Reiter's Syndrome Revisited" Annals of Internal Medicine Vol 84; May 1976. The authors located 5 of the 10 sailors who developed the post-dysenteric Reiter's and HLA typed them. 4 of the 5 were HLA B27 (+). The one who was negative for HLA B27 had a much less severe clinical course. As an aside, in teaching Family Practice Residents or the occasional medical student, I like to point out these classics of rheumatology. A recent resident exclaimed, "Why, Dr. Wilson, that article was published the year I was born. " That made me feel a bit like a landmark; hopefully a classic.

So the mechanism of infection triggering an autoimmune disease in a genetically susceptible individual seems well established. Another important study by Calin looked at healthy blood donors who were B27 (+) with no clinical signs of arthritis or associated inflammatory conditions. Over the next decade 20% of these individuals developed a B27 (+) rheumatologic condition. We assumed an infectious episode was the trigger; and noted that the presence of HLA B27 is not a harbinger of definite disease developing; most B27 (+) patients did not develop a clinical disease. If we could not pinpoint a definite preceding infection like shigella dysentery we accepted the possibility that a subclinical infection acted as the trigger or perhaps an undetectable viral illness. While we will later discuss other possible triggers, this model suggested a unique future role of human genome mapping in the prevention of disease. I pictured genome mapping of the individual at birth. As we recognized the association of specific genetic patterns with disease susceptibility, would we have a role for vaccinations against specific infectious triggers for individuals? For example vaccination against Shigella for the B27 (+) sailor might avoid having Reiter's Syndrome triggered by exposure to the infectious agent. Would complete genome analysis let us know that the individual with a particular genetic makeup needed a certain panel of vaccines to avoid having other autoimmune diseases triggered? It won't be that simple, however.

One of the special things about practicing in Lynchburg for a while is the opportunity to see family related conditions. Over 25 years ago I saw a female patient with atypical chest pain who was B27 (+). This was before we had cardiac cath in Lynchburg and I referred her to UVa where she was found to have aortitis (inflammation of the aorta) causing her pain and the main manifestation of her B27 (+) condition. About 5 years ago I was called by Dr. Dave Frantz. He was operating on a 57 yr old white female and noted that the coronary artery bypass grafting was complicated by inflammation of the aorta. When I saw the patient later in the office in consultation, she said "Your father took care of my mother 25 years ago." Well, my father was not a physician and had died with cancer my freshman year at Duke. Either I looked pretty good at this time for my age; or more likely looked pretty old back then. In any event she was B27 (+) and the manifestation in her particular family was aortitis. In some families

the B 27 marker may be associated with eye inflammation or inflammatory bowel disease often along with arthritis. These conditions are not rare and I would not be surprised if there wasn't a B27 (+) individual in our audience right now. Of more importance it explains why we see unique expressions of sometimes common diseases in families. Osteoarthritis, the most common form of wear and tear arthritis, involves changes in the cartilage making up joints and beginning as early as our twenties. Why is it that in some families the osteoarthritis is manifested by hand changes and in other families everyone has hip or knee replacements with less hand involvement? Even though it is the same type of cartilage making up the various joints, some people talk about family "fingerprints"; slight inherited changes that result in their familial expression of osteoarthritis. My patient and her mother mentioned above had their family fingerprint of the HLA B27 manifested as inflammation of the aorta.

There were many benefits in having 2 years of military service with the Navy: a free child, enduring friendships with people like Dr Burton (remember the developer of Obecalp?), and the opportunity to have an understanding of the range of normals in medicine. In internship and residency training at the medical center the patients were obviously very sick; you rarely considered if this could be a normal variant. The first year in the Navy doing active duty sick call along with discharge physicals we were dealing with a young population of generally healthy individuals with injuries, trauma, and acute infectious illnesses. We would occasionally pick up a heart condition missed at the induction physical. We spent some time teaching the corpsmen. As a whole, they were more inclined to the surgical discipline. "A chance to cut is a chance to cure" was the surgeon's mantra, right Stuart, Graham, and Eric? In internal medicine our attitude was "Don't just do something, stand there and think." One corpsman Lonnie Touchstone always gave me grief. "Don't forget to get that family history, Doc Wilson" he'd snicker as we checked out the child's ear ache or sewed up a laceration.

The next year was dependent sick call and retirees. One day I was asked to see a 15 year old boy with abdominal pain. Physical exam and lab tests were normal except for a serum alkaline phosphatase level greater than 1050 U/L (nml 30 to 85). Actively growing children or patients with healing fractures may have two to threefold elevations. I prepared the family for a likely bone or liver cancer diagnosis. Fortunately, however, subsequent bone and liver scans, xrays and further blood tests were normal. Returning to the family history I asked: "Did anyone in the family ever have any bone or liver problems?" The mother recalled that her husband at the time of his discharge physical had to have a liver biopsy done. Eureka! The liver biopsy was done because he had an elevated alkaline phosphatase. The biopsy was normal. His repeat blood test at this time was still over four times normal. I contacted all the paternal relatives and their doctors strewn across the country finding significant elevations in several members of the father's family. Upon returning to Duke the next year to complete my training I had blood samples sent from the various relatives to confirm the elevations by tests done at one time in one lab. You have a copy of the article subsequently published in the New England Journal of Medicine (Nov 1979) and a comment about the article in the 1981 Year Book of Pathology. Benign familial elevations of alkaline phosphatase had not been previously described. Unfortunately there were no ways to Google the problem. There were volumes of medical references for each year and researching the topic involved hours in the med school library but hopefully it saves some patients from extensive workups and unnecessary worry as we learn that some genetic variations are not associated with clinical disease. I'm still glad I asked more about that Family History, Lonnie.

