

ACUTE ARREST OF CEREBRAL
CIRCULATION IN MAN



REVISITED

Lieutenant Ralph Rossen (MS) U.S.N. R.,

Herman Kabat, M.D., Ph.D.

and

John P. Anderson

•

1942

•

**The Anderson Institute for
Biological Research**

Red Wing, MN

PRESENTED BY BRIAN A. SMITH

National Dysautonomia Research Foundation

Acute Arrest of Cerebral Circulation In Man

Acute Arrest of Cerebral Circulation in Man

Researchers, physicians and students that are familiar with the nervous system know that several centers around the globe have developed a reputation as centers of excellence in autonomic nervous system research. The importance of autonomic research has led to the formation of study groups and conferences that are held in North and South America, Europe, Australia, and Asia. Leading Universities have established research facilities that have made important discoveries that are helping direct improvements in patient care, and allowing physicians to better understand the complex problems faced by patients who are impacted with autonomic dysfunction. With this said it may come as some surprise to many that a small town, located along the banks of the upper Mississippi river, may have had as much importance to the world of autonomic research as any of these large academic institutions. Red Wing, Minnesota has played an important role for individuals impacted with Dysautonomia, and other illnesses, both today and in the past.

Red Wing is important to the world of autonomic research for several reasons. Of primary importance is the fact that Red Wing is home to the National Dysautonomia Research Foundation, a patient support and education organization that provides help to over one million people impacted with autonomic dysfunction. In addition, Red Wing is also known as the town where researchers found the first family with a genetic mechanism that was identified as a cause for orthostatic intolerance. But Red Wing has a history that reaches back to a study that was completed during the early period of World War II. The study, often cited as the earliest reference in many research studies, is critical in our understanding of the supply of oxygenated blood to the brain, and how a disruption in this process can quickly lead to symptoms that many with autonomic dysfunction suffer with daily. The study also brought together a team of researchers whose work would impact our country in ways that few would have expected from such a small town.

Research in Red Wing, Minnesota

In the early 1940's, a small group of scientists began an important project at a research facility located in Red Wing Minnesota. Situated on the grounds of the Tower View



Complex, the Anderson Institute for Biological Research was the next step in a long history of research completed by members of the Anderson family. In 1902, Alexander Pierce Anderson invented a process that led to the first “puffed” cereal and the founding of the Anderson Puffed Rice Company. Beginning in 1915 and ending eleven

years later, Alexander built the Tower View Complex that is situated in the bluff country of Red Wing. The complex, located on a large working farm, served not only as the home for Alexander and his family, but also as home of the labs for the new company. Fully self sufficient, the Complex contained a water tower, underground tunnels and a fully functional research laboratory.

After the relocation of the cereal company in 1941, Alexander's son, John P. Anderson, established the Anderson Center for Biological Research on the Tower View site. Joining John P. Anderson at the new facility was Dr. Ralph Rossen, the former superintendent for the State Hospital located in Hastings, Minnesota, and Dr. Herman Kabat from the National Institutes of Health in Bethesda, Maryland. Together, these men worked to produce a landmark study that is referenced today by researchers in several areas of medical science.



World War II and the Anderson Institute

The entry of the United States into World War II brought about a series of problems that required scientific efforts to help solve. Pilots were flying aircraft that could attain higher altitudes, generate faster speeds and were being asked to use these aircraft to descend rapidly in order to complete dive bombing missions. Unfortunately, some of these pilots suffered from a loss of blood supply from these maneuvers that led to a period of unconsciousness. The war department was quite concerned about this problem and numerous centers



across the country were involved with research efforts to help study the mechanisms of this problem, and to look for ways to eliminate pilot blackouts. The team in Red Wing developed a project to address this issue.

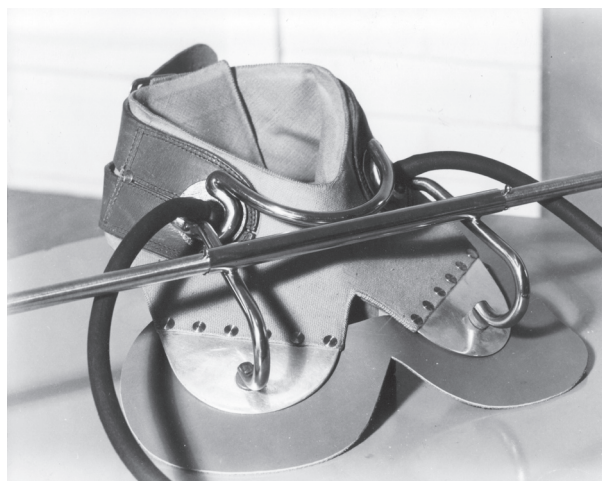
A unique study was designed that would focus on better understanding the process that occurs when blood supply is reduced to the brain. This study would focus on mimicking this reduction of blood supply and then attempt to learn how pilots might avoid blacking out, or recover faster if a blackout occurred. The team also was interested to see if testing could be done on potential pilots to see if they had a tendency to black out earlier, or later than the average person. Each of the members of the research team brought important strengths to the study that assured it's success.

