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Volume 1 Issue 1

About EUMR

Mission Statement:

The mission of the Emory Undergraduate Medical Review shall be for Emory undergraduates interested in medical or health related careers to engage in scholarly discourse with their peers and medical professionals all over the country by producing semesterly hard-copy and online copy journals. The journal will feature summaries of medical research and medical opinion articles, including both undergraduate and higher degree possessing authors, and all articles are reviewed by MDs/PhDs. EUMR will also endeavor to put on educational events relevant to students interested in medical or health careers.

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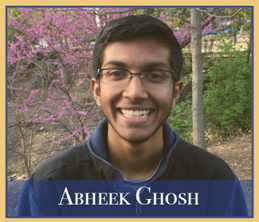
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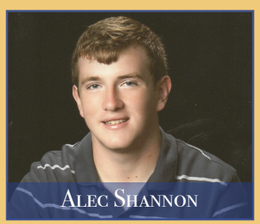
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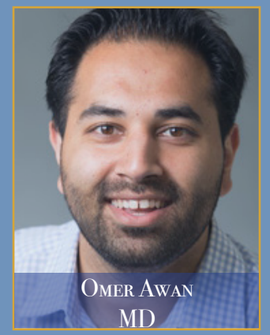
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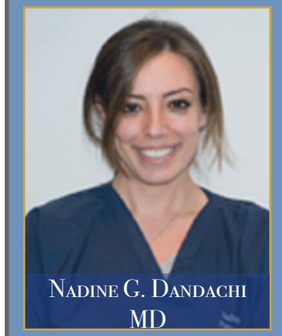
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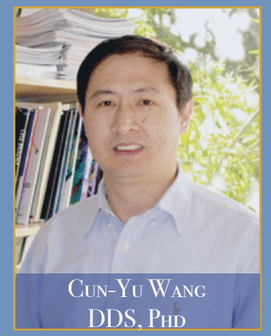
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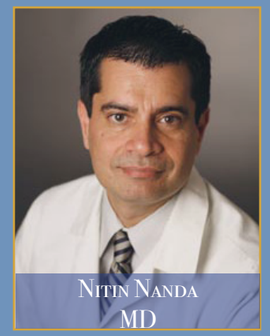
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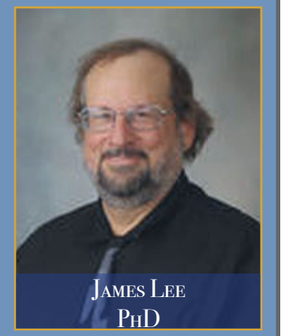
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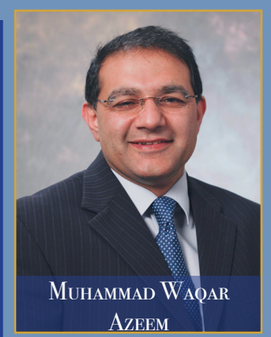
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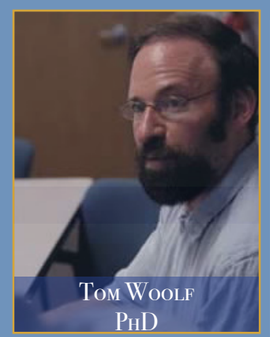
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Letter from the President

Dear students, professors, doctors, and science enthusiasts,

The Emory Undergraduate Medical Review (EUMR) presents its first issue written by executive board members themselves. The depth of topics ranging from synesthesia to global tuberculosis patterns will surely engage your analytical mind while encouraging you to continue your intellectual development in the biomedical sciences.

With our first issue, EUMR aims to clearly define its purpose: to keep undergraduates engaged with interesting and important topics in the medical world by publishing peer-reviewed student-written articles. EUMR is honored to have an Advisory Board of reviewers representing professionals from impressive research institutions around the country. The articles you will read come with both curiosity and legitimacy.

As I imagine EUMR's future, I imagine the scholarly discussion it facilitates to gradually expand across more campuses of undergraduates and scientists. The bridge EUMR creates between undergraduates and doctors can apply to many more institutions than just Emory. EUMR plans to further develop its presence on Emory's campus in the coming year while initiating new chapters at other institutions. Enjoy our first issue and please contact me if you are interested in involving yourself with The Emory Undergraduate Medical Review.

Cordially,

Maheen Nadeem
President of the Emory Undergraduate Medical Review

Letter from the Advisor

Hello, Welcome to the Emory Undergraduate Medical Review. In this journal, founded and run by Emory undergraduate students, you will be exposed to cutting-edge research in the biomedical field. Biomedical research is advancing at an unbelievable pace. Every week I read about new and exciting breakthroughs in the field. Here are a few examples of some of the hot research areas.

Genetics and Proteomics: Our understanding of the human genome and the functions of the proteins produced by those genes are advancing at an unprecedented rate. That basic science knowledge will lead to a much better understanding of human biology, but will also provide the necessary foundation for research into the underlying causes of human diseases and the development of new therapies for those diseases.

Epigenetics: It wasn't long ago that the field of epigenetics did not exist. We now know that variability in gene expression depends upon much more a person's DNA sequence. How those epigenetic differences impact a person's vulnerability to disease is an area of active research.

Bioinformatics: With the flood of new genetic information the need arose for a field that melds computer technology and genetics. Genome-wide association studies are now routinely used to determine whether there are single nucleotide polymorphisms in the population that are associated with a disease.

Personalized Medicine: As we learn more about how each person's genetic makeup affects their responses to drugs we can choose the right drug and the right dosage for each patient with greater precision.

Cancer Treatments: Breakthroughs in our understanding of the underlying biology of cancer cells is enabling more targeted approaches to seek out and destroy cancer cells instead of using the blunderbuss approach of traditional chemotherapy.

Nanotechnology: The field of nanotechnology may seem far removed from medicine, but it is not. For example, nanoparticles are being developed to specifically seek out, bind to and destroy cancer cells.

Prosthetics: The design and development of new prosthetic devices is advancing rapidly. Recently, the FDA approved Argus II, a retinal implant that restores some vision to the blind. In addition, brain-implanted neuroprosthetic devices, such as BrainGate, are being developed to help paraplegics and quadriplegics.

Neuroscience: This is another field that is exploding. Here are just two examples. The technique of optogenetics is quite new, but has already made a tremendous impact. Using genetic tools to make specific classes of neurons light-sensitive, scientists can now elucidate the function of neural circuits with unprecedented detail and control an animal's behavior just by turning on a laser. Functional Imaging. This technique enables us to study the functions of different parts of the human brain in ways that were unthinkable until recently. This has lead to a flood of new knowledge about brain function.

I hope that I have given you a feel for why research in the biomedical field is so exciting. I hope that you will at the very least read this journal, written by your fellow students, on a regular basis. But also realize that there are many hundreds of labs at Emory doing cutting-edge biomedical research. Reach out. You can be part of this exciting field yourself.

Sincerely,

Michael D. Crutcher, Ph.D.
Faculty Advisor, Emory Undergraduate Medical Review
Director of Undergraduate Research, Neuroscience and Behavioral Biology

Preventing the Next Epidemic:

Recent Advancements in the Fight Against TB

Authored by: Somnath Das

Edited by: Dr. Waqar Azeem, MD

The World Health Organization (WHO) recently released its 2014 Global Tuberculosis (TB) Report, and the document's conclusion was frightening. It asserts that while TB rates are declining, it "remains one of the world's deadliest communicable diseases" (WHO, 2014). The report goes on to say that the death toll from TB remains far too high if the WHO's Millennium Development Goal for 2015 of reducing TB incidence is to be met, and that healthcare gaps in developing countries are linked to "unacceptably low" treatment rates for Multi-Drug Resistant (MDR) TB. There are, however, signs of emerging hope in the scientific world that point to better outcomes for TB patients.

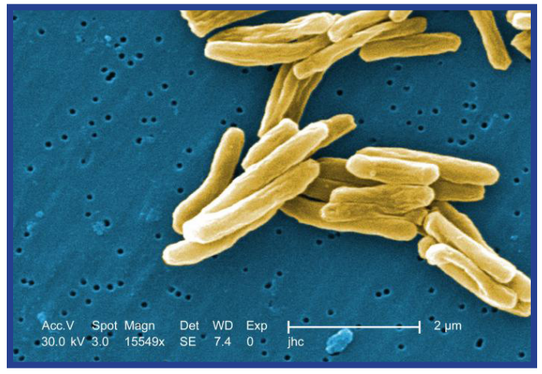

Figure 1. High resolution image of Mycobacterium tuberculosis captured using electron microscopy. (Source: CDC, 2013)

"Development and usage of successful medications have yielded mixed results. Historically speaking, Streptomycin used to be the drug of choice in combatting Mycobacterium tuberculosis, and it has seen modest success even in modern applications."

To many in the developed world, tuberculosis remains a disease of the past. The disease, which primarily affects the lungs, is largely on the decline in affluent countries, affecting less than 10,000 in the United States in 2013 (CDC). The 2014 WHO report states that globally, TB mortality fell by around 45%. This trend has largely been due to the development and distribution of antibiotics specific for the pathogen that causes TB in most cases: Mycobacterium tuberculosis. Screening has also played a huge preventative role, especially in medical areas where the disease could spread rapidly.

Development and usage of successful medications have yielded mixed results. Historically speaking, Streptomycin used to be the drug of choice in combatting Mycobacterium tuberculosis, and it has seen modest success even in modern applications. While the drug was clinically potent, the need for combination therapy arose as the drug usage gave rise to different strains. Other drugs, such as isoniazid and pyranizamide, were developed, but it was the introduction of Rifampicin that saw the dramatic reduction of TB treatment times (Zumula, Nahid, & wthe first line of drug-sensitive TB, but the drug itself presented some challenges. For example, Rifampicin has been shown to inhibit antiretroviral drugs which is a major problem for those suffering from both HIV and TB.

