University of Nevada, Reno

A Clinical Approach to the Complications and Diagnostic Methodology Associated With Pernicious Anemia

A thesis submitted in partial fulfillment
of the requirements for the degree of

Bachelor of Sciences in Biology and the Honors Program

by

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May, 2012

UNIVERSITY OF NEVADA RENO

THE HONORS PROGRAM

We recommend that the thesis
prepared under our supervision by

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entitled

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be accepted in partial fulfillment of the
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Bachelor of Sciences in Biology

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May, 2012

Abstract

Pernicious anemia is a type of anemia falling in the category of megaloblastic anemias – a group of anemias in which red blood cells are larger than normal. This type of anemia is characterized by a deficiency in Vitamin B12 – a vitamin necessary for the production of red blood cells. With successful treatment, pernicious anemia can be successfully managed allowing those who suffer from it to live with their diagnosis. However, if treatment is not sought, subsequent sequelae may ensue in the form of disease. Such sequelae include gastric cancer, neurological disorders, achlorhydria, and concomitant iron deficiency anemia. This paper will discuss the biological mechanisms and complications associated with pernicious anemia; specifically, the complications which have somewhat unclear mechanisms of occurrence. This information will be used to gain a further understanding of pernicious anemia.

Table of Contents

List of Figures

I. Introduction to the Condition

Deficiency Anemias – a deficiency in healthy red blood cells due to the lack of red blood cell building materials– are very common in the United States. They frequently are associated with deficiencies in Vitamin B12, folic acid, or iron ("Pernicious Anemia", 2010). The class of anemia known as megaloblastic tends to be slightly more severe if not treated upon the onset of early symptoms including fatigue, pallor, and light-headedness. This type of anemia can cause debilitation in the sense that it may be difficult for red blood cells to get from their site of production – bone marrow – into the blood stream. This debilitation results from a Vitamin B12 deficiency, preventing red blood cells from properly dividing, and thereby causing for these cells to become too large ("What is Pernicious Anemia?", 2010).

The term "pernicious" was given to this specific type of anemia when the disorder was first diagnosed in 1849 (Minney, 2010 and "What is Pernicious Anemia?", 2010). Pernicious means deadly – and this disorder was deadly before the advent of methods to deliver Vitamin B12 to patients with a deficiency. Pernicious anemia is a term reserved only for an autoimmune response towards gastric parietal cells. It is misused as being synonymous with B12 deficiency anemia that also causes a megaloblastic anemia. Thus, one can have a B12 deficiency anemia (due to poor diet) or a Pernicious Anemia that results in a B12 deficiency Anemia ("Pernicious Anemia", 2010).

As with other autoimmune disorders, pernicious anemia has a significant heritable component and thereby, has a genetic basis for inheritance (Banka et. al, 2011). Regardless of this genetic predilection associated with those diagnosed with the disease, pernicious anemia is easily treated with a prompt diagnosis. Treatment ranges in its

administration but can be as simple as providing patients with Vitamin B12 supplements. Over the counter supplements are not used – they must be delivered via intramuscular injections; using orally administered therapy is not an option ("Vitamin B12 Deficiency: Case Studies", 2009)

The reason that oral therapy is not a viable route of treatment lies in the biological mechanism of pernicious anemia. Vitamin B12 is found naturally in various common foods (poultry, eggs, dairy products, etc.) – making it unusual for healthy individuals to develop anemia from lack of B12 in their diet. The reason that oral therapy is not successful becomes much clearer when the method of absorption of Vitamin B12 is explored. In order to effectively utilize B12, a protein known as intrinsic factor (produced in the stomach) must bind to B12 when absorption occurs in the last portion of the small intestine. Pernicious anemia results when the body does not produce enough intrinsic factor due to an autoimmune response against gastric parietal cells (the cells responsible for producing intrinsic factor). Resultantly, it becomes evident that using B12 orally administered therapy would have no effect due to the immune-mediated destruction of intrinsic factor. To overcome this complication, B12 can be injected directly into muscle tissue, bypassing the absorption process of the small intestine and can thus be utilized effectively by the body. If the individual was simply B12 deficient, supplements via oral administration would work well ("Pernicious Anemia", 2010).