Dr. Kabat came to Red Wing equipped with some critical

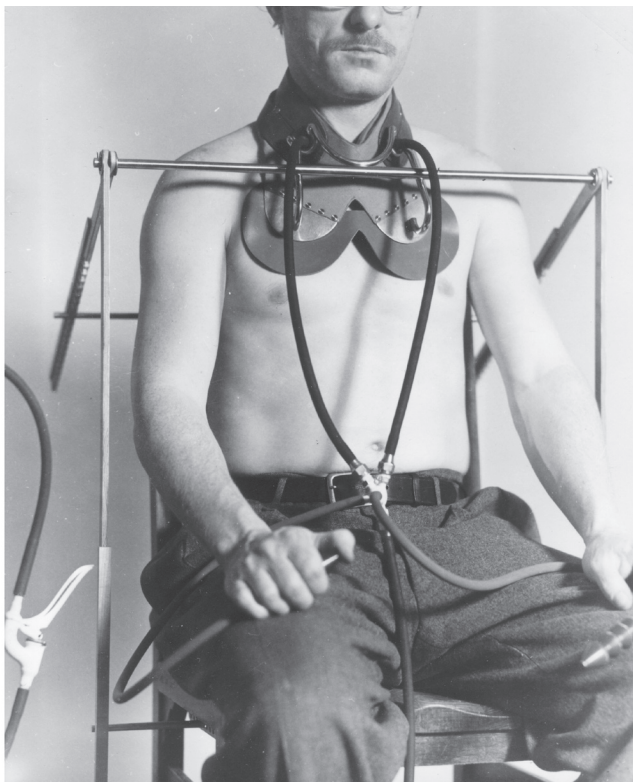
knowledge about this problem. He had conducted previous experiments on dogs that involved long term reduction of blood supply to the brain, and was familiar with the effects that could result from hypoxia. His research showed that a disruption in blood supply to the brain could last up to six minutes before causing permanent damage to the animal. This process and understanding became the basis for the research done at the Anderson Institute.

The KRA Apparatus and Studies

John P. Anderson worked to develop an adapted version of the device used on the animal studies conducted by Dr. Kabat. The device, now known as the KRA Apparatus, was a leather collar with a bladder that connected to a compressed air tank. The researcher and the subject were both able to stop the test at any time by releasing their finger from a cut off switch that allowed for deflation of the device in 1/8 of a second.



