This book exposes the dangers of the bio-waste creatinine and its connection to Chronic Kidney Disease and related maladies. The book educates from a medical standpoint how to avoid potential renal problems by avoiding creatine-dense foods and over-the-counter creatine monohydrate.

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Preface

Creatine was discovered in 1832, followed shortly there after by the identification of creatinine in the mid 1800's. Interest in these muscle associated molecules was initially esoterical, hence the information generated from the very early creatine/creatinine investigations was relegated to the dusty pages of scientific literary obscurity. Creatine went relatively unnoticed, outside of scientific circles, for about the next 120 years. Only in the mid to latter half of the 1990's, did the athletic industry, in their never-ending quest to uncover new untapped, non-doping performance enhancing substances, for a hungry athletic market, take a closer look at the usefulness of this natural dietary constituent of meat.

At the time of its initial discovery, creatine was labor intense and expensive to isolate. But now industry had learned to synthesize creatine monohydrate in virtually limitless quantities making it a marketable product. Synthetically produced creatine monohydrate, in its various formulations, has become one of the sports nutrition industry's top-selling supplements. Today, creatine monohydrate sales are upwards of almost 3 million kilograms worldwide, yearly.

While creatine monohydrate has found its way into every level of the athletic and fitness industry, its journey has not been without some controversy. The early part of this millennium has seen a tidal wave of opponents and proponents, all arguing the safety, merits, and ethics of using this synthetic, highly ergogenic, material.

While creatine can be thought of as essential *'bio-fuel'*, creatinine – irrespective of its origin – must be considered *'bio-waste'*. While no one in the scientific arena questions the safety of normal physiological-level creatine, the occasional controversy arises when the physiological creatine level is artificially maintained at super-physiological levels (abnormal for the respective individual). In such instances, the amount of this *spent fuel* generated can increase significantly, along with its potential to cause physiological burden and unknown negative impact over time. It is this latent potential, suggested in some of the animal studies, as well as occasional antidotal human reports, that has caused the sounding of a cautionary note with regard to the perpetual, chronic use of large gram quantities of creatine monohydrate.

While the author of this work acknowledges that it may be possible for a few individuals, who are embracing a meat-saturated lifestyle, to ingest as much as 3 – 5 grams of meat-creatine daily, raising and sustaining their potential creatinine burdened naturally, it is also likely that excessive creatinine will be generated (on a long-term bases) from the regular ingestion of large amounts of commercially available creatine monohydrate. Hence, a portion of the discussion in this book will refer to creatinine generated from synthetic creatine monohydrate.

Also of interest, in the scope of this discussion, will be the creation of by-products or product *contaminants* – creatinine, as well as secondary products such as dicyandiamides and dihydrotriazine, and their potential to cause long-term physiological impact. Such materials can potentially be generated (in minute quantities) during various steps in the manufacturing process.

Of equal interest is the potential creatinine has shown (in some studies) to be able to be transformed into one or more substances which either are, or may act in, a mutagenic and/or carcinogenic capacity.

The purpose of this book is not to address the occasionally heated, and undeniably controversial, issues surrounding the efficacy, immediate safety, or overall merits or ethics of creatine monohydrate use by individuals (as young as 9 years old), who are involved in today's sports industry. Instead, this work will take a close analytical look at the potential excess **creatinine** – the end product of all endogenous and exogenous creatine(s) – has to cause dangerous physiological burden, against the backdrop of pre-existing (and often undiagnosed) renal disease, which today exceeds 20 million people in the U.S. and millions more worldwide.

Chapter 1

Keeping a 'Bio-mechanism' in Perpetual Motion

Introduction – The Body Human

"How wondrous is the body and all its workings".

What poet and artist alike have unknowingly praised in sonnet and media is in fact infinitely more complex than any physical rendering could have ever depicted – the intricate inner workings of our living machine – the body.

The body is truly an amazing machine, without a man-made mechanical equal. Even in the 21st century, we are just now beginning to unravel the mysteries of its most intricate processes which are in a state of bio-mechanical 'perpetual motion'. What regulates the creation and/or sequestering of specific amino acids, the formation of a specialized protein, or an enzyme whose existence is measured only in seconds, and most important – how is it all kept in harmonious synchronized motion?

For the most basic biological processes to continue uninterrupted, the body requires a means of mobilizing energy throughout the system. To accomplish this, various eloquently designed mechanisms, and 'facilitators', are created. These facilitators mobilize and direct high-energy raw materials to intercellular sites for 'refinement' and processing. The newly synthesized products are then shuttled to sites of use, undergo further modification (in some instances), and finally 'spent' components, or fuels, are either transported via chaperone, or simply allowed to circulate back to an appropriate waste 'recycler' or, in many cases, the biological sewage 'disposal system'.

Creatine - Bio-Fuel of Life

No discussion of creatinine could ever be complete without a close look at its starting material – creatine.

Creatine represents a form of '*bio-fuel'*, a physiologically essential nitrogenous compound.