Clinically, it is fairly simple to evaluate a patient's symptoms for pernicious anemia. One of the main clinical presentations of most anemias is fatigue ("Vitamin B12 Deficiency: Case Studies", 2009). Although the differential diagnoses that accompany such non-specific symptoms may be numerous, the presence of fatigue provides the

trained clinician with enough grounds to further investigate using modern diagnostic tools. The main diagnostic method used is a complete blood count, colloquially known amongst physicians as a CBC. The results of a CBC allow the physician to identify gross changes in red blood cell morphology. Results that identify mean corpuscular volume (the measurement of the average *size* of RBC's) in excess of 100 femtoliters indicates that a macrocytic process is occurring ("Complete Blood Count: The Test"). A trained clinician would then be prompted to test for the two most common culprits of a macrocytic picture – Vitamin B12 and folate (Sowers). Performing a serum B12 level allows the physician to examine the quantity of Vitamin B12 in the blood. If this value is much lower than the acceptable value, then it becomes fairly clear that a Vitamin B12 deficiency may be the etiology of the disease. An additional test that can be used is known as a reticulocyte count – a test that checks for the presence of immature red blood cells. If the count is higher than normal in addition to the previously discussed findings, then anemia becomes more suspicious on an individual's list of differential diagnoses. Perhaps the most specific test for pernicious anemia is known as the Schilling Test. The Schilling Test tests specifically for Vitamin B12 absorption using radioactively labeled B12 and by checking for the presence of this radiolabeled B12 in the urine ("Schilling Test", 2011). It must also be noted that Vitamin B12 deficiency slows the conversion of methyltetrahydrofolate to folate – leading to a perceived folate deficiency and a phenomenon known as a methyl tetrahydrofolate trap. Additionally, a physician can test for the levels of gastrin – a protein secreted to stimulate release of gastric acid from gastric parietal cells. If the protein is elevated, then the gastric parietal cells in the body are most likely not functioning properly – whether it is from a weakening in the stomach

lining or autoimmunity. This process is elaborated on in the "Literature Review" section. If any of these tests come back positive, then the physician will administer a shot of B12 – first weekly, and then monthly. Diagnostic, as well as confirmatory, tests will be repeated after a duration of time to ensure that the problem was pernicious anemia ("Pernicious Anemia", 2010). These tests will be further discussed in the "Case Presentation" portion of this thesis.

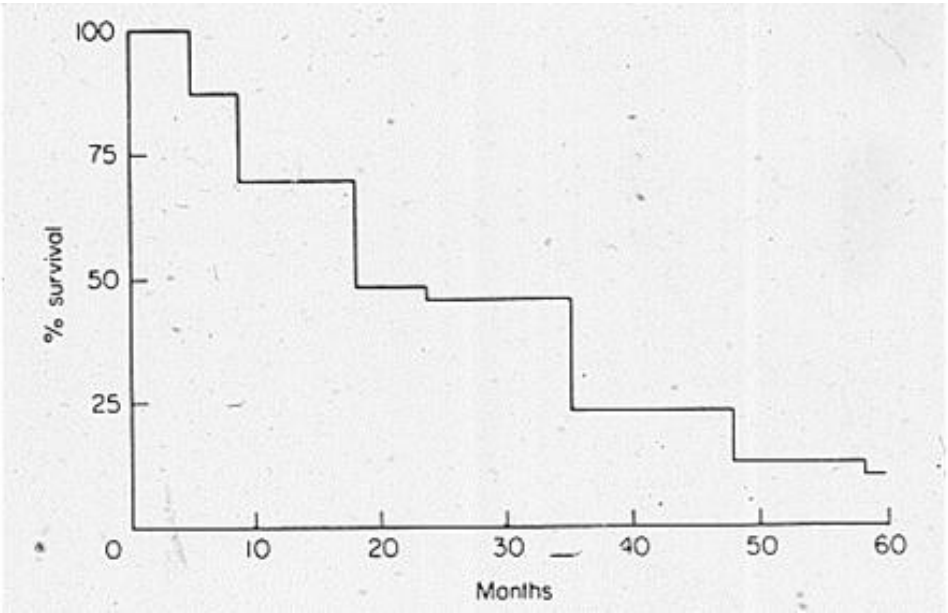
If not treated early, pernicious anemia can lead to a series of complications. Since a deficiency in red blood cells reduces the rate of oxygen exchange, this can instill many long term implications. Pernicious anemia is recognized to lead to both neurological problems and gastric polyps – abnormal growths on the mucosal lining of the stomach – which thereby increase the risk of gastric cancer ("Pernicious Anemia", 2010). The biological mechanisms of these sequelae will be explored in further detail in this paper.

II. Historical Background/Social Context

The term "pernicious" was given to this specific type of anemia when the disorder was first diagnosed in 1849 (Minney, 2010). Pernicious means deadly – and this was the case in several patients before the advent of methods to deliver Vitamin B12 to patients with a deficiency ("What is Pernicious Anemia?", 2010). A cure was accidentally discovered by the combined efforts of George Whipple, George Minot, and William Murphy from 1920-1926 (Minney, 2010). It was clinically observed by the aforementioned scientists that through ingesting raw liver, patients would receive iron and intrinsic factor which were necessary to absorb Vitamin B12. This method cured humans that had pernicious anemia, as they were replenished with the intrinsic factor that their bodies could not effectively produce. Conversely, there was a downside to this

discovery of ingesting raw liver – it took copious amounts of natural liver to cure these patients diagnosed with pernicious anemia. It wasn't until 1928 that Edwin Cohn came up with an improved solution. He was able to prepare a liver extract that was 50-100 times more potent than products coming from natural liver (Minney, 2010). This allowed for effective and efficient treatment of pernicious anemia. In 1934, Whipple, Minot, and Murphy won the Nobel Prize in Physiology and Medicine for their groundbreaking research in the treatment of pernicious anemia. Today, treatment has become significantly easier and does not require intrinsic factor at all. Rather, B12 is injected directly into muscle tissue to bypass the need of intrinsic factor during B12 absorption in the small intestine ("Pernicious Anemia", 2010).