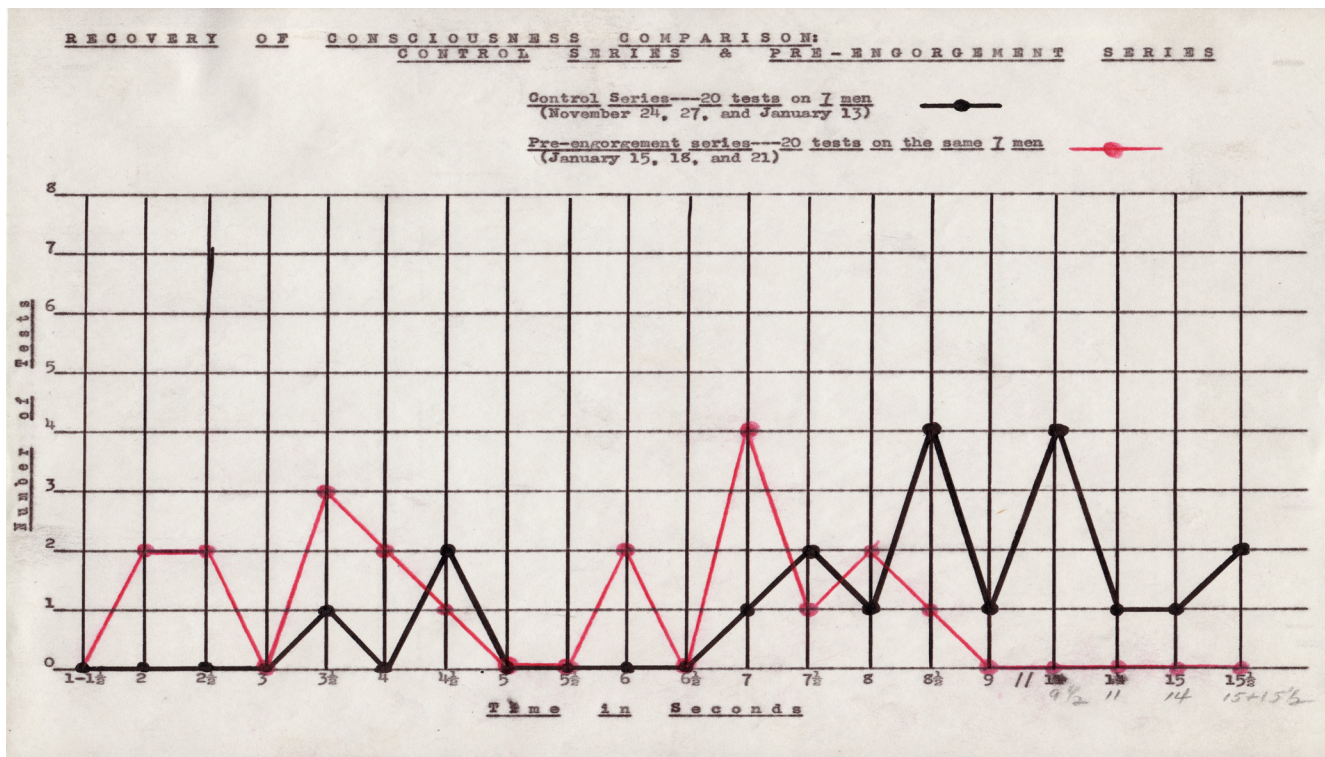
To test the new device, the researchers developed a protocol using themselves as the subjects of the test. In February, 1941 the first tests were performed on the investigators and their research associates, comprised of seven normal subjects. These seven subjects were given 20 trials, with the duration of cerebral anoxia varying from 6 to 30 seconds. Satisfied with their results and the lack of any health



The first version of the cuff with the cutoff valve



The revised cuff with straps added



Comparison of Control (—●—) to Pre-Engorgement (—●—) Recovery



*Cole Younger
Stillwater Prison*

Tower View

The year was 1876. A young 13-year-old farmboy met a group of strangers on horseback who were looking for directions and water. After helping the seven strangers and providing them with information on how to get on to the town Northfield, the young man got back to what he was doing. The riders were the James and Younger gang, whose were about to make the biggest mistake of their illustrious careers. The young farm boy was Alex P. Anderson, who would go on to fame as a scientist and the inventor of puffed cereal. Anderson revealed this encounter with the outlaws in an essay about Silurian fossils, an indication of where his true interests lay. In addition to being a farmer, he studied phrenology, the science of reading character by feeling the bumps of the skull. He worked as a botany professor, researched tornadic winds, wrote poetry and was an avid supporter of the arts. Ironically, many of the subjects that participated in this study were housed at the same prison where the Younger brothers - Cole, Jim and Bob - were sentenced to 25 years in prison in 1876.

concerns, the team began their research on several groups of volunteers, as well as a small group of hospitalized patients at the Minnesota State Hospital. While the tests on the hospital patients were important, this review will focus primarily on the normal, healthy volunteers who participated in the study.

The KRA cuff was applied to the lower third of the neck and was inflated to a pressure of 600 mm of mercury in 1/8 of a second. This combination of the rapid time and high pressure prevented any pre-engorgement of blood to the brain. The deflation of the cuff was accomplished quickly, with the release of pressure occurring in a fraction of a second. The subjects were kept in a seated position and the researchers used electrocardiograph and electroencephalograph devices during several phases of the experiments. Subjects underwent repeated tests of the standard protocol. Additional studies were completed in an effort to learn more about what mechanisms might decrease the blackout time or speed up the time of recovery.

The first studies were completed on a group of 66 normal male volunteers at the Minnesota State Prison at Stillwater, Minnesota. The initial KRA cuff did not completely stop the blood supply in the vertebral artery, so a new device was created that allowed for an improved blockage of blood supply. Straps were added to the device that allowed for the cuff to be securely positioned on the subject. The improved cuff allowed for an increase in cervical pressure and to confine the pressure to the lower third of the neck. As a result, the device worked to occlude more successfully the vertebral arteries at their origin from the subclavian arteries. The new cuff also proved to provide more consistent results from the same subjects. This new cuff was used to study a second group of subjects, which consisted of 54 normal male volunteers from the St. Cloud Reformatory, in St. Cloud, Minnesota.