Over the past 30 years of practice a more common example of an apparently benign inherited lab test abnormality has been a modestly elevated CK in black families. Levels of 200 to 400U/L often prompt a consultation to rule out inflammatory muscle disease. Usually the patient is male, there is no objective muscle weakness, and neurologic investigation with EMG are normal, showing no signs of inflammatory

muscle disease. The literature says that some families with the apparent benign elevation of CK have family members more likely to develop malignant hyperthermia when given general anesthesia. Always ask about any of the family having unusual reactions when undergoing surgery. I have not detected any of these cases but see familial CK elevations one to two times yearly.

As we celebrate the 200th year anniversary of Darwin's birth we might further wonder about genetic makeup that relates to survival of the fittest or benefits natural selection. Huntington's disease is caused by a mutation that lengthens a gene known as huntintin, increasing the number of repeated sequences it contains. Levels of a protein p53 seem important; animals with the mutation develop the disease only if they make p53 protein. The intriguing observation among Huntington's patients has been a lower incidence of cancer and larger family size—survival benefits (Scientific American Feb 2008 "Disease for Darwinism"). In our modern society, sickle cell disease is related to severe complications with painful crises and vascular catastrophes which significantly alter or even shorten lives. How could this have been selected for? What happens to plasmodium vivax and other forms of malarial parasites in the sickled cell? They die and the life cycle is interrupted. Before the advent of antibiotics and public health measures for malaria, sickle cell trait had some advantages. Malaria remains a significant worldwide health problem, and there are some areas of the world where the sickle cell trait maintains a protective effect. The geographical setting has implications for the significance of genetic expression.

In academic medicine the caveat is: "Beware the doctor who has seen a case." However, when he sees two similar cases, he has an association and when 3 or more cases occur, he has a series. Unusual presentations of diseases raise special considerations. When a physician considers a typical case of lupus he pictures a young black female with rash often across the cheekbones and nose (malar rash) with patchy baldness, arthritis, and active renal failure. Almost 30 years ago I saw my first unusual presentation of lupus. TN presented as a 32 year old white male with lupus manifested by arthritis, skin rash and the rapid development of the complication of aseptic necrosis of the hips requiring total hip replacements . He died September 2002 with a very unusual presentation of lymphoma of the small intestine. A series of articles were published in the Archives of Internal Medicine December 1990. One study showed the risk of non-Hodgkins lymphoma (the type TN died with) was approximately 50% higher among Vietnam veterans. A few years later I saw EM a 46 year old white female nurse for followup of her lupus illness. Family history included a sister with rheumatoid arthritis. The patient's lupus presented as a skin rash when she returned from Vietnam in 1972 later manifested mainly by arthritis and inflammation of the lungs and heart (serositis and pleurisy) when I began seeing her in 1984. She died in December 1988 after sudden onset renal failure with heart involvement from lupus. JT was referred to me at age 42 with arthritis and an unusual skin lesion of his right lower leg. Again a white male with lupus that rapidly became fatal over a week's time with a bleeding complication of the lungs. I recently saw another of my unusual male patients with a connective tissue disorder—Sjogren's Syndrome. He is 62 now and has had a chronic course with joint pains and sicca (dry eyes; dry mouth) symptoms. Unusual presentations of diseases usually seen more often in females and usually in young black females. The morbidity and mortality were much worse than expected. Any connection? All were born in the early to mid 1940's, and as my peers, they all served in Vietnam with exposure to Agent Orange. The man with Sjogrens Syndrome remembers crawling through jungle brush with the Agent Orange dripping off the foliage.

One of my friends works as a rheumatologist in the VA hospital system. I tried to interest him in investigating this association in his patient population. I don't believe he was encouraged by the powers that be in the VA. Most of the published investigations have looked at the association of Agent Orange with cancer and none have looked at the association with connective tissue diseases. However, there is

an interesting book Home Before Morning—The Story of an Army Nurse in Vietnam by Lynda Van Devanter. In addition to an insight into the toll the war experience took on her emotional and mental character, in the Afterword to her book she describes the development of "an autoimmune, collagen vascular disease, which the doctors concluded was the result of exposure to toxic chemicals. Vietnam was the only place I'd ever had such exposure. " She became ill in November 1994 and died at age 55 in November 2002. She had a daughter in 1985 born with heart and intestinal defects possibly connected with chemical exposures in Vietnam. She knew several of her fellow nurses from Vietnam days who had children with birth defects. They subsequently, through government hearings, had legislation passed requiring the VA to provide assistance to children with birth defects associated with their mother's exposure to chemicals in Vietnam. Do these cases suggest a different mechanism triggering disease in genetically susceptible individuals? Chemical or other environmental factors as well as infectious agents may serve as triggers. As you may know there are several studies relating greater cancer mortality among workers exposed to dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin). One derivative of this chemical used as herbicides and insecticides (2,4,5-trichlorophenoxyacetic acid) was a constituent of the defoliant Agent Orange.

While the population of concern for Vietnam exposures that might trigger an inherited tendency for autoimmune diseases is dying out, the concept of chemical environmental triggers is suggested by further observations. In May 1981 denatured rapeseed cooking oil was found to cause a scleroderma-like disease in almost 1/3 of the exposed individuals in Spain. This was named the Toxic Oil Syndrome and was felt to be caused by anilides in the denatured oil. Scleroderma is one of the connective tissue diseases—a spectrum of diseases which include rheumatoid arthritis, lupus, polymyositis, Sjogren's Syndrome, and mixed connective tissue disease. Did the patients who developed the illness have a genetic predisposition expressed by exposure to the anilide? The illness had features typical for scleroderma including a (+) ANA test in up to 80% of patients early in the disease. In genetic investigations they found a higher incidence of human leukocyte antigen (HLA) DR3 and DR4 (remember the association with RA). In the review article (Seminars in Arthritis and Rheumatism Feb 1986) the authors in the discussion talk about other exposures felt to cause scleroderma-like syndrome: drugs such as bleomycin, injectable Talwin (pentazocine), cocaine, appetite suppressors (remember Fen-fen?), and silicone implants (remember my prior talk "Booby Trapped Plastic Angell").