Figure 1 shows the survival rate of patients with untreated pernicious anemia.



<u>Figure 1:</u> The survival in 321 cases of untreated Pernicious Anemia (Streiff, 2000)

If treated early, death as a result of pernicious anemia is highly unlikely as Vitamin B12 is readily available – in diet especially with the advent of food fortification.

Therefore, the name “pernicious” anemia is no longer accurate because with treatment, this disorder is not deadly.

III. Review of Literature of Complications Associated with Prolonged Pernicious Anemia

Pernicious anemia itself is not exceedingly harmful, if successfully treated. Nevertheless, if left untreated, it can lead to a series of complications that can cause severe problems. Untreated pernicious anemia has been identified to lead to gastric cancer, neurological damage, and achlorhydria. In the following section, these sequelae will be deliberated on in detail:

A. *Increased Chance of Gastric Cancer:*

A research team at the Denmark institute of pathology (Boysen et. al, 2011) has found suggestive evidence that gastric cancer associated with Epstein-Barr Virus (EBV) is more common amongst those with pernicious anemia than among those without it. This research was linked back to an original study in 1955 that claimed that occurrence of gastric cancer was more prevalent amongst patients with pernicious anemia (Zamchegk et. al, 1955).

The finding from the Denmark institute of pathology is likely due to the fact that pernicious anemia increases prolonged inflammation and causes a decrease in stomach acid. These symptoms make patients more susceptible to viruses such as EBV because stomach acid is normally vital to serving as a barrier to pathogens – including viruses. These complications in pernicious anemia patients result from the immune-mediated attacks on the cells in the stomach which secrete stomach acid, the gastric parietal cells discussed previously (Lahner & Annibale, 2009).

This study clearly shows that gastric cancer induced by EBV is more common in those with pernicious anemia. Since this study analyzed a vast database of pathology and cancer results in Denmark, this research has yielded solid conclusions that help explain the occurrences of complications of pernicious anemia. Nonetheless, this article emphasizes that further research must be done. Since it is not yet fully understood *why* those with pernicious anemia are more susceptible to gastric cancer, further exploration into the currently proposed mechanisms is important. In addition, this study showed that one very specific subset of gastric cancer, a type known as signet-ring cell carcinoma, is much more rare in those patients with pernicious anemia than those without this disorder (<2% vs. 21%).

B. *Neurological Damage:*

A primary study out of the Department of Neurology at the Mayo Clinic (Woltmann, 1919) suggested that pernicious anemia can lead to secondary degeneration of the nervous system through the formation of plaques on the posterior and lateral portions of the white matter of the spinal cord. However, it is delineated that pernicious anemia is unlikely to cause this nervous degeneration without the concurrent diagnosis of a different condition. One hundred and fifty patients were tested and it was seen that those with pernicious anemia in combination with leukemia, diabetes, Addison's disease, tuberculosis, and/or other conditions exhibited degeneration of the nervous system. This study is highly important to the field of pernicious anemia as it is one of the primary works of literature to illustrate the link between pernicious anemia and neural degeneration.

A novel study out of Johns Hopkins University Medical Center (Singer et. al, 2008), presented that a patient with pernicious anemia exhibited myeloneuropathy after the administration of an inhaled anesthetic – nitrous oxide – during a dental procedure. Myeloneuropathy is characterized by a neuropathy that affects the myelin sheath, a layer surrounding axons of neurons which is responsible for rapidly propagating a response. Figure 2 shows this neuropathy results from the lack of the conversion of homocysteine to methionine, a reaction normally catalyzed by Vitamin B12.