Also known as methyl guanidine acetic acid, creatine is one such intermediate high-energy facilitator. Creatine is absolutely indispensable. If the body were suddenly divested of all creatine, life would cease.

Creatine is a non-protein, amino acid molecule. Its role in cellular energy regulation is intimately interconnected with life's processes, and based on the extremely complex biochemistry of metabolic supply and cellular energy demands (Persky and Brazeau. 2001). All of the creatine which is synthesized by the body (endogenously) is synthesis by direct involvement of three organs - the kidneys, liver, and pancreas using arginine, glycine, and methionine (Burke. 1999) as the basic amino acid building blocks **(Fig. 1)**. The initial step in the molecular creation process is a basic coupling reaction of arginine and glycine via an A-G transferase enzyme. Products of this rapid reaction are ornithine and guanidinoacetate. The guanidinoacetate molecule itself then undergoes rapid methylation, which occurs via S-adenosyl methionine (or SAM-e), an enzymatic cofactor involved in methyl group transfer, originating primarily in the kidneys.

FIGURE 1 - Basic amino acid coupling reaction - a two step process in the creation of endogenous creatine

Step #1 Arginine + Glycine ⟶ **Ornithine + Guanidinoacetate**

(A:G – amidinotransferase)

Step #2 Guanidinoacetate + ***(Me)-SAMe*** ⟶ ***Creatine***

Once syntheses are complete, creatine travels to the site of utilization *(predominantly skeletal muscles)* **(Fig. 2)**.

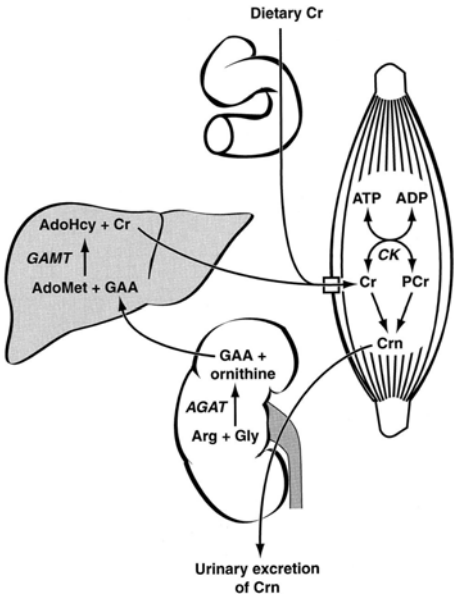

FIGURE 2 - The major paths of creatine (Cr) metabolism in the mammalian body. For the most part, between 94-95% of all Cr is found in skeletal muscle tissues. Because muscle has almost no Cr-synthesizing capacity, Cr has to be transported to the site of need. A muscle cells daily demand for Cr must be met by intestinal absorption of dietary Cr or by Cr biosynthesis.

[Used with permission – Wyss M. and Kaddurah-Daouk R., 2000]

It has been estimated that approximately 94-95% of all creatine in the body is in close proximity to the skeletal muscles. Most of the remainder of all inter-corporal creatine can be found in the brain, kidney, and liver (Balsom et al. 1994; Casey and Greenhaff PL. 2000).

Creatine is rapidly transported across the cell membrane via a sodium dependent transport 'gating mechanism' (Ganguly et al. 2003). Because creatine is an essential constituent of all muscle fiber bearing tissues, its role in the metabolic transfer of energy, and subsequent chain of events, is absolutely critical. One of the most important features of creatine is the fact that it can, via its chemical property, find the appropriate high-energy phosphate molecule and undergo reversible binding (**Fig. 3**).

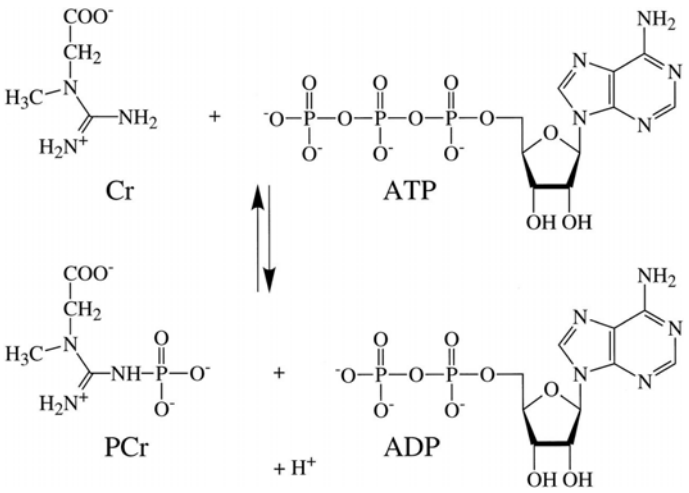

FIGURE 3 - The creatine kinase (CK) reaction. PCr, phosphorylcreatine; Cr, creatine.