A similar association was being found at about the same time—a condition called the Eosinophilia-Myalgia Syndrome (EMS). This condition also mimicked scleroderma and was fatal in a significant number of patients. Stopping the tryptophan and treatment with steroids was helpful in some, but once the condition was triggered it caused a persistent autoimmune disease in many patients. Over the counter tryptophan sold in the health food stores (remember, no FDA oversight on these supplements at that time) was helpful as a sleep aid, antidepressant, and PMS medication. In 1989 one company in Japan began to make the tryptophan for commercial use and altered one step in the purification process. Investigation revealed a contaminant of L-trytophan felt to be responsible for EMS. The similarity to the Toxic Oil Syndrome is remarkable and it is noted that aniline was used as an adulterant of the rapeseed oil implicated in TOS and a similar chemical, anthanalic acid, was used in the fermentation process used to produce the L-tryptophan implicated in EMS. So as early as 1990 (a nice series of articles on EMS and editorial are in the New England J of Medicine March 29, 1990) we had evidence that environmental triggers in genetically predisposed individuals included not only infectious agents but chemical and perhaps other environmental agents. Do you think our environment is more or less friendly as far as exposures today?

As the field of molecular genetics has advanced is there any mechanism to suggest the effect of such environmental triggers on the inherited human genome to account for these observations? Epigenetics may play a role here. Epigenetics may be defined as "a change in the state of expression of a gene that does not involve a mutation but that is nevertheless inherited in the absence of the signal (or event) that initiated the change (**Curr Biol** 2007)"or "nonmutational phenomena, such as methylation and histone modification, that modify the expression of a gene." Methylation of DNA is an increasingly studied mechanism. Errors in DNA methylation accumulate with age (remember our 1st observation of some genes more strongly expressed as we become older?). In colon cancer this mechanism is felt to be at work by DNA methylation affecting tumor-suppressor genes. In lupus we have appreciated for years the phenomenon of Drug-induced lupus. Medicines such as hydralazine and procainamide have been known to cause this disorder for years probably by DNA methylation of T cells. Of interest, the majority of patients will develop a (+) ANA test (lupus blood test) after several years on the meds but only a few develop clinical lupus. A marker for this is anti-histone antibodies; again related to epigenetic effects (methylation, acetylation, phosphorylation) this time affecting the chromatin (histone is a simple protein that combines with a nuclear acid to form a nucleoprotein). Even medicines specifically for the treatment of RA have been associated with causing autoimmune disorders as side effects. Penicillamine (Depen) can cause pemphigus, myasthenia gravis, and lupus as side effects in the rare patient. Even the new agent Remicade (infliximab), an injectable biologic agent, is associated with the development of ANA and drug-induced lupus at times. Like the question of autoimmune disease stimulated by exposures like silicone breast implants, while evidence does not merit a class action suit, I would still suggest that environmental exposures—both chemical and infectious can trigger autoimmune and other diseases in certain genetically susceptible patients.

Let me take you way back. In the fall of 1969 I started my medical school clinical rotation on the internal medicine service. Our mentor was one of the godfathers of medicine, Dr. Eugene Stead, Jr. He had an interesting training philosophy—you learned medicine by being there and there was a connection between authority and responsibility. The person who shouldered the responsibility for the patient had the ultimate authority. If the medical student worked up the patient and took primary responsibility for the patient, no one else could write orders on the chart. All flowed through the student—or intern if there was no assigned student. Consultants, residents, and fellows had to convince the primary physician to follow through with their recommendations for diagnosis and treatment. Great authority and a great teaching method. I remember my first patient in this rotation. RH was a 78 yr old black farmer from eastern North Carolina admitted with anemia and back pain; a tipoff for myeloma which he had. At that time there was a study by Dr. Michael Potter regarding the development of myeloma in mice induced by plastic injected intraperitoneally. As an aside, my first patient taught me a lesson in communication. As with any anemic patient, we asked him to "save his stools" so we could check for blood loss. As we stood at his bedside during my presentation to the attending, we noted a terrible smell. On inquiry, in his bedside table, wrapped neatly in toilet paper were 3 to 4 days of stool specimens. Lesson? Be careful what you ask for and you can never be too clear in your instructions. Now, years later we see the mechanism of chronic immune stimulation possibly underlying the development of lymphoma or plasma cell dyscrasias (JAMA 2008: "Anaplastic large-cell lymphoma in women with breast implants"). An intriguing article appeared in the September 22, 2008 Arch Int Med titled "Chronic Immune Stimulation and Subsequent Waldenstrom Macroglobulinemia". They found a 2-3 fold elevated risk of WM in persons with a personal hx of autoimmune diseases with autoantibodies and elevated risks associated with hepatitis, HIV, and rickettsiosis. More evidence for the association of autoimmune conditions and infection. We have known for years that patients with RA or Sjogren's Syndrome had an increased incidence of lymphoma, perhaps a sequelae of chronic inflammation and hopefully diminished in incidence with therapy for their inflammatory disease.

As Lewis Carroll wrote in Alice in Wonderland, "It just gets curiouser and curiouser." There are some worrisome caveats regarding your personal genetic information-- the information might be used by employers to avoid hiring someone with greater likelihood of certain diseases; the health insurance companies might use the information for exclusions of coverage or realize that it's all "pre-existing"; the lawyers will go beyond class action suits against silicone breast implants and Polident and realize that it's all your parents' fault—they are responsible for your genetic makeup and many subsequent exposures. But beyond this there is great potential for benefits.