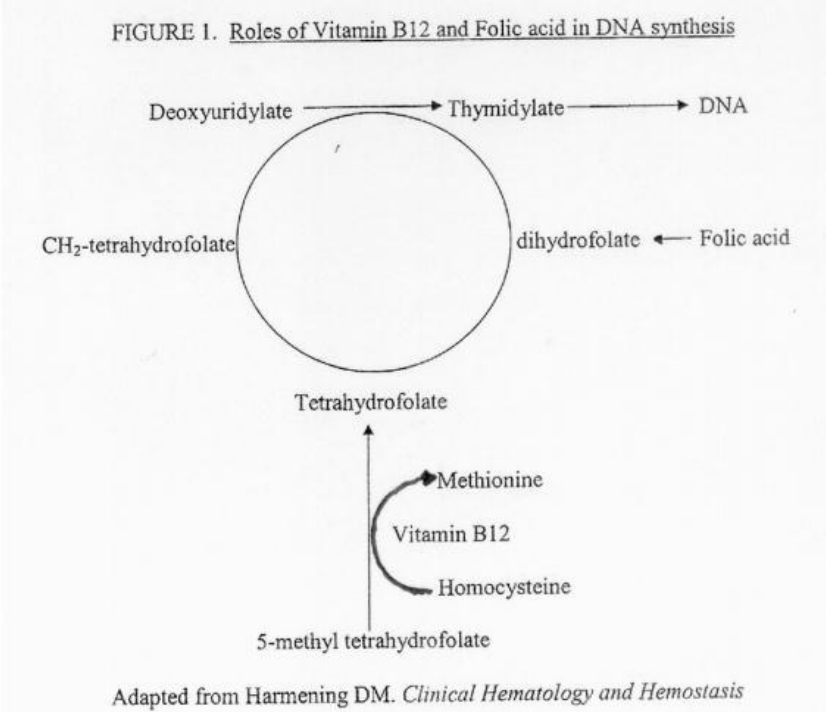


Figure 2: Role of Vitamin B12 in DNA Synthesis (conversion of methyl tetrahydrofolate to folate) and Neural Development (conversion of homocysteine to methionine).

The reason that nitric oxide triggered the myeloneuropathy is because nitrous oxide is known to irreversibly inactivate Vitamin B12 by oxidizing it. The combination

of a lack of Vitamin B12 absorption as a result of pernicious anemia and the inhibitory effects of nitrous oxide led to the neuropathy in this patient.

Symptoms of this neuropathy included weakness, cognitive impairment, and bladder dysfunction. In 4 out of the 16 patients studied, simply increasing levels of Vitamin B12 in the serum was sufficient to decrease neuropathy and resolve symptoms very quickly. However, in the rest of the patients, it took weeks to months and required early recognition of the symptoms, withdrawal of exposure to nitrous oxide, and copious amounts of Vitamin B12 to achieve similar results.

This article is significant because it illustrates that pernicious anemia, especially in the presence of nitrous oxide, can cause neuropathy to develop. The fact that increasing serum levels of Vitamin B12 causes relief and ultimate cessation of neuropathy demonstrates that the neuropathy *does* result from pernicious anemia mediated B12 deficiency. This is specifically due to the prevention of B12-regulated homocysteine conversion to methionine, an amino acid vital to protein synthesis. With this study, a clear mechanism for neuropathy as a result of pernicious anemia is delineated.

C. *Achlorhydria:*

A research team from the University of Pennsylvania School Of Medicine (Merriman et. al, 2010) has recently conducted a study that links pernicious anemia to a decrease in bone strength. They concluded that patients with pernicious anemia have a higher risk of getting a hip fracture. This is persistent even after having years of Vitamin B12 therapy. The mechanism that is responsible for this decrease in bone strength in pernicious anemia patients is chronic achlorhydria. Chronic achlorhydria is the state in

which the production of gastric (hydrochloric) acid in the stomach is absent or low. This leads to 3 pathways which are detrimental to bone strength and health: 1) increased Vitamin B12 *mal*absorption, 2) hypergastrinemia, and 3) calcium malabsorption.

Increased Vitamin B12 malabsorption is detrimental to bone health because Vitamin B12 plays an integral role in bone development. Vitamin B12 is responsible for maintaining osteoblasts, cells responsible for bone formation. Resultantly, when Vitamin B12 is not present, bone growth via osteoblasts is slowed significantly. This can lead to decreased bone mineral density and an increased fracture risk (Merriman et. al, 2010).

Hypergastrinemia is an increase in gastrin in the blood. Gastrin is a peptide hormone that is normally used to stimulate secretion of gastric (hydrochloric) acid from the gastric parietal cells within the stomach. However, in pernicious anemia, these cells are limited due to an autoimmune response. Therefore, gastrin cannot bind to gastric parietal cells and is resultantly seen in the bloodstream. This has been shown to cause hyperparathyroidism and increased bone turnover, both of which decrease bone health (Merriman et. al, 2010).

Calcium is absolutely essential for bone growth. Therefore, it is evident that calcium malabsorption is detrimental to bone health and growth – thereby increasing the risk of fractures.

Another highly interesting point that this research team brought up is that patients with pernicious anemia and achlorhydria exhibit notably similar symptoms with decreased bone health as patients who take long-term PPI's. PPI's are proton-pump inhibitors which decrease gastric acid secretion to control heartburn and acid reflux disease. A decrease in gastric acid is exactly what achlorhydria is. Therefore, the link

between pernicious anemia patients and long-term PPI patients is evident. As a result, the information found in this study can be implemented to try and prevent side effects that PPI-using patients may be experiencing (Merriman et. al, 2010).