One of the current methods scientists have considered in the context of new treatment options is the synthesis of an effective TB vaccine. While there are vaccines available against TB, Michael J. Brennan argues that "[they] are inconsistent in protecting against the predominant adolescent or adult form of TB, notably pulmonary or lung-TB" (2012). This report was particularly interesting in that it asserts

TB Incidence in the United States, 1953-2013
TB Cases and Case Rates per 100,000 Population

Year	Number of Cases	Rate
2013	9,582	3.0
2012	9,945	3.2
2011	10,517	3.4
2010	11,163	3.6
2009	11,520	3.8
2008	12,895	4.2
2007	13,282	4.4
2006	13,727	4.6
2005	14,061	4.8
2004	14,498	4.9
2003	14,835	5.1
2002	15,055	5.2
2001	15,945	5.6
2000	16,309	5.8
1999	17,499	6.3
1998	18,287	6.6
1997	19,751	7.2
1996	21,210	7.9
1995	22,727	8.5
1994	24,205	9.2
1993	25,103	9.7

Figure 2. Recent data shows that in the past decades, TB rates are largely on the decline in developing nations. Figurec collected by the CDC have shown that the incidence of TB in the United States has lessened significantly over the past 20 years. (Modified from: CDC, 2014)

that there is no current vaccine blueprint for the development of TB vaccines. This is due to the fact that there is no credible biomarker for vaccine success. Brennan's report points to IFN-γ, a signaling molecule in the immune system, as a possibility; however, he states that it "appears to not be a useful biomarker in protection." According to Brennan, current research has produced as much as fifteen candidates for potential vaccines. However, the need for an essential biomarker, as well as for funding and implementation, remains at large.

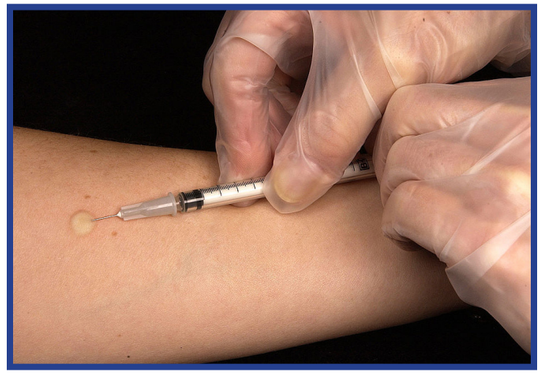

Figure 3. The PPD is a TST commonly used to test for infection. While it has been effective at keeping TB incidences down in hospitals and other healthcare areas, the test is not holistic enough to be a true incidence detector of TB. (Source: CDC PHIL, 2003)

"When compared with Western medicine, Chinese therapies provide a fascinating take on how certain doctors treat disease and can prove to be much more potent in pathogen clearance in some cases."

Consideration of multiple treatment options for TB has been fairly broad, ranging from immunotherapy to Chinese herbal remedies. Xia Zhang and Jing Guo wrote about the latter in their 2012 report. Their report found that Garcilin, a compound synthesized from garlic, has been proven to inhibit TB proliferation. Chinese therapies have not only been useful in the treatment of drug resistant TB but have also played a role in reducing the negative side effects from TB drugs. An example cited in the report was about how "Pulsatilla chinensis can suppress the hepatotoxicity of rifampicin and isoniazid and thus plays a protective role for the liver." When compared with Western medicine, Chinese therapies provide a fascinating take on how certain doctors treat disease and can prove to be much more potent in pathogen clearance in some cases.

New drugs are also constantly emerging. While there are numerous antibiotics available for the treatment of drug-sensitive TB, there are still many challenges ahead in the context of anti-TB drug synthesis. In the 2013 report "Advances in the development of new tuberculosis drugs and treatment regimens," Zumula state:

> "In addition to a fully validated safety profile, there are a number of other factors that a new TB drug should fulfill: be more potent than existing drugs in order to reduce the duration of therapy; should inhibit new targets so that MDR-TB and XDR-TB [extensively drug resistant Tuberculosis] can be treated…and show no antagonism to other TB drugs or drug candidates so that a regimen comprising at least three active drugs can be constituted." (Zumula, Nahid, & Cole, 2013.

Many former TB drugs have been repurposed for new strains of TB according to this report; however, Zumula also points to the rise of new antibiotics that have yielded compelling results in clinical trials.

The review particularly highlights a class of compounds called Benzothiazinones in their effectiveness against TB, which Zumula labels as "the most potent inhibitor of M. tuberculosis ever described." An example of a drug in this class that has yielded results similar to the widely used Rifampicin is BTZ043. This drug in particular shows promise because it works against drug-resistant TB strains and has shown no antagonism to other common TB drugs in clinical trials. The drug works by inhibiting DprE1, an enzyme that catalyzes compounds necessary to form mycobacterium cell wall components. Zumula praises anti-DprE1 drugs' potential, going on to report that, as of 2012, these drugs are in preclinical development.

Another critical aspect towards halting TB infection propagation is diagnosis techniques. Payam Nahid highlights this in his 2006 report: "Although truly major advances that would revolutionize TB diagnosis and treatment have not been realized, we are beginning to see the innovations that have been prompted by the recognition of the economic potential of the market for new diagnostic tests and treatments for TB[…]" Traditionally, a simple TB skin test (TST) was used in order to detect past infection and was often used to screen medical personnel for latent infection. While the tests have been effective in this respect, Nahid specifically points out that TSTs are very limited in scope and can produce false positives (Nahid, Pai, & Hopewell, 2006).

Nahid's report goes on to highlight an emerging type of TB test called the Interferon-γ (IFN-γ) assay (IGRA). In immune cells, interferon plays a critical role in the immune response to antigens by acting as a cytokine, a signaling molecule. By stimulating white blood cells with M. tuberculosis and measuring

their IFN-γ secretion, scientists can see which cells are specific for the pathogen. Madhukar Pai also reviewed this assay in 2008, concluding that the test has an "excellent specificity" and was unaffected by TB vaccines that cause a false positives in TSTs (Pai , Zwerling, & Menzies, 2008).

"In the context of IGRA assays, Pai points out that the assays do not directly detect the pathogen itself; rather, they aim to detect a remote immune response to a subsequent restimulation by pathogenic antigen. Therefore, there is significant room for outcomes that are contradictory to what a patient may be experiencing."

Pai's report does bring up some interesting caveats for the usage of an IGRA in the detection of TB. As stated before in the discussion about vaccines, there is no current credible biomarker of TB protection yet to be identified by researchers. This fact presents a problem both in vaccination and latent infection detection. In the context of IGRA assays, Pai points out that the assays do not directly detect the pathogen itself; rather, they aim to detect a remote immune response to a subsequent restimulation by pathogenic antigen. Therefore, there is significant room for outcomes that are contradictory to what a patient may be experiencing. Pai credits this error to the lack of a "gold standard" for TB: a credible blueprint that scientists can base TB diagnosis and models of pathogenic proliferation off of.

While the rate of TB-related deaths is declining, scientists and public health officials remain cautious about stating its status as an eradicated disease. Its global mortality rates are falling, but there seem to be trends in data that indicate drug resistant strains are on the rise. The countries in which TB rates are the highest are often developing ones, meaning that critical healthcare gaps pave the way for additional problems for those battling the disease. Scientists have worked tirelessly to provide potent drugs and procedures to combat the disease; yet, as literature shows, the need for a credible TB "gold standard" remains to be seen. Thus, the eradication of TB is at its final frontier: an attainable goal that requires much to be done.

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Bionic Bioinformatics:

The Power of Computation in Medicine

Authored by: Lindsay Hexter

Edited by: Ben Langmead, PhD & Tom Woolf, PhD

Bioinformatics has emerged as a field of its own, enhancing biomedical research with computational power.

"The wealth of information now available, as a result of widespread next-generation sequencing (NGS) technology, is both a burden and a blessing; genomic data has numerous applications in the medical field, but it can also be overwhelming if not handled with appropriate techniques."

The wealth of information now available, as a result of widespread next-generation sequencing (NGS) technology, is both a burden and a blessing; genomic data has numerous applications in the medical field, but it can also be overwhelming if not handled with appropriate techniques. As this branch of research grows, however, the significance of sequence analysis has become more prevalent with the help of computational methods (Willet & Wade, 2014). Specifically, it can be used to identify mutation hotspots, or sites where a mutation is more probable to occur based on previous genomic analysis. This leads to new ideas for how genomic information,

Figure 1. FASTA format of a sequence is arranged as such, with an identifier at the beginning, followed by a short description and the sequence.

bioinformatics, can lead to improvements in human health, what I feel can be called "Bionic Bioinformatics."

Proteomics is the study of protein sequences, rather than the study of genes that code for them. This area grows from the genomics analysis and is now strongly connected to extracting meaning from the primary sequence data, especially because this budding field has applications in oncology and evolution. A reference genome must be obtained before fully analyzing a new genome; it has DNA representative of a species, so that variants in the targeted genome can be compared to the template genome (Willet & Wade, 2014). Next, researchers can tackle analyzing the new genome with a variety of approaches. This can then be narrowed further to focus solely on analyzing protein sequences that arise from specific genes of interest.