Personalized medcine is a new discipline driven by human genome knowledge. Genome-wide association studies (GWAS) are now providing genetic markers for common chronic disorders including diabetes, heart disease, Crohn's disease, and several cancers. Immunogenetics and pharmacogenetic are already letting us individualize (personalize) drug therapies—for instance warfarin dosing for anticoagulation (NEJM); wiser use of azathioprine for arthritis or cancers; avoidance of statin –induced muscle disorders. There is an excellent editorial by Dr. Bernadine Healy (an academic medicine cardiologist who was the first female physician to head the NIH) in U.S.News & World Report April 14,2008 titled "The Infinite Variety of Humans." She points out the frustration of doctors "when insurance companies deny care over the phone or when faceless bureaucrats " affect the doctor's decisions based on "template care"—a probably unintended consequence of evidence-based medicine. Personalized medicine will allow us to consider what's special in that individual patient, because one size does not fit all. An example of personalized cancer care relates to how the array of genes affecting cancer become targets for drug design. Herceptin counters a gene found in20 to 30 % of women with breast cancer that makes it especially aggressive. For these women, the drug is lifesaving. For women without that gene, the drug would not be beneficial and expense and side effects of the drug would be avoided. Knowing early risks for disease can bring about targeted prevention and more personalized diagnostics and therapy. While awaiting the more sophisticated human genome studies, this rheumatologist has found it helpful to **ask the siblings as well as Aunt Clara.** In families where several members have RA it's important to know which medical regimens worked and which were not tolerated. The success or failure of one regimen in a sibling is a reflection of the familial pharmacogenetics and can direct your choice toward various meds and help avoid ineffective or meds that are not tolerated. I suspect this will apply to therapies in many other areas beyond rheumatology and oncology.

In the June 2007 **Arth&Rheum** journal, the author of an article titled "Are We at a Stage to Predict Autoimmune Rheumatic Diseases?" writes: "The capability of prediction will be valuable only if preventive measures can be adopted. Knowledge is accumulating to recommend avoidance of exposure to UV light, specific diet, avoidance of specific chemicals (silica, toxic oil and the like—add Agent Orange), use of specific contraceptives or vaccines, and..administration of vitamin D."While he is directing his comments primarily to rheumatic diseases, the concept of **prevention** is the goal of the evolving knowledge regarding clinical genetics. Immunogenetics allow us to recognize the various illnesses the individual is predisposed to. Can we modify the genome itself? This is difficult---as the old TV add used to say: "It's not nice to fool mother nature!" At least not yet; but hopeful for the future. Immunogenetics give us information for genetic counseling to hopefully avoid or better understand risks for future generations. Pharmacogenetics are already helping direct therapies. Some infectious triggers may be approached with vaccinations and some environmental triggers (meds or occupational exposures) may be avoided. Currently it is difficult to identify all the potential infectious or environmental triggers (which are probably constantly changing and increasing). So, to a degree, we are back to what we do—treat the phenotypic expression of your genotype---but hopefully with more

knowledge from family history and its genetic implications. But perhaps there is a way to **modify the expression of the genotype.**

I call this the **D-noument.** Come on, you know I wouldn't leave **D** out of this! **Immunomodulation** is a popular concept in rheumatology. We want the immune system to behave properly. That is, react strongly to prevent infectious diseases but don't overreact against self. For some time the early use of Plaquenil in the ANA (+) patient who did not fulfill diagnostic criteria for lupus or other distinct connective tissue disease was felt to decrease the patient's likelihood to develop an overt clinical disease. Now the combination of Plaquenil and vitamin D supplementation may be even more effective. I am now seeing patients whose followup ANA tests are negative. This is a very sensitive test with many false (+)'s but rarely false negative results.

Systemic Inflammatory Response Syndrome (SIRs) is being appreciated more frequently. Some have speculated that the mortality from Avian (Bird) Flu was related more to the excessive inflammatory response, which may have explained a greater morbidity and mortality in younger patients who produced the severe inflammatory response. Similar concerns were evoked once again with the swine flu outbreak initially in Mexico in April 2009. There is speculation that Vit D might modulate that response. I would love to know the vitamin D status of the children who had the sometimes fatal community-acquired MRSA. With the swine flu pandemic threatening, my grandchildren ages 3 to 6 take 2000 IU of Vitamin D daily in a gummy bear vitamin D preparation.

If we consider the complement system, the association of excessive inflammatory response following infection may be more understandable. The complement system is a cascade of reactive proteins forming part of the body's infection and inflammatory response mechanism. If a patient has an inherited deficiency of early components (C1, 4, 2, 3) there is a greater chance to develop an autoimmune disease such a lupus and a lesser increased incidence of infection with encapsulated organisms such as strep pneumoniae. On the other hand patients with inherited deficiencies of late components such as C8 and C9 have a greater likelihood to present with recurrent neisseria infections (gonorrhea and meningitis) and less frequently lupus. So in one small area of the genome the complement system influences inflammatory and infectious diseases.

While complement deficient patients remain a rarity, each year I will see the effects of parvo virus. Fifth's disease in children with fever and slapped cheek appearance is well known. The adult manifestation of parvo virus can mimic lupus. I was called to the ER 12 years ago to see a 36 yr old white male with lupus. Skin rash, severe polyarthralgias and polyarthritis had him essentially immobile and labs showed leucopenia, thrombocytopenia, and elevated sed rate. I remember the number of years ago because when I saw him he said, "Doc, I feel terrible. I feel like I'm 50 years old."—my age at that time. These patients often have a transient (+) ANA test and sometimes low complement levels. The infection-autoimmune story remains intriguing. They usually respond rapidly to low dose prednisone and are able to be tapered off over 4 to 6 weeks.