Overall, it is appreciated that pernicious anemia leads to achlorhydria which consequently leads to the aforementioned 3 pathways that considerably decrease bone health. This study conclusively establishes a link between pernicious anemia and a decrease in bone health and an increase in bone fractures, despite treatment with B12. This is significant because it indicates that even though B12 is the primary treatment for patients with pernicious anemia, it does not necessarily effectively control against hypergastrinemia and calcium malabsorption, both of which decrease bone health. Therefore, the study suggests that those with pernicious anemia should continue to receive B12 supplements *and* make sure to have periodic bone density evaluations to check for bone health (Merriman et. al, 2010).

IV. Case Presentation

A. Subjective:

James Maximus is a 61 year old, Caucasian, Christian male who complains of fatigue, difficulty concentrating, slight loss of appetite, pale skin, and feeling lightheaded upon standing up quickly. He has been experiencing these symptoms for the past 4 months. His concerned daughter, Joanna Kim, has brought him in to see you, the general internist on duty.

The nurse on duty records his vital signs as follows:

Height: 6’3” **Weight:** 225 lbs. **BP:** 160/91

Temp: 98.7˚F **HR:** 79 bpm **RR:** 17 breaths per minute

BMI: 28.1

B. Objective:

Upon initial examination, you observe an elderly Caucasian male who appears to be well nourished and well developed in no acute distress except for notable pallor and exhibiting some of the symptoms described– fatigue, difficulty concentrating, decreased appetite, and lightheadedness upon standing up quickly.

History of Present Illness:

When asking of the patient's previous medical history, you find that he denies any recent weight loss, diarrhea, emesis, fevers, chills, diaphoresis, fecal incontinence, hematochezia, melena, dysuria, polyuria, hematuria, changes in visual acuity, diplopia, syncopal episodes, dysphagia, or any previous trauma.

Family History:

His family history is negative for any neurological or psychiatric disorders. The patient informs you that his father was diagnosed with Diabetes mellitus type 1 and his grandfather had rheumatoid arthritis, both of whom are deceased.

Past Medical History and Medications:

The patient is currently on medication to control his stage 2 hypertension – 5 mg daily of Lisinopril (an ACE inhibitor) for the past 3 years as well as occasional 600mg doses of ibuprofen (an NSAID) for periodic headaches caused during arguments with his wife. In addition, he is on Centrum Silver Men 50+ OTC multivitamins. He denies any allergies. He denies any past surgical history. He tested negative for sleep apnea after his

previous physician ordered a polysomnogram 2 months prior to his appointment with you.

Social History:

The patient denies the use of any cigarettes, tobacco, intravenous drugs, or illicit drugs and states that he consumes alcohol 1-2 X's a week. The patient states that he once worked as a hedge fund manager but is currently retired. His diet consists of coffee in the morning and chicken breast with vegetables for lunch and dinner.

Physical Examination:

HEENT: Normocephalic, atraumatic, no tumors, contusions or hematomas; notable pallor in the palpebral conjunctiva; Pupils equal, round and reactive to light, accommodate; Extra-ocular movements intact; Tonsils visualized with no exudates; No erythema present; Notable pallor in the oropharynx; Tympanic membranes clear.

Neck: Neck is supple with full range of motion; Nontender to palpation; No bruits are audible; No lymphadenopathy; No thyromegaly.

Back: No paraspinal tenderness upon palpation.

Lungs: Normal vesicular lung sounds bilaterally; Lungs are clear to auscultation bilaterally. No crackles, wheezing, or rhonchi audible.

Heart: Regular rate and rhythm. No murmurs, rubs, or gallops. No aortic or carotid bruits noted.

Abdomen: Nonprotuberant; Bowel sounds audible in all 4 quadrants; borborygmi present; Nontender to light and deep palpation; No organomegaly; no palpable masses.

Rectal: Rectal tone is normal; No rectal fissures, dilated varicosities, or excoriation.

Extremities: No pitting edema or cyanosis; normal capillary refill.

Integument: Pallor; no erythema.

Neurological: Cranial nerves: II – Visual acuity 20/30 in both eyes (not corrected). Normal fundoscopic exam. Normal visual fields with no detected scotoma.

III, IV, VI – Extraocular movments intact. Pupils equal, round, and reactive to light, accommodate.

V, VII, XII – Facial sensation is normal in the V-I, II, III distribution. Masseter strength is intact. No dysarthria noted.

VIII – Hearing is normal (not corrected).

XI, X – Gag reflex present.

XI – Muscle strength is present and is bilaterally equal.

Motor: Normal muscle bulk with high definition. Muscle strength with all muscle groups – 5/5.

Cerebellar: Normal exams – finger-to-nose, heel-to-shin, and rapid alternating movements.

Deep Tendon Reflexes: 4+; Negative for babinksi sign.