To show an application of this technology, I will describe a project I worked on at Johns Hopkins University that involved using computational approaches to study the genetics of cancer. I entered into this exciting new field under the supervision of Yanif Ahmad and Ben Langmead from Computer Science and Tom Woolf from the Medical School. With other faculty, Dr. Woolf has been studying a system that concerns the control of PIP2 and PIP3 levels in biomembranes, so per his suggestion and with my interest in the system, I began researching this topic as well. I studied the proto-oncogenes PTEN and PI3K that code for enzymes regulating PIP2 and PIP3 levels, which have major implications in human health and cancer research. These proteins are involved in regulating cell growth, metabolism, and survival. PTEN is a tumor suppressor gene, while PI3K stimulates cell growth; mutations in both of these proteins can trigger the formation of a malignant tumor with the potential to metastasize, so studying changes in these two particular genes is one of many important directions that cancer research must follow. The mammoth amount of data available on these genes from databases like NCBI, SwissVar, and COSMIC was compiled into a SQL database using Python scripts.

SQL, or Structured Query Language, is a type of programming language used for the special purpose of managing data. Adding data using this technique is essentially like creating a table, with as many classifiers as desired. For each mutation acquired, I added classifiers to the database that included the gene, organism, FASTA, amino acid sequence, variant type, description, mutation, date retrieved, and database. The description is important because it relates to the pathogenicity of the mutation, such as whether it is cancerous or if it is prone to cause another disease. FASTA is the format in which protein or nucleotide sequences are arranged; the top line is an identifier, while the lines below make up the actual

sequence. Therefore, the significance of computation is highlighted here because an enormous amount of data was contained to a much smaller and more manageable database that was relevant to a specific topic.

Predicting mutations in human sequences is based not only on existing knowledge of human mutations, but also on those of animals; thus, looking

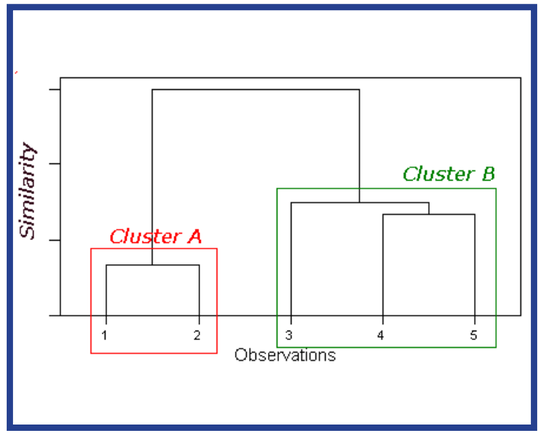

Figure 2. This figure is an example of how groupings in a dendrogram are arranged; items that are closer together become one cluster, and therefore a hierarchy of clusters can be created based on distance.

at evolutionary relationships was also key because the more similar two sequences are, the more DNA has been conserved in the evolutionary process and the more likely the mutations will be the same. Because the type of organism was included in the classifiers on each protein sequence, analysis could be specified to test particular organisms against one another; for example, a test could be run on solely human sequences, or it could compare human and mouse sequences. These tests are performed using sequence alignment tools; in this project, two sequence alignment tools, MUSCLE and BLAST, were utilized to compare the similarity of two sequences. Computation is so important here because comparing two sequences manually would have taken an exponentially longer amount of time. Programs like these can then lead to percentages of similarity that can be used to create dendrograms and phylogenetic trees. A phylogenetic tree shows the evolutionary relationships among different species; in conjunction with dendrograms, which are structures to represent evolutionary distance, this tree would provide depth to the search for mutation hotspots. Bioinformatics can thus connect different themes in biology, allowing for a holistic approach to problems that can be rooted in genomics.

"The significance of computation in general relates to the incredible efficiency of completing tasks that would be impossible manually."

Another unique feature of computation is machine learning, which is teaching a computer how to classify something based on a training set of data. The machine will attempt to classify the data and then record its accuracy score by comparing its own results to the expected classifications. When these accuracy scores are good enough, researchers can use computers to lend insights on new, unclassified data. Hence, computation has the potential not only to support and organize existing knowledge, but also to draw new conclusions about previously uncategorized data. The machine-learning tool I used is called Weka, which is a collection of machine learning algorithms written in Java. The problem posed with this tool, however, was its incompatibility

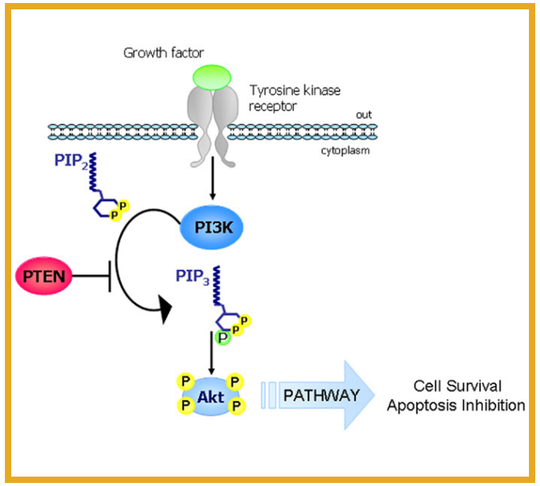

Figure 3. This pathway shows the interaction among PTEN, PI3K, PIP2, and PIP3. PTEN is a tumor suppressor gene that regulates the signaling of PI3K; in turn, PI3K causes PIP3 to activate AKT, which then phosphorylates substances in the cell that regulate metabolism, survival, growth, and other functions.

with the database of PTEN and PI3K sequences; once translated to the correct file, specifically from a database SQL file to a CSV (comma separated variables) file, tests could be run on the data; a great option in this tool is to run analysis on data based on particular classifiers. The description, for example, could be used to compare the similarity of certain sequences. Furthermore, if the goal was to compare evolutionary relationships, the similarity algorithms could be run specific to the classifier "organism," using the cluster algorithm in Weka. A cluster is defined as sequences that may be related; thus, clusters of evolutionary 'close' sequences can be obtained, which can indicate important pathogenic information. Because of the wealth of data available from the recent peak in genomic sequencing,

however, there are so many sequences that have not been tested for their significance in diseases. These unclassified sequences can then be put into a database and tested against known pathogenic sequences, which may lead to mutation predictions. Machine learning, coupled with sequence alignment tools, is consequently a very practical way to predict what mutations are likely to occur, and their implications in pathogenicity.

The significance of computation in general relates to the incredible efficiency of completing tasks that would be impossible manually. The consequences of genomics, though, also have applications in medicine. Informatics technologies, as they have become increasingly cheaper, allow for genetic profiling as a new tool in disease treatment. It could be applied to genetic disorders, oncological analysis, and pharmacogenomics screenings. In the first case, exome analysis can be used as much more manageable data to find mutations and define the genetic disease of a patient. In the other two cases, therapy can be specified based on the "individual's genetic ability to metabolize" certain drugs, so that money will not be wasted on treatments that are statistically improbable to work (Yu, 2014). A really interesting application of informatics is psychiatric genomics; a greater understanding of neuropsychiatric disorders allows for more effective treatment, similar to with genetic disorders (Alawieh et al., 2014). The pathophysiology of diseases can be determined by combining pathogenic associations of certain genes, studying gene regulation, and using proteomic analysis (Alawieh et al., 2014). The result of this can lead to insights about predisposition, severity, and relapse of a disease (Alawieh et al., 2014). Therefore, incorporating computational techniques into clinical diagnoses can enhance treatment and provide for better and more specific healthcare.

"Increasing knowledge of evolutionary relationships could also enrich medicine, as information about mutations in other organisms might parallel those in humans to provide a whole new background of genetics to disease treatment."

Computational biology has the potential to revolutionize many branches of medicine, as techniques previously unfeasible have become possible. Informatics conveys its own problems, however, since the sheer amount of data now available must be categorized and analyzed in some way, in order to be useful. The power of computation might give a genetic background and understanding of disease, allowing for more precise and less costly treatment. Increasing knowledge of evolutionary relationships could also enrich medicine, as information about mutations in other organisms might parallel those in humans to provide a whole new background of genetics to disease treatment. This new approach to diseases relates to the bigger picture that is the interconnection between biology and computer science; with advanced technologies applied to biological concepts, health problems can be solved and research can be greatly enhanced.

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Parkinson's Disease and the Art of Tango

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Edited by: Cory Labreque, PhD

Beyond the steamy, sensual stereotypes that Hollywood often depicts in film, tango is a rather more intimate dance that originated from the somber roots of Argentina. Interestingly, perfecting the art of tango demands more than pure athleticism. One must also embrace inner passion with his or her dance partner.

In addition to the social, entertaining side of the dance, tango can improve quality of life and happiness. In a different light, tango exhibits the potential to heal. Clinical researchers and healthcare providers have conducted studies that investigated the effects of adapted tango on patients with Parkinson's Disease (PD). The dance is adapted because only the simple and feasible tango steps are used during the study.

Figure 1 (Left). Patients with Parkinson's Disease participate in adapted Tango programs demonstrate improve mobility and balance.

Figure 2 (Right). Adapted Tango presents many basic challenges of movement for participants, including constantly turning and shifting weights between legs to follow the rhythm of the music.

Especially prevalent in the elderly, PD is a progressive degenerative disorder that mostly affects dopamine-producing nerve cells in the substantia nigra of the midbrain. Dopamine is a neurotransmitter that plays an essential role in the cellular communication between different parts of the brain that modulate muscle movement controls. Hence, common symptoms of patients with PD include trembling, muscle stiffening, slow movement, and problems with balancing (Parkinson's Disease Foundation; Poinier & Wooten, 2014).