A more common problem is statin-induced muscle disorders—myalgias, myositis, sometimes rhabdomyolysis. The recent **NEJM** article discussed the frequently inherited tendency for this problem ("SLCO1B1 Variants and Statin-Induced Myopathy—A Genomewide Study" Aug 21, 2008). Several years ago my cardiology friend Dr. John Starr and I became interested in the role of vitamin D and CoQ to treat or hopefully avoid this problem. John will not start a statin in a vitamin D deficient or insufficient patient until vitamin D has been supplemented and CoQ (up to 400mg/day) added. We feel that it prevents some of these episodes and may allow subsequent use of statins in patients who require them but were

bothered with muscle symptoms on an initial trial. There was a subsequent **NEJM** article discussing a synergistic effect on muscle or vitamin D and coenzyme Q perhaps through a shared effect on glutathione reductase enzyme. A nice example of **modifying the genetic expression**. We may find that some therapies allow us to **substitute** a therapy and **avoid triggering** the problem. Some interesting studies over a year ago looked at the mechanism of action of statins such as simvastatin. They suggested that the mechanism of action was to increase the patient's vitamin D level. Was there any way a simple, cheaper vitamin with few or no side effects could substitute for the statins?

Again, observations from the rheumatologist's family practice give some clues. For over 50 years we have known that patients with RA, lupus, and probably most inflammatory disorders have an increased incidence of cardiovascular disease. We have felt that it related to the inflammation, and controlling this might decrease the cardiovascular problems. As you've seen over the last 10 or so years, cardiology has become more interested in the CRP (C-Reactive Protein). It's a measure of inflammation we've used in rheumatology for over 40 years. Last year at the national heart meetings the intriguing study came out by the Crestor makers, that even if your cholesterol readings were normal, if your CRP was elevated, you should take the statin. From the rheumatology standpoint it confirms that there's more to the story than cholesterol. A futuristic editorial asked if vitamin D might take the place of the statins (many drug companies trembled at the news). Stay tuned.

The most recent lesson in genetics from my practice involves a 75 yr old, white male retired minister seen with gait problems. He has mild tremor of the hands and I thought most likely represented the early onset of Parkinson's Disease. Neurologic consultation did not confirm the diagnosis. In follow up visit the patient mentioned that two daughters were diagnosed with Fragile X Syndrome manifested by primary ovarian insufficiency. I found this interesting and assumed that as a potential male carrier he would not have any clinical manifestations. Wrong. The November 26, 2008 issue of JAMA has an article "Testing for Fragile X Gene Mutations Throughout the Life Span." In December I ordered my first directed genetic test and the patient was identified as a carrier of the permutation allele in the FMR1 gene. The test analysis mentions that individuals with permutations are not expected to have clinical signs of Fragile X syndrome, although older men may develop neurological deficits, such as gait disturbances and intention tremor. Premutations in males are not expected to expand to full mutations in offspring. As in my patient's case the daughters are of normal intelligence but have ovarian insufficiency. However, full mutations have been noted to develop in their daughters' children. One daughter is undergoing genetic counseling and investigating a possible pregnancy. Interestingly the genetic disorder results in clinical disease through trinucleotide repeat expansions similar to muscular dystrophy (DMPK) and Huntington disease (HD). Of further interest, female carriers are at a higher risk for hypothyroidism (50%) of cases and fibromyalgia (42%). We need to **rethink the significance of carriers of genetic diseases** and **remember to ask about unusual disorders affecting children and grandchildren**. As the husband and wife authors Hagerman mention in their article..."Some clinicians might assume they will rarely if ever encounter one of these disorders; that assumption would be both false and unwise." A more standard rule in clinical medicine is: You see what you know. There are probably many encounters which are simply never recognized.

What does this mean to your own future phenotypic expression? Let's hope that the medical promise of clinical genetics does not get submerged in bureaucratic reaction to identity security (such as HIPPA and Red Flag Rules). First of all, you will be reading more and more about genetics. Try to find a recent issue of the NEJM that does not have an article related to genetics. The April 23, 2009 issue has several excellent editorials and a review article "Current Concepts: Genomewide Association Studies and Human Disease." Hirschhorn in his editorial comments: "The main goal of these studies is not

prediction of individual risk but rather discovery of biologic pathways underlying polygenic diseases and traits." Editorial by Kraft and Hunter echo this feeling in "Genetic Risk Prediction—Are We There Yet": "...the identified variants do not contribute more than a small fraction of the inherited predisposition." It should be exciting in the future to see the effects of this knowledge in areas of genetic manipulation of the genome and better genetic counseling. Pharmacogenetics are already proving useful as alluded to above. As pointed out previously, the value of prediction is in allowing preventive measures. I cannot think of anyone in a better position to practice preventive medicine than our primary care physicians. While I cannot predict that you will be routinely undergoing genomic mapping, I can surely predict that you will experience health care reform. Proposed health care reform through managed care, health insurance companies, and the government are better termed "health care restriction". At the end of confounding the ordering of tests and the prescription of therapies, decreasing or denying payment for services, or sticking our Medicare patients in the donut hole, yes, there will be health care savings---but don't mistake that for reform. That is bogus reform. True health care reform would be health care improvement and savings by disease prevention. This I see as a unique, key role for understanding family history and evolving clinical genetics. It addresses the questions of : What are you from? What has determined what you are now? What are you becoming? How do we modify these factors for your best health?

A RHEUMATOLOGIST'S FAMILY PRACTICE

EVOLVING CLINICAL GENETICS

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BEYOND THE DROSOPHILA

November 19, 2009

1. ID? 'Bout what? Phenotype/Genotype
2. Your star power
3. **Family History**—exposures and possible triggers that might affect the expression of the genotype
4. **Genomics**—study of functions and interactions of all genes in the genome, including their interaction with environmental factors.
5. Ask Aunt Clara—DTC testing
6. **Human Genome**—3 billion base pairs of chemicals that makeup DNA; 99% Human and chimpanzee DNA nearly identical (I hear Darwin chuckling); 99.7% base pairs identical in all individuals (Hello, Cuz). 10 million show variations (SNPs—single nucleotide polymorphisms); Commercial DTC gene testing looks at 1 million SNP variations—i.e. missing at least 90% of variation
7. Wellderly
8. **Familial association of autoimmune diseases and related conditions**
9. **Some genes become more strongly expressed as we get older**
10. **Infection may trigger off an autoimmune disease in a genetically susceptible host**; Over there, Over there. Navy Shigella and the B27 story
11. **Some genetic variations are not associated with clinical disease**
12. **The geographical setting has implications for the significance of genetic expression;** Huntington's chorea; Sickle cell disease
13. **Chemical or other environmental factors may trigger disease in genetically susceptible individuals**; Agent Orange; Toxic Oil Syndrome—Spain; Eosinophilia-myalgia syndrome and tryptophan
14. Ask the siblings; remember your children are related (Fragile X story)
15. **"D"-nouement**—immunomodulation; statins; flu; personalized medicine

Sir William Osler (1892) "If it were not for the great variability among individuals, medicine might as well be a science and not an art."