C. Assessment:

Based on the symptomology present, you suspect a possible anemia. You order a complete blood count (CBC) with differential

The following are the results:

CBC:	**Patient**	**Normal**
RBC	1.14 x 10^6/_l	4.7-6.1 x 10^6/_l
WBC	3.6 x 10^3/_l	4.8-10.9/_l
Hematocrit	12.7%	42-52%
Hemoglobin	4.4 g/dl	14-18 g/dl
MCV	111.4 fl	80-94 fl
MCH	38.7 pg	27-31 pg
MCHC	34.7 g/dl	33-37 g/dl
RDW	22.1%	11.5-14.5%
Platelets	76 x 10^3/_l	130-400 x 10^3/_l
MPV	9.3 fl	7.4-10.4 fl
Differential:	**Patient**	**Normal**
PMN	29%	39-68%
Bands	1	2-10
Lymphs	67	16-45
Monos	3	3-14
NRBCs/100 wbc	2	0

(Sowers)

After observing hypochromia (decreased hemoglobin), megaloblastic anemia (increased MCV with normal MCHC), leukopenia (decreased WBC), thrombocytopenia (decreased platelet count), you believe a megaloblastic/macrocytic anemia is the cause – the most common being either a Vitamin B12 deficiency or a Folate deficiency.

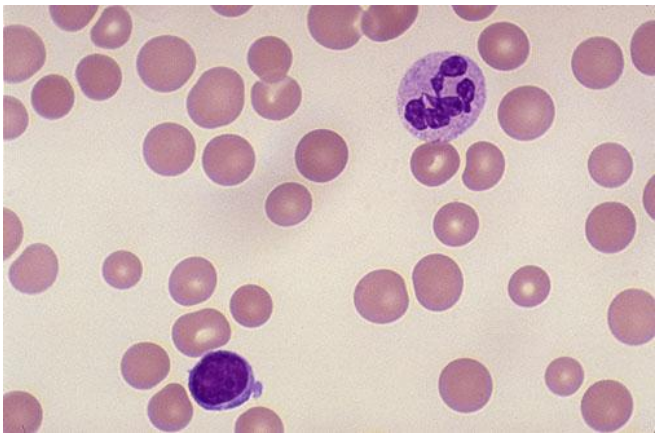
You order a reticulocyte count, a serum B12 test, and a blood smear to determine which type of megaloblastic anemia is present.

The following are the results:

Reticulocyte count:	**Patient**	**Normal**
Reticulocytes	2.6%	0.5-1.5%
Retic, Absolute	29.0 x 10^3/_l	22.5-88.5 x 10^3/_l
Retic, Corrected	0.7%	0.4-1.7%

B12/Folate Studies:	**Patient**	**Normal**
B12	<100 pg/ml	200-950 pg/ml
Folate	12.7 ng/ml	3.7-19.0 ng/ml

(Sowers)



(Aslinia et. al, 2006)

After observing an increased reticulocyte count, decreased serum levels of B12, and large/oval shaped RBC's on the blood smear, you confirm a *B12 deficiency* megaloblastic anemia is present.

Further Diagnostic Results:

To confirm and specify, you order MMA (methylmalonic acid) and Hcy (homocysteine) tests. The following are the results:

MMA: Patient: 0.6 µL/L Normal: <0/4 µL/L

Hcy: Patient: 18 µL/L Normal: <10 µL/L

Because the levels of both of these compounds were elevated, you confirm that the patient has a Vitamin B12 deficiency megaloblastic anemia. You recall that the patient's family history indicates the presence of autoimmune disorders.

You order an Intrinsic Factor Blocking Antibody test to test for pernicious anemia, an autoimmune form of macrocytic anemia.

The test comes back positive. The patient is diagnosed with **pernicious anemia**.

D. Analysis of Diagnosis:

With pernicious anemia, clinical diagnosis will be fairly straight forward. However, just like with any other disorder, there are numerous disease states that share symptomologies. In order to prevent these differential diagnoses from hindering the efficiency of a case study, multiple tests can be performed after preliminary symptoms are observed clinically. The main symptoms associated with pernicious anemia include: pale skin, fatigue, diarrhea, loss of appetite, loss of concentration, and shortness of breath.

The major tests used to diagnose pernicious anemia include a complete blood count (CBC), a reticulocyte count, a MMA (Methylmalonic acid) test, a Schilling test, serum levels of folate/folic acid and B12, and serum levels of gastrin present in the body.