Results

From the use of the KRA cuff, the team of researchers showed that our brains are highly dependent upon a steady supply of oxygenated blood for us to remain conscious. Based upon the subjects tested, a lack of blood supply for as little as 4 seconds, or at most 10 seconds, led to a loss of consciousness. The response to a re-supply of blood was also rapid, ranging from 3 to 11.5 seconds. The subjects showed a consistent pattern that was noted during the experiments:

Fixation of eyes: Subjects were asked to follow a pendulum or the examiner's finger when the pressure was applied. At ½ to 1 second of time before losing consciousness, subject's eyes would become fixed. When asked afterwards, subjects stated they still could see, but could not move their eyes.

Turning up of eyes: Some subjects showed a turning upwards of their eyes just as they lost consciousness.

Visual Symptoms: Prior to losing consciousness, many subjects experienced visual symptoms that included blurred vision, rapid narrowing of the field of vision, streaks, spots or twinkling lights.

Anoxic Convulsions: After losing consciousness, several subjects experienced generalized tonic/clonic type convulsions. These lasted for a brief time (6-8 seconds) and happened predominately after the release of the pressure cuff. If the blood supply was restored when the subject's eyes became fixed, no convulsions occurred. If the restoration began several seconds after eye fixation began, the seizure activity was more severe and prolonged.

Paresthesias: Approximately half of the subjects described a variety of symptoms including numbness, tingling and shooting pain. In one instance, a subject had an electric shock type of pain that caused him to release the trigger and stop the device. These pains were felt throughout the body, but were most frequently reported in the hands, arms, head and face. Subjects reported these symptoms several seconds prior to losing consciousness.

Loss of Consciousness: Subjects lost consciousness at about one second after fixation of their eyes. Some subjects reported an awareness of some events with an inability to move prior to complete loss of consciousness.

In addition to the standard test, the KRA cuff was also used for testing the effects of various agents that might impact either the resistance of the human brain to acute anoxia or on recovery time from a blackout. The research team completed studies that focused on “pre-engorgement” of the brain, by providing the subject with a small amount of pressure to force blood into the brain. Seven subjects were exposed to 80-85mm of mercury for 15 – 18 seconds that obstructed venous return, yet did not interfere with arterial supply to the brain. After this pre-engorgement phase, the subject was provided a one second interval before being exposed to the full 600mm of mercury. The results for these subjects showed that the time to loss of consciousness was not changed, however time to recovery was significantly impacted. Subjects recovery time improved by 2-3 seconds.

The research also analyzed the role of vitamins on blackouts. An experiment using B complex vitamins was designed to see if there was any difference in faint or recovery times. Although only a small study sample was looked at, there was a suggestion that these vitamins may also act to speed recovery time. The study recommended that further investigation be completed before any conclusions could be drawn.

The research team noted several important points from this study, as well as from the work done on patients in the Hastings State Hospital:

Pulse Rate: For periods of arrest of cerebral circulation up to 30 seconds, there is no marked change in the pulse rate; After 40 seconds, a slowing is often noted which can be prevented by atropine; After restoration of circulation, a temporary increase in pulse rate is often observed.

Blood Pressure: In 20 tests on these patients blood pressure was recorded; a 15% rise or fall in systolic blood pressure was observed, with no apparent change in diastolic pressure.

Corneal Reflex: Usually this reflex is lost between 5 and 15 seconds but may disappear as late as 30 seconds. The corneal reflex returns within 5 to 10 seconds depending on the duration of the anoxia.

This reflex was tested in 150 trials on the hospital patients. The loss of this reflex was quite constant for the individual; for example, one patient showed loss of this reflex on 3 successive days at 11 seconds, 12 seconds and 11 seconds; another patient at 5, 6 and 5 and 6 seconds for four trials.

Abdominal Reflexes: These reflexes disappear soon after loss of the corneal reflexes and return very soon after recovery of consciousness.