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LAM Light

July 1989
A newsletter for members of the Lynchburg Academy of Medicine
Vol. 3 No. 7

On My Mind

Roe, Wade and Gabler

Remember 9th grade biology? Detailed dissection of the preserved earthworm and dead Rana pipiens held a great fascination. Taxonomy introduced us to some semblance of organization in the animal and plant kingdoms. (King Philip Came Over From Greece Saturday). One thing which impressed me was the chemical analysis of the human body. Costwise, the combinations of carbon and hydrogen and nitrogen and many trace elements only amounted to about $2.00 (must be at least $20.00 by now).

Even more striking was the concept of elan vital — that is, the vital force of life. A drop of water from the aquarium with its array of microscopic organisms fascinated me. I was not repulsed as some classmates with thoughts of never swimming in the pond again, but rather was intrigued with the constant activity of microbes such as the paramecium or the slow oozing and plodding of the amoeba.

Fluke-like planaria in the aquarium were most amazing for their ability to be chopped into small pieces each of which could regenerate into a viable planarian. Surely, the cost of their body chemicals would be minute compared to ours, and yet only when put together and endowed with the vital force did these elements represent life. We could easily gather together all of the necessary chemicals and elements, but could never instill the elan vital.

Years later, I thought about this

"The years of medical school, internship and residency produced a more cynical view of the human animal. It was easier to concentrate on the vital signs, physiology and disease processes if you could return to treating the biologic animal rather than the entire person."

Continued on page 2...

MSV Notes

Survey points out physician concerns

by William H. Barney, M.D.

Several times this column has referred to the survey sent to all Virginia physicians earlier this year. Results now available make it possible to draw some conclusions.

Eleven thousand questionnaires were mailed, and to date 6,600 have been returned. The replies have been analyzed in three ways. The first 4,500, received by the established deadline, were sent to Chicago to be fed into the AMA computer. A smaller, but representative sample, was computer studied by MSV's own public relations firm. And finally, members of the Executive Committee of the MSV, with the help of our executive vice-president. read individually a number of replies along with some accompanying letters. The results of the three studies were very similar but the conclusion reached by AMA and MSV were somewhat different.

The major goal of the survey was to determine why MSV is losing support of Virginia physicians. Many concerns were expressed, i.e. not

continued on page 4...

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On My Mind

once again when reading about Dr. Albert Schweitzer in his book *Out of My Life and Thought*. Dr. Cully Lippard and I have been Schweitzer fans for some time. Schweitzer's concept of "reverence for life" was manifest in Africa while building the hospital at Lambarene. Schweitzer hated to destroy life, whether insect or plant life, in order to make way for the construction of his clinics, hospital and living area.

Cully Lippard and I became aware of our similar Schweitzer interests when I purchased his bust of Albert Schweitzer at a Doctor's Day luncheon soon after arriving in Lynchburg. "Object de arte" I told Sandra. "Keep it at the office," she told me. Those of you who have been to the office have seen Albert posed appropriately on the shelf of my credenza between patient gifts of a ceramic owl and eagle. This was surely the bargain of bargains at the silent auction. Cully still asks about "Albert."

College years complicated the 9th grader's ideas of biological life and high school student's idealisms of Albert Schweitzer. Sociology leanings and greater awareness of the world taught that human life was a composite of many things beyond the vital signs. Family and interpersonal relations, socioeconomic background, race and prejudice were great concerns. Rational decisions about family size, birth control and abortion could have profound future effects on family members achieving their full potential and maximum human development. It seemed most reasonable that Ibsen's Hedda Gabler should have had the benefits of rational decision and control over her own life when she found that she was pregnant. The Roe vs. Wade decision seemed to confirm this attitude.

The next years of medical school, internship and residency produced a more cynical view of the human animal. It was easier to concentrate more on the vital signs, physiology and disease processes if you could return to treating the biologic animal rather than the entire person. This was easier with attitudes expressed in the *House of God* when you treated "Gomers," "Turkeys," and "Dirtballs." It was self defense of our insecurities.

Internship reinforced the scientist's approach. July began with cardiology and CCU rotation. Every third night in the hospital to answer cardiac arrests often involved a sprint from the Baker House on call room (but you weren't asleep anyway with the anxieties and internship insecurities) to the CCU where the nurses handed off in relay style a 35-pound defibrillator and yelled directions to help you try and find Strudwick Ward in the next two to three minutes. Incredibly complicated patients happened to fall on the service I was assigned to — however, at the end of that month, I left the rotation and there had been no deaths.

Off to the rheumatology rotation with a welcome respite and probably an imprinting for future training and practice style — some seriously sick patients, but at the end of a month, no deaths.

Off to the VA for Neurology, with an array of myasthenia gravis and Guillain Barre problems — but after a month, no deaths.

The intensive care unit with its magnificent nurses beckoned next.

continued on page 3...

LAM Light

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2025 Tate Springs Road
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Phone: 804-846-6150

Editor:
Jeffrey W. Wilson, M.D.

Information may be called in or sent to
Mary Ann Tucker at the Academy office.

...continued from page 2

On My Mind

Some severely ill patients requiring respirators or peritoneal dialysis, one with total body failure whom we affectionately called "Crash," but with great resident supervision by the likes of Dr. Janet Hickman, at the end of the month — no deaths.