In order to effectively declare the disorder as pernicious anemia, the CBC must note an elevated mean corpuscular volume, a depressed serum vitamin B12, and an elevated reticulocyte count (Cattan, 2011). The Schilling test is used to test for B12 absorption and is specific for pernicious anemia. First, 2 forms of B12 are administered – an intramuscular injection and an orally administered pill. The B12 from the injection is absorbed by body tissues, specifically the liver. Normally, the B12 from the pill will be absorbed through the G.I. tract and since the body already has its liver receptors for B12 saturated by the injection, much of the ingested B12 will be secreted in the urine – leading to roughly 8-40% radiolabeled B12 in the urine (“Schilling test”, 2011). Patients

with pernicious anemia cannot absorb B12 through the G.I. tract and thereby demonstrate <5% radiolabeled B12 in the urine in the first 24 hour urine study. The Schilling test can further be used to determine whether this decreased level of radiolabeled B12 in the urine results from a lack of intrinisic factor, a bacterial infection, or a deficiency in pancreatic enzymes. If <5% radiolabeled B12 is observed in the urine, and this decrease can be attributed to a lack of intrinsic factor, pernicious anemia is likely the source.

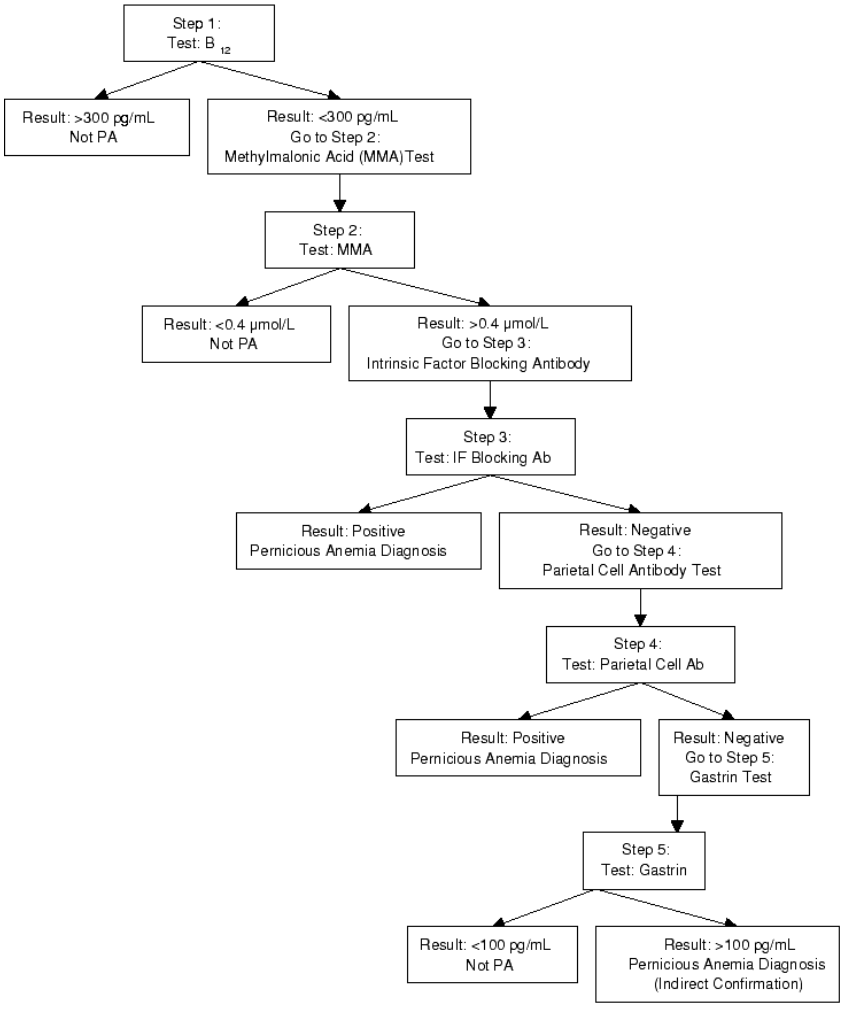
Furthermore, the levels of gastrin should also appear to be higher than usual. Additionally, the MMA test must show an increased level of MMA. According to Singer et. al (2008), "Cobalamin (B12) is required for… the generation of succinyl coenzyme A from methylmalonic acid." Since B12 is low in patients with pernicious anemia, it would be expected that this reaction would not occur as often, leading to a buildup of methylmalonic acid (MMA). It must also be noted that Vitamin B12 deficiency slows the conversion of methyltetrahydrofolate to folate – leading to a perceived folate deficiency, as seen in Figure 2 mentioned on Page 9. This deficiency is considered perceived because if an individual has a B12 deficiency due to pernicious anemia, this has no effect on their *absorption* of folate.

Furthermore, physicians can test for the presence of antibodies against intrinsic factor and/or gastric parietal cells by observing serum levels of these antibodies. If these antibodies are present, an autoimmune response is exhibited and pernicious anemia is likely the cause.

If all these aforementioned diagnostic criteria are met, there is a high degree of certainty that the patient has pernicious anemia. An additional and much simpler way to screen for a B12 deficiency is to administer a shot of B12 to the patient and if their

condition improves (less fatigued), it is particularly likely that an underlying B12 deficiency was the etiology of their symptoms. However, this method is not likely implemented in a clinical setting.