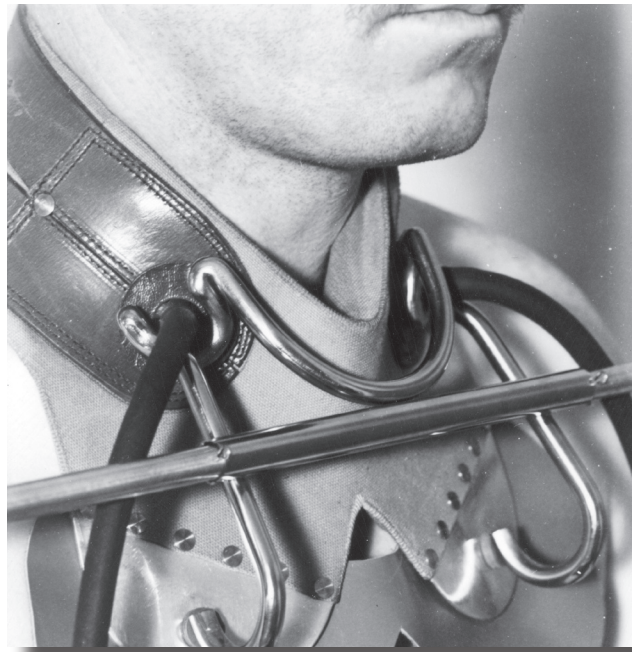
Other Reflexes and Signs: The Hoffman, Babinski, Gordon and Rossolimo signs may appear on one or both sides after 30 or 40 seconds of anoxia. They always disappear within a few seconds after restoration of cerebral circulation.

The appearance of these reflexes occurs after disappearance of the corneal and abdominal reflexes. Appearance of pathological reflexes is not a constant phenomenon.



Ski Jumping

In the 1880's Norwegian immigrants introduced the sport of Ski jumping to the United States. Soon, the sport was becoming a popular winter activity in towns throughout the Midwest. Red Wing became home to one of the more popular clubs, the Aurora Ski Club. Several national championship ski jump events were held in Red Wing and the first recognized North American distance record was set in Red Wing by Mikkel Hemmestvedt. Hemmestvedt flew a distance of 37 feet from a jump located in the Red Wing bluffs.



Close-up view of Cuff 'A'

Eyes: Ophthalmoscopic observations were made on a number of tests. No change was noted in the optic nerve head or in the retinal arteries while a slight to moderate dilation of the retinal veins were noted which disappeared immediately on deflation of the cuff. The pupils usually dilate during cerebral anoxia.

Engorgement: With complete arrest of cerebral circulation, the eyes and the face remain white and these subjects usually show blackout.

In rare instances a subject has failed to blackout with relatively prolonged anoxia without showing engorgement.

Engorgement, consisting of gradual reddening of the eyes and face, occurred in 35 out of the 73 subjects and in 60 out of 184 trials in the Minnesota State Prison group of subjects with the older cuff which was not held down to the lower part of the neck.

In some subjects, engorgement appeared in some tests and not in others. A number of subjects, showed marked tendency to engorgement and were quite consistent in repeated tests.

This phenomenon appears to be the result of some continuation of arterial inflow of blood into the head, with venous occlusions preventing outflow, and therefore relatively incomplete cerebral anoxia.

In subjects who engorge, there is blanching of the sclera on release of pressure with complete blanching in about

two minutes.

With the new cuff, which is held down to the lower third of the neck to apply pressure to the first part of the vertebral artery where it is surrounded by muscle, engorgement has become very infrequent.

In the St. Cloud group of 53 subjects, only 4 showed engorgement.

The observation has also been made that a greater total pressure achieved by increasing the width of the inflatable tube may also aid in preventing engorgement.

Unusual Responses: Two men (one in the Stillwater series and one in the St. Cloud group) presented reactions that were somewhat unusual.

The Stillwater subject on the 5th trial (second one for the same day) became somewhat sick to his stomach and vomited. Upon examination it was found he had a red throat and a temperature of 100. He was kept in bed a day and then had no other apparent trouble. On this trial he blacked out at 9 seconds.

The second subject had a severe reaction on his 3rd trial at 5 ½ seconds. He had a tonic and clonic seizure mainly in orbicularia oculi muscles. He became conscious and then fainted for a few seconds. This happened 3 times. He appeared perfectly well within one hour. Temperature normal. B.P. 111/80, and was neurologically negative on two examinations that afternoon. (His story is as follows)