Next would be a general medical ward rotation at the VA. Had any intern gone through his medical internship year with no deaths? By golly, if they could get the patient to me alive, I knew I could keep him alive. Pride before the fall. A 35-year old man was admitted to me in acute renal failure, possibly a post streptococcal glomerulonephritis. A "great case." Arrangements underway to secure a bed on the intensive care unit where I would handle his peritoneal dialysis, a favorite procedure of mine (prior to joint injections). Could we have the bed? Fine, we will transfer him down in just a minute. "Dr. Wilson, stat to 7A ward."

Perhaps a uremic seizure followed by an arrhythmia-induced cardiac arrest—but, still, a young man with reserves of young physiology and young anatomy—surely we could bring him back. Forty five minutes later, and no response, the resident suggested that we stop the code. The vital force was gone. A humbling lesson that unfortunately has since been repeated too many times. You may balance the vital signs, the chemistries and the physiology, but there is much about the elan vital that should keep you in awe.

Pro-life, pro-choice, pro-fession, Roe, Wade, and Gabler. As a physician, I am left with more questions than answers.

Jeffrey W. Wilson, M.D.
Editor

MEDICAL INTELLIGENCE

INHERITED ELEVATION OF ALKALINE PHOSPHATASE ACTIVITY IN THE ABSENCE OF DISEASE

JEFFREY W. WILSON, M.D.

SERUM alkaline phosphatase activity was markedly elevated in a young man without an apparent underlying disorder. The unexpected finding of an elevated alkaline phosphatase level in the patient's father prompted an investigation of other family members.

SUBJECTS AND METHODS

A 15-year-old boy, 160 cm tall and weighing 41 kg, complained of abdominal pain. The results of physical examination and laboratory studies, including complete blood count, urinalysis and analysis of blood components, were normal, except for a serum alkaline phosphatase level greater than 1050 units per liter (normal, 30 to 85) (Bessey–Lowry–Brock method[1]).

Subsequent evaluation revealed normal values for liver function in routine tests, for activities of gamma-glutamyl transpeptidase, 5′-nucleotidase and leucine aminopeptidase, and for parathyroid hormone. A liver scan, a bone scan and radiographs of the skull, chest, hands, lumbosacral spine, pelvis and knees gave normal results. On repeat examination values of phosphatase activity were 1740, 2280 and 2040 units per liter. Alkaline phosphatase activity, determined by polyacrylamide-gel electrophoresis, was increased in liver and bone isoenzymes.

The patient's father had previously had an alkaline phosphatase level of 423 units per liter and a liver biopsy whose results were interpreted as normal. The level in a later liver-biopsy specimen was normal. Levels were obtained in the propositus, his father and members of the immediate family by repeat determinations, as well as in other relatives by their personal physicians, who used different laboratories.

RESULTS

The family pedigree and alkaline phosphatase levels are presented in Figure 1. Serum levels of alkaline phosphatase in the father, paternal grandfather and two aunts were two to four times the normal value, and were even higher in the propositus. The pattern suggests an autosomal dominant form of inheritance.

From the Division of Rheumatic and Genetic Diseases, Department of Medicine, Duke University Medical Center, Durham, NC (address reprint requests to Dr. Wilson at the Lynchburg Endocrinology and Rheumatology Clinic, 2000 Tate Springs Road, Lynchburg, VA 24501).

DISCUSSION

Twofold or threefold elevations of alkaline phosphatase activity normally occur during active skeletal growth or repair. Abnormal elevation in children may be associated with disorders such as polyostotic fibrous dysplasia, osteogenesis imperfecta, familial osteoectasia, hereditary osteolysis, bone malignancies, rickets, primary hypophosphatemia and cystic fibrosis.[2-4] These conditions are usually associated with obvious abnormalities detected by physical examination, chemical analysis of the blood or radiological studies. The elevations in this family were not related to any apparent underlying disease or familial disorder.

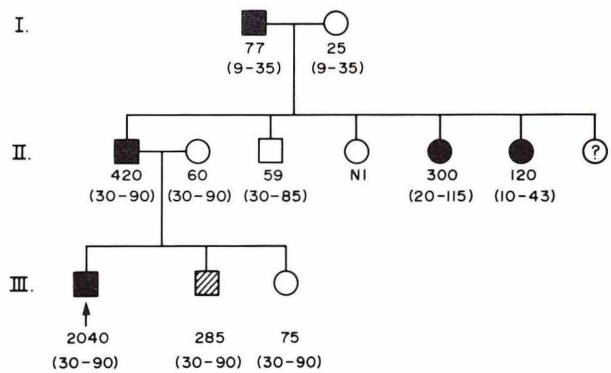

Figure 1. Family Pedigree and Serum Alkaline Phosphatase Levels.

Boxes and circles represent male and female members, respectively. Solid symbols indicate the members with elevated serum alkaline phosphatase activity, open symbols the members with normal activity, the circle with a question mark a member for whom no test result was obtained, the arrow the propositus and the crosshatched box a member with activity in the upper limits of normal for active skeletal growth. Below each symbol is the level of alkaline phosphatase (units per liter), with the normal range in parentheses (normal according to particular laboratory performing assay); NI indicates normal test result.

Previous investigators have studied variation in alkaline phosphatase isoenzymes in normal subjects, and found elevation of intestinal phosphatase isoenzyme in those secreting ABH and in those of B and O blood groups,[5-8] but the twofold to fourfold elevations of total serum alkaline phosphatase that occurred in this family were not noted. The propositus, who belonged to the A-positive group, had increased activity of liver and bone isoenzymes.

The description of this family demonstrates benign familial elevations of serum alkaline phosphatase in a pattern suggesting autosomal-dominant inheritance.

I am indebted to Edward W. Holmes, Jr., M.D., for suggestions in the preparation of the manuscript.