Figure 3 shows the simplified steps needed to diagnose pernicious anemia, without the need of the Schilling Test:



<u>Figure 3:</u> Diagnosis of pernicious anemia without the utilization of a Schilling Test with each step explained in detail above (Crowley).

Still, complications in diagnosis can arise. One example includes when testing for cervical cancer through a pap smear. Pernicious anemia can affect epithelial cells that line inner passageways (such as the vagina). As a result, if a female patient has pernicious anemia, she may get a false positive pap smear. This inaccuracy can be avoided if the physician already knows that the female has pernicious anemia by diagnosing it from the aforementioned steps.

E. Plan for Care/Treatment Plan

For pernicious anemia, the plan for care and treatment is considerably simple and depends on the severity. If detected early, the treatment is B12 injections into muscle tissue weekly for the first few months until blood levels of B12 are stabilized to between 200-950 pg/ml and then monthly injections from there on ("Pernicious Anemia", 2010). In addition to this, clinicians recommend taking other vitamins and nutrients that help in blood cell development – these include folic acid, vitamin C, and iron. The aforementioned treatment plans apply to low severity cases. In high severity cases where neurological damage or gastric cancer is present, protocols for those disorders must be followed and they are often immensely debilitating – since both of these complications involve difficult clinical treatment plans. For one complication though – achlorhydria, it was suggested that routine bone density evaluations are performed to ensure that patients are not at risk for bone fracture (Merriman et. al, 2010).

You explain to the patient that with this diagnosis, the patient must maintain Vitamin B12 therapy for the remainder of his life. You inform him that failure to do so may result in possible complications including neurological damage. You also notify the patient to notify his family members, as autoimmune disorders have a genetic basis.

You then start the patient on intramuscular Vitamin B12 injections – 2 doses of 1000 µg each week for two weeks, followed by monthly injections.

After the second week of injections, the patient reports that he is experiencing elevated levels of energy, increased appetite, and improved concentration.

When the patient returns one month later for his monthly injection, you order a CBC with differential and a serum B12 test to confirm that the patient's red blood cell and Vitamin B12 levels have stabilized. After reviewing the results, it is noted that the levels have significantly improved.

V. Discussion

Pernicious anemia is a disorder that results from an autoimmune response against host gastric parietal cells, leading to malabsorption of Vitamin B12. The mechanism for this malabsorption is well known and studied – an autoimmune response inhibits the production of intrinsic factor, which is vital for Vitamin B12 absorption. In addition, diagnostic methodology and treatment are fairly well established. However, the ambiguities of the mechanisms of the multiple sequelae of pernicious anemia remain. The goal of this thesis was to attempt to obtain research on these various complications and come up with preliminary methods of their means of occurrence.

In reference to one complication of pernicious anemia, gastric cancer, it was seen that gastric cancer associated with Epstein-Barr Virus is more common amongst those with pernicious anemia than among those without it (Boysen et. al, 2011). This finding is most likely due to the fact that pernicious anemia increases prolonged inflammation and causes a decrease in gastric (hydrochloric) acid production – since gastric acid is also produced by gastric parietal cells. These symptoms make patients more susceptible to

viruses such as EBV because gastric (hydrochloric) acid is normally vital to serving as a barrier to pathogens – including viruses. However, this study just expresses how EBV can easily make its way into patients – it does not show how gastric cancer is directly caused by pernicious anemia. The team who conducted this study calls for further research to attempt and establish more coherent and conclusive data.

In reference to another complication of pernicious anemia, neurological damage – specifically neuropathy – it was found that the lack of the conversion of homocysteine to methionine, a reaction normally catalyzed by Vitamin B12 causes this neuropathy (Singer et. al, 2008). In addition, it was observed to be aggravated by the induction of nitrous oxide, a common anesthetic. This article is highly significant because it demarcates a clear mechanism by which pernicious anemia acts to cause neuropathy.

Finally, in reference to a complication of pernicious anemia, achlorhydria, it was noticed that that pernicious anemia leads to achlorhydria which then leads to 3 pathways that significantly decrease bone health – 1) vitamin B12 malabsorption, 2) hypergastrinemia, and 3) calcium malabsorption (Merriman et. al, 2010). This study was an excellent contribution to this field of study as it established a conclusive link between pernicious anemia and a decrease in bone health. It also suggests that those with pernicious anemia should continue to receive B12 supplements *and* make sure to have periodic bone density evaluations to check for bone health. Previous to this study, this was not a method that physicians routinely implemented into their follow-ups on patients with pernicious anemia. Utilizing this information significantly increases patient care.

With the information presented in this thesis, the mechanisms of certain sequelae of pernicious anemia were established. This is highly beneficial to research as this information can soon be utilized to provide more effective patient care.

With courses ranging from an introduction to molecular biology to immunology, I have obtained the necessary background information to complete this thesis. With the culmination of the knowledge and understanding I have obtained through my undergraduate coursework, I have accomplished this arduous task.

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