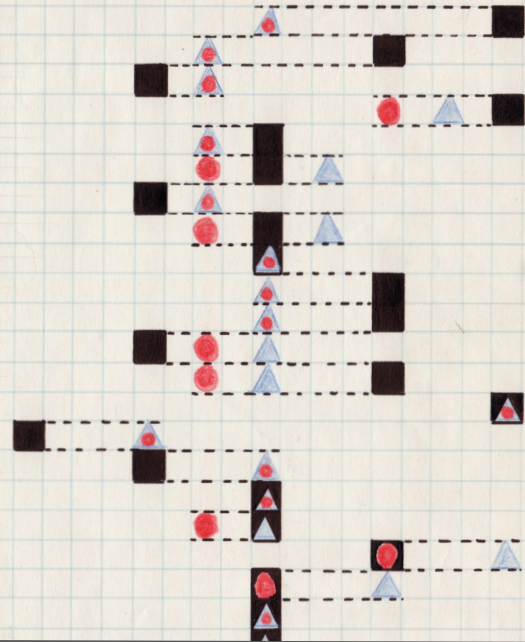
BLACKOUT

St. Cloud Group - Cuff No. 3
Ages 18-24
(In this series the vertebral arteries were eliminated.)

Each number represents one subject

<u>Legend</u>	
■	<u>1st. trial - August 24, 1942</u>
▲	<u>2nd. trial - August 25, 1942</u>
●	<u>3rd. trial - August 31, 1942</u>
▲	<u>1st. and 2nd. trials</u>
●	<u>1st. and 3rd. trials</u>
▲	<u>2nd. and 3rd. trials</u>
▲	<u>1st., 2nd., and 3rd. trials</u>

Graph presents 22 cases
who had definite blackout
for three successive trials.



"I heard the count of 5 then it seemed as if someone hit me on the left side of the head. Head felt light like a feather; knees weak. The first thing I remember was Dr. Rossen's hand on my wrist; that I saw rather than felt. Headache seemed to come on sort of fast, and then partly leave. The jolt felt much like being knocked out in a fight. The blackout did not come like the first two, but everything went pitch-black when I felt the jolt. I know of being asked how I felt a few times, but I couldn't quite tell you how I felt until a few seconds afterwards, after my head cleared up. Knees felt weak and tired while walking to hospital. Felt faint while coming downstairs in the case. Strong coffee relieved lightness from head for awhile. (written at 11:45 a.m.)"

"1:00 p.m. Knees good, Very slight headache, Shakiness entirely gone."

Summary Data

With the complete arrest of cerebral circulation, blackout is constant on repeated trials. This indicates that differences in sensitivity observed in different subjects may be a measure of the sensitivity of the brain cells themselves to acute anoxia.

The variations observed in different subjects appear to be great enough to constitute a basis for classification of potential pilots.

In 341 tests made on 129 normal males in the age group 20-25 inclusive, no deleterious effects were observed.

The characteristic reactions resulting from acute anoxia from arrest of the cephalic circulation in man are sudden blurring of vision, constriction of the visual fields, fixation of the eye balls, loss of consciousness, and anoxic convulsions, which are tonic and clonic in type and rarely persist for more than a few seconds.

Very rapid recovery of all functions was noted.

Discussion

When looking at the results from this study, especially with the knowledge that we have today, it seems apparent that Kabat, Rosen and Anderson duplicated the same set of symptoms that plague many patients with orthostatic intolerance and orthostatic hypotension. Although the onset of symptoms may not occur as rapidly as when applying 600mm of mercury to the neck, for the individual

impacted with these conditions, the symptoms are strikingly similar. Visual problems, a sense of knowing what is happening without being able to respond, fixed stares and syncope are all common problems that affect the individual who suffers with Dysautonomia. Of note are the peripheral nerve symptoms that occurred in the subjects. Many patients with autonomic dysfunction complain of similar symptoms that perplex their physician. An understanding of the benefits of improved blood supply to the brain would be of value to patient care. It may also be of importance to understand what the long term effect of blood supply shortage is on the brain cells.

An obvious concern for anyone looking at this study in today's light is the use of inmates and hospital patients as subjects of the study. What is important to understand is the research climate that existed at the time of the study. The use of inmates as research subjects was not only a common practice at that time, but one that was condoned by the government, medical associations and the public as a whole. The American Medical Association established a set of guidelines in 1946 that covered the use of inmates, requiring the following:

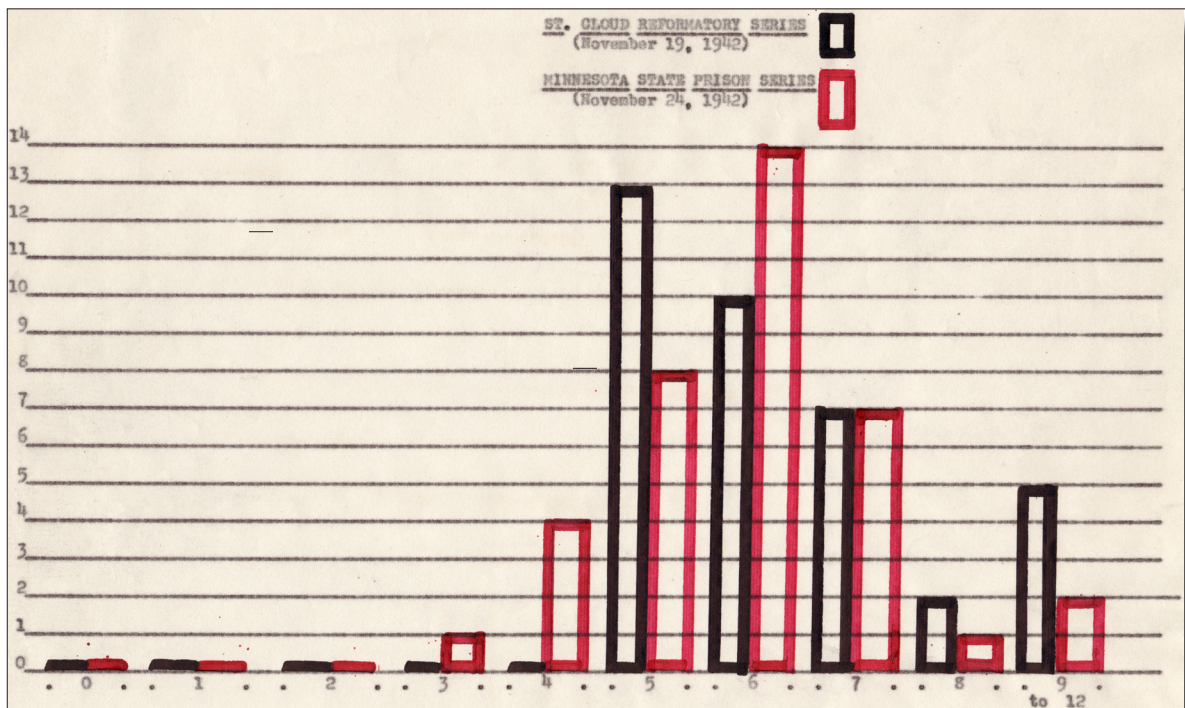
1. *The voluntary consent of the individual on whom the experiment is to be performed must be obtained*
2. *The danger of each experiment must be previously*

investigated by animal experimentation, and

3. *The experiment must be performed under proper medical protection and management.*

The care given by this team went beyond the guidelines of the time: animal studies were completed, all inmates were informed and were volunteers, medical experts were on hand for all trials and the researchers went so far as to become the initial subjects for the experiments. Patient follow-up was completed to assure there were no harmful effects from the experiments. Numerous examples can be cited of much more extreme studies that were conducted using prisoners as research subjects. In fact, as late as 1972 the FDA noted that as much as 90% of all new drugs were initially tested on prisoners.

Another important point that needs to be reviewed when looking at the use of inmates for this study is the atmosphere that prevailed across the country regarding the need for everyone to help in the war effort. The purpose of this study was to help pilots who were at risk, or dying due to blackouts. The problem was enough of a concern that Hollywood even played a role, producing "Dive Bomber" in 1941, a movie starring Errol Flynn that focused on the scientific efforts to help pilots who were passing out. Volunteering for this study allowed prisoners a chance to participate in the war effort. Letters from the prisoners who were subjects of these tests include statements of their



Loss of Consciousness Time - St. Cloud (-□-) Stillwater (-□-)

patriotism, as evidenced by the following excerpt:

Dear Dr. Rossen,

May I extend my sincere thanks for your kind letter of September 3rd. If my services were of any use whatsoever, I shall consider myself well repaid.

Should you, or anyone else, at any time in the future, desire my services for any type of test which may aid our United States in attaining complete victory, do not hesitate to call on me.

Clearly, the young men who were in prison were concerned about the war effort. Several of the inmates volunteered as many as nine times.

The use of hospital patients was likewise a common occurrence at that point in time. The guidelines that are in effect today were not put into place for many years after this study was completed. It wasn't until 1963 when the National Institutes of Health addressed this issue and it took three years of review before policy was put in place regarding informed consent of patient subjects in research. With an understanding of the practices in place at the time this research was completed, the ethical standards of the day were clearly met by the research team. While it is easy for us to wonder how these patients could be used as research subjects, we need to understand that Dr. Rossen

was interested in learning if patients might improve with this technique.