Though some studies may indicate genetic correlations in patients with PD, the disorder is overall categorized as idiopathic--meaning that the disease does not have a particular defined cause for the degradation of the neural cells (Poinier & Wooten, 2014). Regardless, early lifestyle adaptations can help improve the quality of life for patients who suffer limited mobility due to PD.

Physical therapists Ryan Duncan and Gammon Earhart - both of Washington University of St. Louis - conducted a study that explored the impact of adapted Argentine Tango on patients with PD. The objective of the study was to compare outcome measures, such as Movement Disorder Society-Unified Parkinson Disease Rating Scales (MDS-UPDRS), gait velocity (forward and backward), and balance tests, of Argentine Tango (AT) participants to the control group who was prescribed to not participate in social dance programs. Selected AT participants would attend the organized dance program twice a week for two years.

By 12 months, AT participants demonstrated significant improvements in motor movement tests compared to the control group. After applying independent sample t-tests and Mann-Whitney U tests, AT subjects were found to score lower on several subsets of the MDS-UPDRS test than the control group. A lower MDS-UPDRS score indicates lesser severity of PD on mobility and activities of daily living.

After one year, any additional improvements in motor outcome measures for AT participants when compared to the outcome measures for the control group were however statistically insignificant. Regardless, the findings are still noteworthy because AT participants overall improved in basic motor functions (see table below), whereas patients in the control group either showed no improvement or increased severity in PD motor symptoms (Duncan & Earhart, 2014).

A current researcher at the Atlanta VA Medical Center, Dr. Madeleine Hackney has also conducted a study that investigated the effects of Argentine Tango on PD patients. In her study, Hackney compared two social dances: Argentine Tango and American Ballroom. Interestingly, Hackney found a greater improvement in motor functions for AT participants than subjects who participated in American ballroom. This may be because the dance moves of the Argentine Tango more closely resemble activities of daily living. Both PD patient groups in the Argentine Tango and American Ballroom dance, however, improved compared to the control group that did not participate in a dance program (Hackney & Earhart, 2009).

An insight for why the dance may be the best form of adapted therapy; tango involves step sequences and is multidirectional. These particularly special characteristics require the dance partners constantly to turn and shift weights between legs—

Table 2. Summary of Results

Instrument	*Result*
MDS-UPDRS III	AT scores significantly lower than control scores over time
MDS-UPDRS II	AT scores significantly lower than control scores over time
MDS-UPDRS I	AT scores significantly lower than control scores over time
Mini-Balance Evaluation Systems Test	AT scores significantly higher than control scores over time
Forward and backward walking velocity	No differences within or between groups over time
TUG	No differences within or between groups over time
Dual-task TUG	Significant interaction; AT group improving and control group worsening, but no between-group differences at any time point
Freezing of Gait Questionnaire	No differences within or between groups over time
Six-Minute Walk Test	AT group at baseline and 12 months > control group at 24 months; controls worsened over time

AT, Argentine tango; MDS-UPDRS, Movement Disorder Society-Unified Parkinson Disease Rating Scale; TUG, Timed Up and Go.

Figure 3. Table borrowed from Duncan and Earhart's Are the Effects of Community-Based Dance on Parkinson Disease Severity, Balance, And Functional Mobility Reduced with Time? A 2-Year Prospective Pilot Study.

all of which help participants improve mobility and balance while still finding enjoyment (Buscaglia, 2011).

Despite these seemingly promising findings presented in all current studies, the results and their implications are limited and require better-controlled accounts between the participants of the adapted dance. PD patients who have known how to tango since they were children may demonstrate different results when compared to patients who are only beginning to learn. The physical location, whether the ballroom is spaciously free or tightly packed like in a milonga, must also be considered. Current prescriptions during the program or other additional exercises outside the dance further make the results not entirely conclusive, as the adapted therapy may not solely be what is allowing patients to recover from the symptoms of PD (Quinn, 2014).

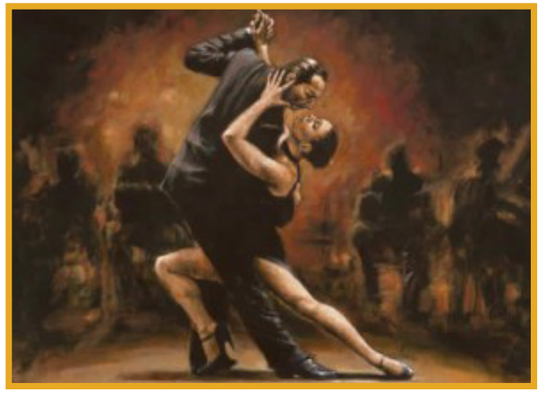

Figure 4. Tango originated from Argentina and exhibits the potential to heal.

Although the use of social dance, as seen with the Argentine Tango, is a relatively new approach to improve the quality of life for patients with PD and other mobile-limiting diseases, science when combined with art proves to be a potential and creative alternative form of healing.

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Common Fitness Misconceptions: Debunked

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Sex appeal, confidence, and (most importantly) health - what do these traits have in common? They are all universally desired goals that can be increased through the development of one's fitness. However, considering the plethora of misinformation circulated by fitness magazines and self-proclaimed "gurus" on the Internet, what fitness truly encompasses and the means of achieving it is debatable.

Physical fitness begins with the development of the musculoskeletal system. Every voluntary movement is dependent on the activation of skeletal muscles. Even activities strictly denoted as

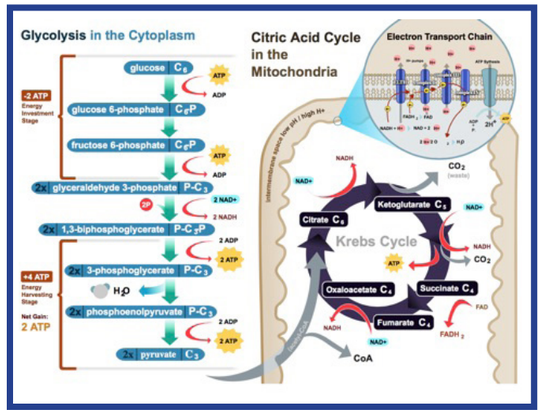

Figure 1: Process of glycolysis and Adenosine Triphosphate (ATP) production, and the Citric Acid Cycle. Glycolysis is one of the main processes in the body that produces ATP, which the body uses for energy. At the very beginning of glycolysis, as seen in the diagram, glucose is the initial "startup" molecule that sets off the rest of the reaction. It should be noted how necessary glucose (and essentially, eating carbohydrates) is towards aerobic respiration, which is consisted of glycolysis, the Citric Acid cycle, and the Electron Transport Chain as displayed.

cardiovascular exercise, or exercise that specifically targets the body's efficiency of processing oxygen, are dependent on a strong body. Without a properly functioning muscular system, muscular imbalances and weakness can make the body more susceptible to injury.

Let's examine three common misconceptions that surround weight training, and debunk them with evidence-based medicine.

Misconception 1: I'm going to get really muscular really quickly if I excercise.

Even though the benefits of weight training for health and injury prevention are well documented, some people express fears such as "gaining too much muscle" or "getting too big." However, muscular gains don't happen quickly enough and aren't noticeable enough to warrant fear. Predispositions and gender can both contribute significantly to one's athleticism and ability to gain muscle mass. Testosterone, an anabolic male sex hormone, is one of the prime differentiators between males and females. It increases protein synthesis to a notable extent (Griggs et al. 1989), and is thus partly responsible for the overall greater muscularity of males versus females. Further, the ACTN3 gene has been identified as a potential contributor to athleticism and sprinting speed, supporting the notion that single genetic differences can yield great effects on physical abilities (MacArthur & North, 2007).

Although there is no scientific consensus on the rate of muscle growth in males and females, the rate itself will always be relatively slow because of natural limiting factors. Hypothetically, from an evolutionary standpoint, muscular growth could be slow because

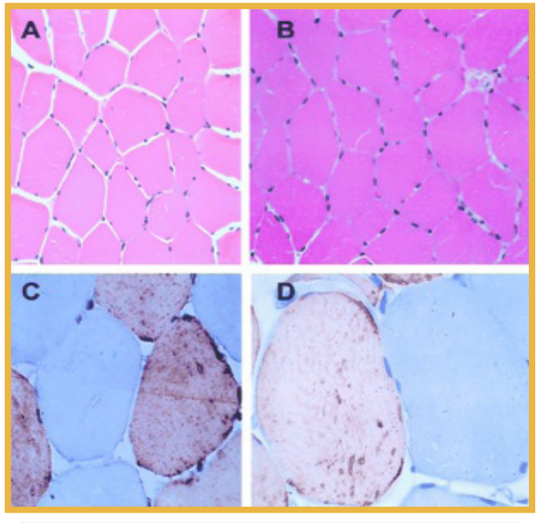

Figure 2. The cross sections of muscle biopsies before and after 20 wk of treatment in one man treated with GnRH agonist and 600 mg of testosterone enanthate weekly. A and C: baseline sections; B and D: sections obtained after 20 wk of treatment. The magnification is 200-fold in A and B and 1,000-fold in C and D. (Source: Sinha-Hikim et al., American Journal of Physiology - Endocrinology and Metabolism, 2002)

of the metabolic costs of muscle tissue. Muscle tissue is metabolically active, or in other words, uses energy. Muscles obtain energy by breaking down Adenosine Triphosphate molecules (ATP), the body's main energy source. The body produces these ATP molecules, primarily, by breaking down carbohydrates and other energy sources into glucose, which is necessary for ATP molecules to be made (See Fig. 1). As we evolved in periods of starvation and fasting, excessive muscle mass would have been a burden because of its large energy expenditure. More muscle mass would have required more ATP, which would have required more glucose to produce that ATP, which finally would have required more food to be consumed to produce that glucose. So, more muscle mass would essentially require more food to

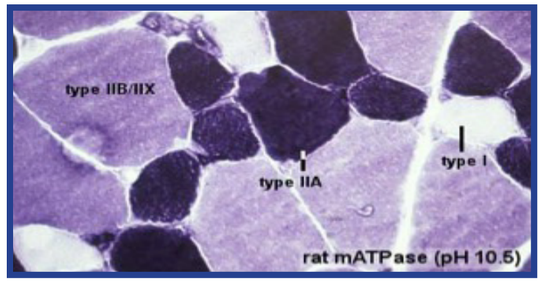

Figure 3. Cross-sectional display of different muscle fiber types and their respective sizes. As seen, the type I, or slow-twitch fibers, are the smallest and produce the least force. The type IIA fibers are intermediate in size and produce more force than the type I fibers. The type IIB, or fast twitch fibers, are the largest and produce the most force. (Source: University of Western Australia, 2009)

survive.