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301:983-984 (November 1), 1979

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in males whereas it is diminished in females. Although the mode of inheritance in the present family conforms to the autosomal dominant pattern, there is a paradox in that women members were more often affected, even taking into account their slightly higher age. The severity of the affliction in the women appeared greater than in the men in terms of the deformity and disability produced. More often, Dupuytren's disease in women tends to remain localized to the palm and so is less prone to produce deformity.

The systematic investigation of inheritance in Dupuytren's contracture is hampered by its frequency in the general population, by its late appearance in life, and by the variable severity of its clinical manifestations even within members of the same family. This study has confirmed once again the importance of heredity in the etiology of Dupuytren's disease. From a clinical standpoint, however, it would seem that the degree of penetrance of the gene is of at least equal importance to its transmission.

▶ [This kindred of Dupuytren's contracture through three generations shows dominant inheritance in the more severe expression in women. The possibility of X-linked dominant inheritance is suggested by the excess of affected females, but the occurrence of both affected and normal females appears to exclude it.—J. B. Graham] ◀

1–43 **Inherited Elevation of Alkaline Phosphatase Activity in the Absence of Disease.** Jeffrey W. Wilson (Duke Univ.) studied a boy, aged 15 years, who was 160 cm tall and weighed 41 kg. Physical examination and laboratory and x-ray studies were normal, except for a serum alkaline phosphatase level greater than 1,050 units per liter (normal, 30–85, Bessey-Lowry-Brock method); repeat alkaline phosphatase determinations gave values of 1,740, 2,280, and 2,040 units per liter. Alkaline phosphatase activity, determined by polyacrylamide-gel electrophoresis, was increased in liver and bone isoenzymes. The blood was of the A-positive group.

Serum alkaline phosphatase levels in the father, paternal grandfather, and 2 aunts were 2–4 times the normal value (Fig 1–21). The pattern suggests an autosomal dominant form of inheritance.

Twofold or threefold elevations of alkaline phosphatase activity normally occur during active skeletal growth or repair. Abnormal elevation in children may be associated with various disorders. The benign elevations in this family were not related to any apparent underlying disease or familial disorder. Reported studies of variation in alkaline phosphatase isoenzymes in normal subjects showed elevation of intestinal phosphatase isoenzyme in those secreting ABH and in those of B and O blood groups, but the twofold to fourfold elevations of total serum alkaline phosphatase that occurred in this family were not noted.

▶ [The genetic control of alkaline phosphatase is complex and poorly understood. Many genes, both structural and regulatory, are involved. This phenotype—autosomal dominant, elevated level of enzyme without evidence of altered structure, and absence of bone disease—suggests that it has resulted from mutation of a regulatory gene.—J. B. Graham] ◀

(1–43) N. Engl. J. Med. 301:983–984, Nov. 1, 1979.

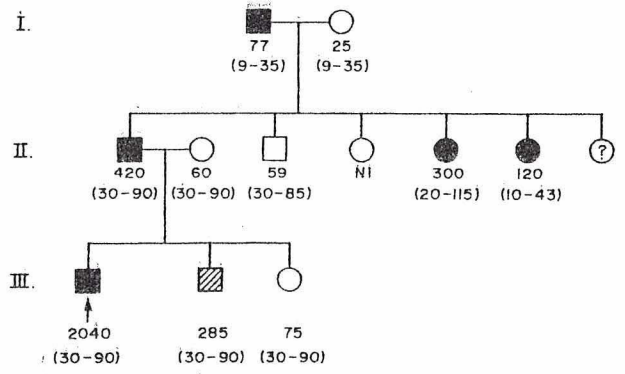

Fig 1–21.—Family pedigree and serum alkaline phosphatase levels. Symbols indicate the following: *boxes,* male members; *circles,* female members; *solid symbols,* members with elevated serum alkaline activity; *open symbols,* members with normal activity; *circle with question mark,* member for whom no test result was obtained; *arrow,* propositus; *crosshatched box,* member with activity in upper limits of normal for active skeletal growth. Below each symbol is level of alkaline phosphatase (units per liter), with normal range in parentheses (normal according to laboratory performing assay). NI indicates normal test result. (Courtesy of Wilson, J. W.: N. Engl. J. Med. 301:983–984, Nov. 1, 1979.)

1–44 **Aspects of Automated Chromosome Analysis: Different Representations of Banded Human Chromosomes and Their Cytogenetic Evaluation.** Chromosome analyses are expensive and time-consuming, and automation is needed to meet increasing demands for the analyses and to obtain quantitative data on variability in the hu-

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Vitamin D and H1N1 Swine Flu

In the September *Vitamin D Newsletter* produced by the Vitamin D Council (go to vitamindcouncil.org) several studies are summarized suggesting a role for vitamin D supplementation protecting our children during this Swine Flu outbreak. The finding of greater morbidity and mortality among younger patients was first noted with the Avian Flu. One cause was a suspected over-response of the patient's immune system after exposure to the virus. In rheumatology some researchers refer to this as the systemic inflammatory response syndrome. A similar mechanism probably is at play in the current Swine Flu. Vitamin D may help to prevent this.

Vitamin D deficiency is common among our children. Researchers at Johns Hopkins and the NIH studied 3500 American teenagers and found 75% to have vitamin D deficiency. Similar results were found in a study of 6000 children (ages one to 21) at Albert Einstein School of Medicine. Ideally, vitamin D levels should be checked in the children and vitamin D supplemented to achieve levels over 40 to 50 ng/ml.

With the shortage of Swine Flu vaccine recently reported in the national and local news consideration should be given to supplementation with vitamin D. With respect to the litigious nature of our society (one reason adequate vaccine supplies are not made in our country), I can only urge you to have your child's vitamin D level checked and treated as indicated. I will point out that my 3 grandchildren (two 6 year olds and one 4 year old) had vitamin D levels checked and all take a 2000 IU supplement daily in the form of a "gummy bear" preparation which they love.

Jeffrey W. Wilson MD

Lynchburg Rheumatology Clinic