It is also important to understand the caliber of the research team that completed this study. John P. Anderson was an accomplished visual artist who was a pioneer in the modern art movement in the United States. He grew up in an environment where research, education and an appreciation for the arts were held in high esteem. His father, A.P. Anderson was an educator, scientist and a supporter of the fine arts who established a legacy of interest for learning in his children. The Anderson Institute's focus shifted after a few years and a new team of scientists came to Red Wing, forming the research and production company that is known today as Central Research Laboratories. John's wife, Eugenie Anderson, would go on to become a key leader in the Democratic Party (DFL) in Minnesota. She was named by President Eisenhower as the United State's Ambassador to Denmark, and then by President Kennedy as the ambassador to Bulgaria.

Dr. Ralph Rossen spent many years after this study investigating the possible use of this knowledge by the military for the betterment of pilots. His primary field of interest, however, continued to be the treatment of mentally ill patients. In 1950, Dr. Rossen was named as the first

Re: Men Examined & Tested
Dr. Ralph Rossen

Dear Sir:

In reply to your letter of the 4th inst. in regard to a recent inquiry made by Dr. Ralph Rossen, Superintendent of State Hospital at Hastings, as to the after-effect of the tests conducted by him.

In this connection I wish to state, that as far as I can determine there were no bad after-effects of any kind. In conversation with several of the men tested, they state they experienced no untowards effects. They seemed very enthusiastic about the whole thing, because they thought they contributed their bit towards the War effort. They were practically unanimous in their assertion that they would submit to further test if called upon to do so.

Sincerely yours,

RAY G. JOHNSON

Ray G. Johnson, M.D.
Prison Physician

commissioner of Mental Health and Mental Hospitals for the state of Minnesota. He became a leader and advocate for improved mental health care. In a report to the Director of Public Institutions in 1951, Dr. Rossen summed up the need for his position by stating:

The vital consideration begins with "One Patient" who was born, who had a childhood, who has all the bodily and emotional needs—and more, in the most cases,—of any human being. Examine all the needs of care and treatment of the one patient and the necessary ramifications of the program are revealed. The development and operation of the program starts from this one patient.

Dr. Rossen wrote two texts on the need for effective, dignified care for the patient, and was a pioneer in establishing modern medical guidelines for this often neglected and misunderstood group of patients.

Dr Herman Kabat received his PhD from Northwestern University at the age of 22. He came to Minnesota in 1942 where he became an instructor in physiology at the University of Minnesota. While there, he began working with Sister Elizabeth Kenney, who had just established the first American location for her treatment of infantile paralysis. Kabat's research indicated that Prostigmin worked to relieve muscle tension in individuals with paralysis or cerebral palsy. This relaxation allowed Kabat to have therapists "retrain" non damaged portions of the brain take over muscle control. Kabat returned to school to get his MD and began treating patients in his home in Washington DC.

Kabat's work on the treatment of patients with paralysis, polio and muscle wasting diseases drew world wide attention. His new technique, now known as proprioceptive neuromuscular facilitation was developed with Margaret Knott and Dorothy Voss. The therapy program was designed to facilitate flexibility, strength and coordination.

Henry Kaiser, known as the "father of modern shipbuilding", and perhaps the most powerful businessman in the West during the time of World War II, had a son that suffered from Multiple Sclerosis. He sent a team of physicians to learn more about the techniques used by Dr. Kabat in hopes that his son could benefit. After sending his son to Dr. Kabat and seeing his success in treating him, Kaiser eventually persuaded Kabat to come to California. There they established the Kabat-Kaiser Rehabilitation Institute in Vallejo. The center developed an outstanding reputation for treatment of patients and is today, as part of Kaiser-Permanente, known as the Kaiser Rehabilitation Center.

Remarkably, the medication, prostigmin, used by Dr. Kabat has recently been advocated as a therapy for patients that experience severely low blood pressure as a symptom of their Dysautonomia.

John P. Anderson, Ralph Rossen and Herman Kabat likely did not realize the importance of the research they were completing in Red Wing. Their study on Acute Arrest of Cerebral Circulation in Man brought to Red Wing a group of people who would help shape our society in the arts, politics, and most importantly in patient health care.

NDRF - National Dysautonomia Research Foundation
PO Box 301
Red Wing, MN 55066
www.ndrf.org

Telephone: (651) 267-0525
Email: ndrf@ndrf.org
© 2007