Several mechanisms contribute to the differing rates of muscular growth. One predominant factor in growth rate is training "age." This is the amount of time that one has been training. In natural trainees, or people who don't use performance enhancing drugs (PED's), a beginner will almost always be able to make faster progress and grow more quickly than an advanced individual. "Beginner progress" is a commonly experienced phenomenon in any endeavor: music, art, reading speed, writing ability, language, etc. In terms of gaining strength, "beginner gains" occur because of the sudden strengthening of the neural pathways to the muscles– similarly to how the pathways strengthen through the learning of an instrument. The motor units essentially "learn" how to fire.

However, when previously trained individuals, who have stopped training, return to training, they can experience faster progress than during their initial training (Egner, Bruusgaard, Eftestøl, & Gundersen, 2013). This is colloquially referred to as "Muscle Memory" in the fitness industry. "Muscle Memory" can also refer to motor unit plasticity (a specified form of synaptic plasticity), in which trainees experience large gains in strength following a reintroduction to training, due to the strengthening of neural pathways to muscles (Gordon & Pattullo, 1993; Dow, 2004).

The body cannot keep growing muscle mass because of several factors. Firstly, the protein myostatin naturally limits the amount of muscle mass that the body can produce, by acting as a negative regulator (Schiaffino, Dyar, Ciciliot, Blaauw, & Sandri, 2013). And although PED's, such as anabolic steroids, human growth hormone (HGH), Insulin-like growth factors (IGF's), and Insulin can help artificially cross the natural boundary of muscle growth (Bhasin et al., 1996), cell membranes can't expand indefinitely (Simpson, Rose, & Loewenstein, 1977). In regard to substances like testosterone, pubescent trainees will also be able to make rapid progress as compared to adults because of their rising androgenic hormone levels. So, for the majority of people with fitness goals, progress will be slow. After years of progressive training, the body begins to plateau and reach its natural limit of muscular growth. Even with teens and beginners, progress is still relatively slow and "beginner gains" evaporate quickly, leaving further gains to be harder and slower.

Despite the intensely restrictive limit on muscle growth that the body naturally provides, the modern bodybuilding scene has completely stigmatized the act of lifting weights. Because of the images of competitors who use PED's, many women, and even men, have sanctioned a certain "persona" from fitness media that promotes fear of getting to the size of professional bodybuilders. Because nearly 80% of U.S. adults fail to meet federal recommendations for general exercise (CDC, 2013), clearly, something isn't getting across to the majority of Americans.

Further, although this fear of "getting too large" is irrational for both genders, it is especially relevant for women. Considering women have significantly less testosterone than men, any muscular gain is going to take exponentially longer to achieve than a male counterpart. Considering that even male muscular growth is very slow after initial "beginner gains," females have no reason to think they'll overdevelop at all within any timeframe, let alone within a short period of time. Huge gains in musculature, for the average natural female, are simply physiologically impossible (See Fig. 2).

Misconception 2: Heavy weights are going to make me huge.

Gaining weight and muscle mass, or "getting huge" is significantly dependent on diet, more so than any training method. This assessment can be corroborated through the first law of thermodynamics, or the law of conservation of energy: energy can be neither created nor destroyed, but can change form.

Thus, any excess energy (food) is either stored as fat-free mass and/or fat mass. The body will be more inclined to turn excess protein into muscle mass when there are damaged tissues to be repaired, especially since muscle mass is encouraged from excess calories

because of the hormonal response from overfeeding (Forbes, Brown, Welle, & Underwood, 1989). If one is sedentary, then excess calories will be more likely to be stored as fat tissue, but as much as 46% of overall weight gain could be stored as muscle mass (Forbes, Brown, Welle, & Underwood, 1989). This hormonal response to overfeeding is partly the basis for why sumo wrestlers, and not bodybuilders, have the largest amount of absolute muscle mass, albeit without reference to body fat (Kondo, Abe, Ikegawa, Kawakami, & Fukunaga, 2005).

Further, excess calories in the form of protein (as opposed to carbohydrates or fat) contribute significantly more to the production of lean tissue, rather than the storage of the excess energy as body fat (Bray et al., 2012). While Bray et al.'s (2012) study displayed that overeating with low, normal, and high protein all produced similar gains in body fat, the normal and high protein diets produced more body mass overall, with the difference being in the form of lean tissue.

One may then ask, "why does it matter how much I eat in total? Can't I just eat a bunch of protein and then gain muscle?" The answer is no. Although there is evidence that higher consumption of dietary protein can help prevent loss of muscle mass in a caloric deficit, skeletal muscle will still tend to decrease in response to a caloric deficit (Carbone, McClung, & Pasiakos, 2012). Further, there is evidence that severe energy restriction hampers anabolic pathways that are responsible for protein synthesis, despite high dietary protein consumption (Mäestu, Eliakim, Jürimäe J, Valter, Jürimäe T, 2010).

With this in mind, digested protein in absence of digested carbohydrates won't go straight to damaged tissues. One of the body's main "goals" is to keep itself alive, not necessarily to preserve unnecessary or unused muscle mass. So, the body will actually break the protein down into glucose for the body to use as energy. This process is called gluconeogenesis, which is the process of digesting non-carbohydrate sources into carbohydrates. This process is essentially why low-carb diets, such as the Atkins diet, are unsustainable. If the bloodstream or diet lacks carbohydrates, any protein or fat that's digested will be used to turn into carbohydrate, along with the release of glucagon by the liver (which is basically a chemical signal for low blood sugar, communicating the opposite of Insulin's signal). The body needs to breakdown materials into carbohydrate because the body uses ATP for energy (See Fig. 1). And, since glucose–which is a carbohydrate–is the primary source of ATP production, the body thus requires glucose to produce energy. Thus, nobody is going to suddenly "get huge" from lifting heavy weights. Without a surplus of calories and proper macronutrient (carbohydrate, protein and fat) intake, almost no gains in musculature will be observable.

Misconception 3: I just want to look more defined/toned, so I'm going to use really light weights.

Looking "more toned" is often described as becoming more defined and gaining slightly more muscle mass. The number one contributing factor contributing to the "definition" of a muscle is the amount of body fat that surrounds it. Unfortunately, there is no specific repetition range or weight use that will inherently change the fat surrounding a muscle. This is similar to how no specific weight used will inherently make a muscle grow. Only diet and metabolic changes can alter weight and body fat, just as muscle mass. And, on that note, no repetition range or weight will change a muscle's outward shape. A muscle can only remain stagnant in size, shrink, or grow. The shape of a muscle and its insertion points are completely genetic and unchangeable. So, truthfully, the most logical way to go about getting more "toned" is to decrease body fat, and increase the size of the muscle.

Let's begin with decreasing body fat, based on the previously mentioned law of conservation of energy. If the body expends more energy than it consumes, then it will lose weight. If the body doesn't have enough food to supply energy, then it will resort to using its own bodily tissues. Ergo, the body will break down fat tissue, and eventually muscle mass in times of starvation, to use for energy. However, in terms of weight loss, the body tends to process and oxidize fat more efficiently when its metabolism increases, as a result of metabolic conditioning. Lack of food tends to result in the metabolism slowing (Martin et al., 2007), so endlessly dieting will ultimately prevent ideal body composition and halt weight loss.

Thus, on top of a slight deficit in caloric intake, metabolic conditioning should be the primary factor in losing weight. A larger basal metabolic rate (faster metabolism) encourages weight loss because of its additionally expended energy. Metabolic conditioning should incorporate HIIT (High Intensity Interval Training) which has been well documented to produce superior metabolic adaptations than traditional endurance activities like jogging, walking, or running (Perry, Christopher, Heigenhauser, Bonen, & Spriet, 2008). These adaptations include increased fat oxidation, increased glycogen content, and an increased number of glycolytic enzymes in the muscles themselves. With all of these adaptations, fat loss alone will not necessarily contribute to the aesthetic development of the body. One needs to develop musculature in order for the fat loss to "show" anything. In comparison, excavating fossils only works if there's a fossil underneath all the dust.

In regard to the muscle growth part of "toning", really light, unchallenging weights just won't cut it. The main contributing factor to what causes hypertrophy (muscle growth) is muscular damage, which is

elicited through metabolic stress and mechanical stress. Unchallenging weights won't stimulate either of those mechanisms. Muscular damage is created when cell membrane is damaged or torn, and calcium ions leak out. This causes the cell's natural equilibrium to disrupt. The body releases chemicals that attract macrophages and lymphocytes to the damaged cell, which help remove cellular debris and maintain the cell's structure. This all ultimately allows the muscle cells to undergo hypertrophy, which in turn will compliment fat loss.First, it relies primarily upon anaerobic glycolysis for energy production, which creates a buildup of metabolites including lactate, hydrogen ion, inorganic phosphate, and creatine.

Metabolic stress primarily occurs by depriving muscle cells of oxygen (hypoxia). This hypoxia increases satellite cell activity, which "donate" their nuclei to the damaged muscle cells when called upon. It also causes more blood to be transported to the muscle, also called "the pump", which causes growth through the perceived threat to the structural integrity of the cell. One commonly used method to bring a muscle to hypoxia is through higher repetition training, which requires the anaerobic glycolytic energy pathway (Strong Curves, Contreras & Kellie, 2013). When hypoxia occurs, the body temporarily converts pyruvate into a substance called lactate, which causes the mitochondrial membrane to become acidic, or have a low pH value (See Fig. 1). This change in acidity is what causes muscles to burn during exercise (Roth, 2006). However, higher rep sets do not entail using puny, unchallenging weights for sets of 15 or 20 repetitions. A muscle cell can only adapt if it recognizes a threat to its structural integrity. So, by definition, if one were to use unchallenging resistance levels for any repetition range, let alone a high repetition range, no stress would be perceived by the muscle cell and little to no adaptations would take place. Thus, high repetition training can be useful for hypertrophy, but only if it produces adequate metabolic stress to subsequently produce an adaptive response.

Mechanical stress is created when a muscle stretches and contracts forcefully enough to cause micro-tears in the muscular filaments. Mechanical tension leads to increased hypertrophy through many different mechanisms, including increased cytokine release, satellite cell activation (as discussed earlier), and activation of the mTOR signaling pathway, which is absolutely crucial for the growth of skeletal muscle and involves IGF's. Mechanical tension can be increased by using heavier weights in both moderate repetition ranges or lower repetition ranges, as long as the total volume of work is relatively equated (Schoenfeld et al., 2014). These sets won't necessarily deprive the muscles of oxygen, but instead will strain the muscles' capacity to produce force and microtear myofibrils.

Although both high, moderate, and low repetition ranges (each with their respective intensities of resistance), can contribute to hypertrophy, each repetition range and respective resistance intensity provides unique adaptations to the body (Campos et al., 2002). In Campos et al.'s study, participants who trained with low repetition ranges, which offer the highest level of resistance, gained more overall strength than any other range. Further, muscular endurance improved the most for the high-rep group. Although all three major fiber types (types I, IIA, and IIB) hypertrophied for the low-rep and moderate-rep groups, no significant increases were demonstrated for the high-rep group. However, the percentage of type IIB fibers (which are required for high force output) decreased, with a concomitant increase in IIAB fibers (intermediate-sized fibers) for all three resistance-trained groups (See Fig. 3 for a cross-sectional view of the size differences of these fiber types). In summation, implementing various techniques that increase mechanical tension and metabolic stress should be used to maximize hypertrophy, since each type of training range yields its own benefits towards muscular development.

In taking all of these debunked misconceptions into consideration, you won't get too muscular, too quickly, or ever look "too" good. The body, while an incredibly adaptable organism, is also incredibly stubborn. Under un-enhanced circumstances, the body prevents rapid changes in body composition because it is always trying to preserve homeostasis. It will only change if it really needs to, and making the body need to change requires significant, consistent, and varied stimuli. In order to provide proper stimuli to actually produce bodily changes, you can't be afraid of challenging things. Don't be afraid to lift. Lift heavy between a low and moderate rep range, and lift slightly lighter with a higher rep range to actually stimulate your body into adaptation. If you want to lose weight, your weight loss will occur primarily as a result of a metabolic imbalance between your ingested food and your expended energy– not some magic pill or diet. To burn fat, get your diet in check and do some interval training to make sure your metabolism is up to par. Eat your carbohydrates to fuel your energy stores, eat protein to repair damaged muscle, and eat fat to keep hunger satiated and regulate hormones. These are just a few rules that will solve countless problems in the journey to health and fitness.

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The Pharmacogenomics of Warfarin

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Recent research conducted in the field of pharmacogenomics has produced alarming results for the nearly two million individuals who depend on anticoagulant medications for survival. By studying the relationship between a patient's genome and his or her response to a medication, researchers have found shocking correlations between certain genes expressed in patients and their metabolism of the drug warfarin.

The drug, an anticoagulant also known by the brand name Coumadin, is designed to thin the blood (through the inhibition of clotting factors) of patients who have a propensity for the

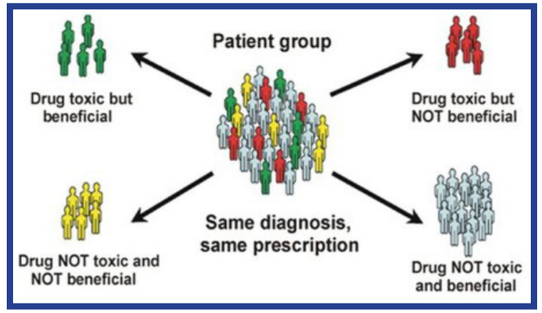

Figure 1. The traditional prescription of a standardized dosage of warfarin risks adverse reactions for a considerable portion of the patient group. Without a proper understanding of a patient's genetic predisposition towards a standardized prescription of warfarin, physicians may unintentionally prescribe doses that fail to achieve an anticoagulative effect or that ultimately cause dangerous haemorrhagic repercussions.

dangerous formation of thrombosis or pulmonary embolisms. Doctors typically prescribe warfarin to a number of patients with previous cardiovascular conditions, including patients who have suffered from heart attacks and strokes, individuals displaying unpredictable heartbeats or propensities for blood clots, and those with artificial heart valves. Improper consumption of anticoagulants may result in fatal repercussions, requiring the continually monitored use of warfarin by healthcare professionals. For the individuals who depend on warfarin for survival, the clear communication of precautions associated with its consumption is critical for the health of these patients and demands a great degree of doctor-patient cooperation.

Pharmacogenomic researchers have been meticulously working to eliminate the dangerous element of uncertainty involving the proper prescription and consumption of warfarin. A publication from the Institute of Medicine examines the genetic implication of warfarin responses and connects the efficacy of warfarin metabolism with the expression of genes that encode enzyme synthesis among distinct ethnic populations (Institute of Medicine, 2010). Without the proper understanding of a patient's anticipated response to warfarin, doctors in the past have risked provoking severe adverse reactions to warfarin in patients displaying extreme sensitivity to treatment—including fatal episodes of bleeding. According to a news release by the Food and Drug Administration, "warfarin is the second most common drug, after insulin, implicated in emergency room visits for adverse drug events" (U.S. Food and Drug Administration, 2013). Armed with knowledge offered by the pharmacogenomic study of warfarin, doctors now possess a more definite command over the prescription dosage in the clinical application of this research.

At the molecular level, humans exhibit nearly indistinguishable genetic identities. Variations that exist in DNA, commonly known as single nucleotide polymorphisms (SNPs), ultimately determine the way in which an individual responds to certain medications--including anticoagulants like warfarin--by encoding the enzymes which metabolize drugs.

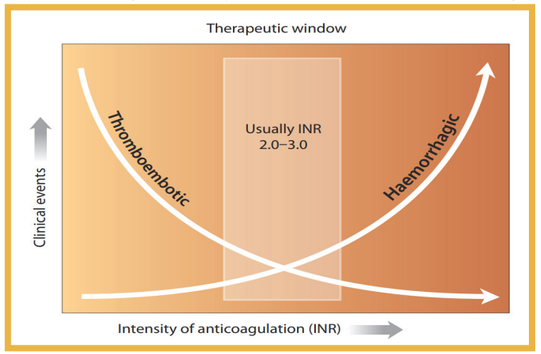

Figure 2. The International Normalized Ratio (INR) measurement indicates the necessary warfarin dosage for a patient based on nongenetic factors, including diet and interactions with other drugs. While the main goal of warfarin is anticoagulation, the excessive consumption of warfarin may result in haemorrhagic effects that are equally dangerous to the patient. In order to consistently achieve a therapeutic effect, the application of pharmacogenomics to warfarin monitoring may better predict the patient's response to the drug and help to avoid the extreme repercussions of unmonitored consumption.

In order to understand the physiological component of pharmacogenomics, the process of drug metabolism within the body must first be explored

to identify the critical enzymes involved in the study of polymorphisms. These metabolic processes occur mostly in the liver: enzymes incite the conversion of medications into chemical substances called metabolites which are usable by the body. Cytochrome P-450 encompasses the family of enzymes that facilitate drug metabolism, including some of the most prominent isoenzymes known as CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 (Lynch & Price, 2007). Therefore, an individual's genome significantly dictates the course of drug metabolism and the overall effect of the drug.

The extent to which an individual metabolizes

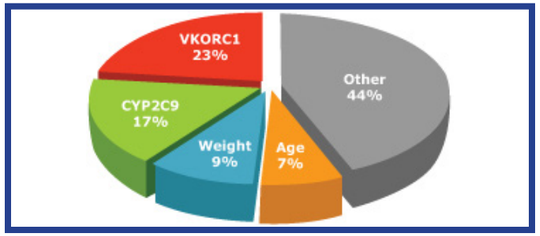

Figure 3. A number of factors contribute to an individual's response to warfarin consumption that are not predicted by genotype. The pie chart shows an overall 40% genetic influence on warfarin response, a significant factor unaccounted for before the recent advent of pharmacogenomic research. By determining an individual's genotype for the CYP2C9 and VKORC1 enzymes, physicians can better identify propensities for an adverse reaction to traditional dosages of warfarin.

a drug remains dependent on genetic variations of enzymes involved in the metabolism of drugs. At the core of this relationship are genetic alleles that encode each of the cytochrome P450 enzymes. An individual who carries two wild type alleles from both parents is classified as an extensive metabolizer with little difficulty in the conversion of drugs to a useable form; reduced enzyme activity occurs, however, when an individual carries both wild-type and variant alleles (Lynch & Price, 2007). Those who are poor metabolizers receive variant alleles, whereas those who receive wild-type alleles are considered "ultrarapid" metabolizers due to the rapid breakdown of medication before the intended effect can be achieved. Drug dosages can be increased in the event that an extensive phenotype metabolizes medications significantly faster than average; similarly, drug doses can be reduced in poor phenotypes to avoid toxic build-up in the body.

Past research in pharmacogenetics has shown that drugs intended for cardiovascular disease demonstrate ostensible variability among ethnic groups and individuals when it comes to treatment effectiveness. Following studies completed on other drugs like clopidogrel and statins, researchers were also able to identify polymorphisms in the CYP2C9 enzyme and connect this data with studies of the drug warfarin. Administered to prevent the formation of thrombosis or thromboembolism, warfarin is an anticoagulant that scientists associate with the enzyme-encoding genes called VKORC1 and CYP2C9.

CYP2C9 polymorphisms dictate the course of metabolism and dosage variations for patients consuming warfarin. An article published in the American Heart Journal titled "Ethnic Differences in Cardiovascular Drug Response" proves that the polymorphisms known as CYP2C9*2 and CYP2C9*3 cause reduced metabolism of warfarin, ultimately requiring significantly smaller doses than extensive metabolizers. The *2 polymorphism specifically commands a reduction in dosage of 0.85 mg daily while *3 polymorphism requires an entire 1.92 mg lower dosage (Johnson, 2008).

The prevalence of these two polymorphisms varies considerably throughout ethnic groups, as displayed in the table relating average dosages with the respective polymorphism (Johnson, American Heart Association, 2008). For Asians and people of African descent, the existence of CYP2C9*2 and CYP2C9*3 remains negligible; within the Caucasian population, however, 8% to 18% of people exhibit the *2 allele frequency and 5% to 13% possess the *3 allele frequency. Thus, the Caucasian population on average requires lower doses of warfarin compared to Asians and people of African descent. The corresponding sensitivity of people who possess these polymorphisms create the possibility of "serious or life threatening bleeding or an out-of-range (>4.0) in carriers of the *2 or *3 of CYP2C9" (Ginsburg & Willard, 2012). By understanding the variability of warfarin response in patients, physicians and researchers can develop a protocol by which genetic information can supplement the knowledge afforded by measurements of the International Normalized Ratio (INR), which is an important measure of clotting risk that also accounts for extrinsic factors outside the area of genetics.

In addition to the CYP2C9 polymorphisms that have manifested in genetic patterns within ethnic populations, an enzyme encoded by the Vitamin K epoxide reductase complex subunit 1 (VKORC1) contains variations that similarly dictate responses to warfarin. Since vitamin K is imperative in the activation of the blood clotting process, warfarin as a medication that negates the body's ability to undergo coagulation. According to a publication in the European Heart Journal, three VKORC1 polymorphisms require varied warfarin administration and patterns again emerge among members of ethnic groups: variants of VKORC1 exist prominently in Asians between 90% to 95%, more subtly in Caucasians at 40%, and even more marginally in people of African descent at 10% (Verschuren, et al., 2011). Similar to warfarin sensitivity incited by the CYP2C9 enzyme, VKORC1 has a mutation known as 1639G>A that further increases the need for smaller dosages as it virtually eliminates activated clotting factors in patients prone to thrombosis or thromboembolism (Johnson, 2008).

The data afforded by the careful study of the genetic correlation with responses to warfarin is an invaluable asset to pharmacology. A direct consequence of pharmacogenetic research on warfarin is the ability for physicians to confidently prescribe appropriate dosages of warfarin to patients and to anticipate the patient's response with greater conviction. According to the Institute of Medicine, an algorithm has been developed by the International

Disparities in Warfarin Dosage among Ethnic Groups

		Warfarin Dosage Reduction	Prevalence within Caucasians	Prevalence within Africans	Prevalence within Asians
CYP2 C9*2		0.85 mg	8-18%	Rare	Rare
CYP2 C9*3		1.92 mg	5-13%	1-2%	2-5%

*Figure 4. The data in this chart is a compilation of the research completed by Julie A. Johnson in the publication titled "Ethnic Differences in Cardiovascular Drug Response" for the American Heart Association. This table compares allele frequencies across ethnic populations and displays the corresponding degree of reduced drug metabolism. The extremity of each metabolic reduction is observed in the average dose reduction, designed to optimize the efficacy of warfarin without the risk of adverse drug reactions. The data collected here reflects an analysis of 8 studies that measured the general dosage reduction for an individual with at least a single copy of either the *2 or *3 variant allele.*

Warfarin Pharmacogenetics Consortium to specifically connect the presence of CYP2C9 and VKORC1 in a patient's genome with definite and reliable dosages, nearly eliminating the contingency for patients to experience dangerous episodes of bleeding (Institute of Medicine, 2010). In addition to the pharmacogenetic algorithm, a number of companies have developed practical approaches to test for polymorphisms within a patient's genome; Nanosphere Inc., for example, acquired FDA approval less than a decade ago for a genetic evaluation called the Nanosphere Verigene Warfarin Metabolism Nucleic Acid Test that identifies the presence of variations in the two prominent enzyme-coding genes (U.S. Food and Drug Administration, 2013).

In many cases, benefits of the genotypic understanding of warfarin responses can be applied to supplement the INR. Extrinsic factors measured by INR, including interactions between warfarin and other medications and foods, extend beyond the inherent limits of pharmacogenomic implication in determining proper prescription dosages. When combined with INR measurements, however, the dosage anticipation based on genetic testing will maximize the degree of certainty with which doctors will prescribe warfarin to patients.

Beyond the successful application of pharmacogenomic research to anticoagulants like warfarin, the field has successfully identified a number of other enzymes that assume a critical role in the metabolization of other medications; for instance, physicians can anticipate the efficacy of tamoxifen in patients afflicted with breast cancer based upon the presence of variations in additional cytochrome P450 enzymes. Overall, the emergence of pharmacogenomics as an important measure of drug-related success in the recent past has actualized visions of a new approach to pharmacology in the form of "personalized medicine." With a better understanding of the connection between an individual's genetic makeup and his or her reaction to a drug, physicians possess the ability to effectively prescribe medications with an assurance that adverse drug reactions will not endanger the lives of their patients.

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Argus II:

Bionic Eye

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Edited by: Nitin Nanda, MD

Bionics is the application of biological knowledge and methods to engineering. Medical bionics specifically focuses on the replacement or enhancement of organs with mechanical versions by functioning as the original body part. While, medical bionic technology is a relatively new phenomenon, but there are some ionic implants that already exist to date. One of which is the cochlear implant, a device used by deaf people. As biology and technology progress, we will see more breakthroughs in bionics,

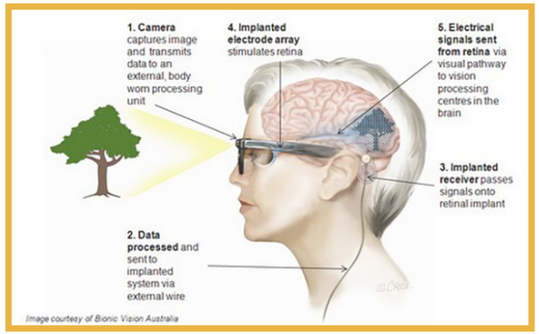
which directly correlates to better lifestyles for many.

One disease that has plagued many is called Retinitis Pigmentosa (RP), which pertains to the damage of the retina, the layer of tissue that converts light images to nerve signals for transmission to the brain for processing (Lusby & Zieve, 2014).

> **"RP is predominantly hereditary and affects 1 in 4,000 people in the United States."**

The cells in control of night vision are most likely to be affected, but in rare cases the retinal cone cells are damaged the most. Cone cells are photoreceptor cells in the retina responsible for color vision. RP can run in families and can be caused by several genetic defects (Lusby & Zieve, 2014). RP often begins affecting people in their early childhood, but does not have a significant impact on patients until later in adulthood. Symptoms include decreased vision in low light situations as well as a significant loss in peripheral vision ("Multimedia Encyclopedia," n.d.). In advanced cases, central vision will be lost. This is where the urgency for answers arises from up. Though there is no effective treatment for RP, there are ways to lessen the effects such as: wearing sunglasses protecting from ultraviolet light. Studies also suggest that treatment with antioxidants such as high doses of vitamin A may slow the disease (Lusby & Zieve, 2014).

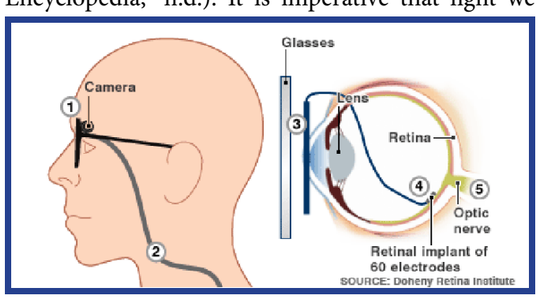
After over two decades of research there is an answer offered by Second Sight. Dr. Greenberg and Alfred E. Mann formed Second Sight in the



late 1990's to develop a chronically implantable retinal prosthesis. Their first generation of implants consisted of 16 electrodes and was implanted in six subjects between 2002 and 2004 ("Second Sight," n.d.).

> **"These subjects were completely blind prior to the prosthesis, but following the procedure could perform a surprising array of tasks with the help of the device."**

After some further research with the help of their six test subjects, in 2007 Second Sight began a trial of their Argus II which is responsible for mending the issue that arises when the photoreceptors in the retina that are responsible for deciphering and sending electrochemical signals are defective ("Multimedia Encyclopedia," n.d.). It is imperative that light we

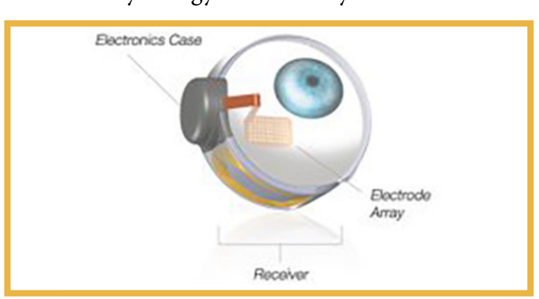


see be transformed into images and with the help of the Argus II, the defective photoreceptors are bypassed completely. Now for the interesting part: "A miniature video camera housed in the patient's glasses captures a scene. The video is sent to a small patient-worn computer (i.e., the video processing unit – VPU) where it is processed and transformed into instructions that are sent back to the glasses via a cable. These instructions are transmitted wirelessly to an antenna in the implant. The signals are then sent to the electrode array, which emits small pulses of electricity. These pulses bypass the damaged photoreceptors and stimulate the retina's remaining cells, which transmit the visual information along the optic nerve to the brain, creating the perception of patterns of light. Patients learn to interpret these visual patterns ("Second Sight," n.d.)."

> **"U.S. Food and Drug Administration approved this device this year, and since then, two procedures have been performed to input this artificial retina system."**

The procedures were performed by Dr. Thiran Jayasundera, M.D., and Dr. David N. Zacks, M.D., Ph.D. at the University of Michigan Kellogg Eye Center. Jayasundera stated, "We are pleased with both patients' progress at this point, and we are hopeful and optimistic that the artificial retina will enable them to see objects, light and people standing before them." The fruits of the labor are not seen for a while after the procedure, however, as the prosthesis does not immediately cure RP. The patient has to go through a lengthy process to adapt to the Argus II, which could take months. It is important to understand that the Argus II does not make one's vision 20/20, but rather distinguish shapes and colors one can still experience their surroundings("U-M Kellogg," n.d.). Linda Schulte, who received the first implant, stated, "I understand that I will not have 20/20 vision and that I won't be able to distinguish faces. But at least I will be able to know that my grandchildren are running across the yard or walking into my house. That would be a miracle to me. ("U-M Kellogg," n.d.)"

The latin word, "Argus" refers to a figure in Greek mythology with 100 eyes considered all-



seeing. Second Sight has taken crucial strides into the world of medical bionics over a course of twenty years to offer us a system that has been proven to work ("Second Sight," n.d.). Argus II has blown other similar technologies out of the water with its ability to survive long-term implantation in the body ("A Bionic Eye," n.d.). As of March 2014, including clinical and commercial use, Argus II has been implanted in over 80 people. Argus II has not had any cases of actual blindness being resolved by the device, but vision has been reported to improve ("Second Sight," n.d.). Considering the 80 people that have received the implant, only two devices have been proven unreliable to date. Furthermore, the longest user of the Argus II is approaching seven years while the closest competitive device has not demonstrated a device lifetime beyond a year ("Second Sight," n.d.). This is epitome of why Argus II has taken off, and continues to be successful. I believe that this is simply the beginning to a plethora of medical bionic technologies that will be introduced in years to come that will completely revolutionize the way we (humans) treat illnesses and disease.

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Synesthesia:

Entirely Genetic or Can it be Taught?

Authored by: Anirudh Gorti

Edited by: Astrid Prinz, PhD

Star athletes, mathematical geniuses, and presidents of the world all have one thing in common: their skills are unique to an extremely small portion of the population. For many years, scientists have attempted to elucidate the question of whether certain individuals are genetically predisposed to cognitive gifts or if those gifts can be taught regardless of an individual's DNA. Included within the category of unique skills is the ability to evoke more than one of the sensory systems with a single stimulus. This condition is known as synesthesia, and is present in 2-4% of the population (Brang D. & Ramachandran V.S., 2011). The phenotype that is present as a result of synesthesia includes the ability to correlate vivid colors with achromatic numbers or letters, visualize colors in conjunction with a specific smell, or hear tones and see colorful projections as a result (Palmeri TJ, Blake R, Marois R, Flanery MA, & Whetsell William, 2001; Gilbert AN, Martin R, & Kemp SE 1996; Banissy MJ et al., 2012).

"The phenotype that is present as a result of synesthesia includes the ability to correlate vivid colors with achromatic numbers or letters, visualize colors in conjunction with a specific smell, or hear tones and see colorful projections as a result."

Synesthesia has been recognized since the ancient Greeks, and has been officially known for over sixty years now (Bachem A, 1949), yet it's neural basis is still unclear. Nevertheless, previous literature indicates that those with a family history of synesthesia are most likely to show symptoms (Barnett KJ et al., 2008). Therefore, the question is whether synesthesia manifests due to genetics, or if the environment influences its phenotype as well. An improved understanding of the genetic basis of synesthesia has important implications. Research has shown that those with synesthesia have increased structural connectivity in the brain, which can result in enhanced intelligence (Rouw R and Scholte SH, 2007; Fischer FU, Wolf D, Scheurich A, & Fellgiebel A, 2014). As a result, it is believed that if synesthesia can be taught to those who are not genetically predisposed to it, an avenue towards increased intellectual capacity could result (Bor D, Rothen N, Schwartzman DJ, Clayton S, & Seth AK, 2014).

"[I]t is believed that if synesthesia can be taught to those who are not genetically predisposed to it, an avenue towards increased intellectual capacity could result."

The University of Sussex recently conducted an experiment in which the researchers attempted to train individuals who did not have synesthesia to perceive achromatic letters as colors (Bor D, Rothen N, Schwartzman DJ, Clayton S, & Seth AK, 2014). The goal of the experiment was to determine if synesthesia-like characteristics could be taught. The researchers conducted a nine-week training program in which fourteen subjects underwent a series of tests. These tests included various forms of the Stroop test, in which an individual is presented the name of a color but the letters are in a different color, and color consistency tests. Furthermore, the subjects were classically conditioned to associate certain colors with startling sounds. After the training, the subjects were given a questionnaire in order to determine the effectiveness of the training.

"Overall, the fourteen non-synesthetic subjects demonstrated synesthesia-like symptoms through the color consistency, synesthetic Stroop task, and classical conditioning tests."

Thirteen letters were used during the training period for this experiment. After the training, eight out of fourteen participants reported associating colors with letters during their daily lives. Furthermore, twelve out of the fourteen participants indicated that they associated personalities to letters. For example, one participant stated that the letter "X" was aggressive (Bor D, Rothen N, Schwartzman DJ, Clayton S, & Seth AK, 2014). Overall, the fourteen non-synesthetic subjects demonstrated synesthesia-like symptoms through the color consistency, synesthetic Stroop task, and classical conditioning tests. In order to see if conditioned synesthesia results in changes in cognitive ability, researchers conducted a series of experiments comparing and contrasting the IQ of a control group and the synesthesia-trained subjects. Most notably, the findings indicated that the synesthesia-trained subjects demonstrated an average of twelve-point increase in their IQ after the nine-week training compared to the control group.

"Most notably, the findings indicated that the synesthesia-trained subjects demonstrated an average of twelve-point increase in their IQ after the nine-week training compared to the control group."

The results from the study have many implications. First, the study indicated that the environment could potentially play a key role in the development of the synesthesia phenotype as researchers showed that the human mind can be trained to experience synesthesia-like symptoms. However, it is important to note that the researchers did not convert non-synesthetic individuals into synesthetic individuals. Instead, they were able to train the mind's sensory pathways to work together similar to how an individual can be trained to associate a sound with fear. Another important implication is that a similar training program can be performed to enhance cognitive ability. A lot of money, time, and research are devoted to understanding how to tangibly improve intelligence. If replicated, results of this experiment indicate that the training program could reliably increase memory and intelligence for an individual. Finally, the attachment of personalities to specific letters can be used to help treat many mental disorders that might lead to depressive states. Instead of administering medications with harmful side effects, physicians could use such a program to train subjects to associate cheerful personalities to letters in the alphabet that are encountered in everyday life.

This study succeeds in enhancing our knowledge about synesthesia and understanding the role that the environment plays in the manifestation of the phenotype. However, further investigation is required before this study has any significant clinical utility. The exclusion criterion was focused only on those with synesthesia. Only fourteen individuals were tested, twelve of whom were females and only two were males. Additionally, the mean age was close to 19 years old. This is age is significant because brains are not fully developed until past that age, which could be a reason that plasticity is more likely to occur (Dosenbach NUF et al., 2010). Finally, the individuals were all students at the same university and their socio-economic background was not listed in the study. This is an issue because it is not clear what kind of educational upbringing the individuals may have had which can influence the results accordingly. Therefore, only a very specific demographic was tested in this study and consequently the results may not be applicable to the general public. This training program needs to be replicated and provided to a wider, more diverse range of people. If the findings are replicated with an entirely different demographic of subjects, the program will have great potential for improving cognitive ability of individuals.

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