[Used with permission – Wyss M. and Kaddurah-Daouk R., 2000]

This process begins with the creation of adenosine triphosphate (ATP) via aerobic respiration. Once synthesized, it then reacts rapidly with 'free' creatine in the cell. This reaction is facilitated using a mitochondria associated creatine kinase. The enzymatic results are the formation of adenosine diphosphate (ADP) a lower energy molecule, and phosphocreatine – a high energy 'storage unit'. Synthesis continues rapidly until an intercellular equilibrium is reached (**Fig. 4**). In a 'depleted' muscle–energy state, the amount of time to repletion-equilibrium may vary. Once phosphocreatine is formed, it

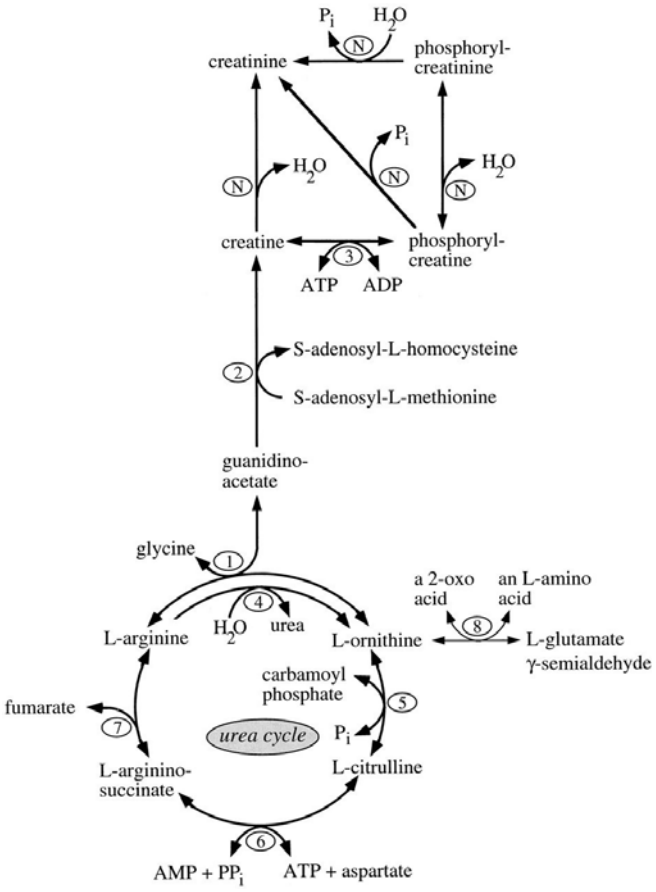

FIGURE 4 - A schematic overview representing the chemical reactions and enzymatic processes involved in the creation and metabolism of creatine and creatinine.

[Used with permission – Wyss M. and Kaddurah-Daouk R., 2000]

remains trapped in the skeletal muscle cell because of its now polar nature which is incompatible with the inner-cell membrane 'gating' transport mechanism. The amount of phosphocreatine that any one cell can contain is a reflection of its energy 'reservoir' capacity. Hence, when ATP is used during exercise (breathing, standing, walking, jogging, etc..) phosphocreatine liberates its high-energy phosphate moiety back to low-energy ADP to replenish the cell's ATP supply. As such, the re-phosphorulation process is

driven forward in a continual cycle with newly synthesized creatine and, to a substantially lesser extent, *recycled* creatine. Despite evidence that a small number of de-phosphorylated creatine molecules can be re-cycled, by in large, the more common fate of used creatine is its conversion to creatinine. Transformation (degradation) process is a continuous, non-enzymatic dehydration reaction. (Pline and Smith. 2005).

In addition to acting as an energy 'shuttle', creatine can also act as buffer. This activity is seen when creatine is in the same spatial association as nerve cells and striated tissue. In order to accomplish this, phosphocreatine spatially moves within these cells. An interesting observation has been made for nerve cell phosphocreatine. It has been shown to accumulate toward the synaptic head. In this capacity, creatine can assist with the management of both high energy, and the more stable synaptic potential energy (Brudnak. 2004).

A Supplement is Born

Whether naturally, or artificially produced, creatine and creatinine are 'locked' in an endless union – the first required to aid in maintaining cellular existence, the second, the inevitable end product of creatine's existence.

Why has a relatively obscure scientific discovery, made over a century and a half ago, become so important to so many today? And more importantly for this discussion, what are the potential consequences of its overuse in those with kidney disease?

Shortly after its discovery in the flesh of freshly killed game, the term creatine was introduced (Kepler. 1929; Bears. 1943). Given the crudeness of

the isolation technique of 1835, this initial muscle-tissue extract was most probably a mixture creatine, creatinine, and sarcosine (N-methyl glycine – an amino acid found in muscles and other tissues [Wikipedia, 2005]) as well as various intermediates. Nevertheless, in 1835 the French scientist Michel Eugene Chevreul's finding was initially considered controversial by the scientific community (Kepler. 1929). Isolation techniques were perfected, and by 1847, Justus von Liebig was finally able to demonstrate that creatine could be reliably isolated from various tissues of any freshly killed animal's carcass. Liebig also noted that the quantity of creatine was greater in wild animals as compared to captive domestic animals. This discovery pointed, in some small way, to the role of creatine in an energy-demanding lifestyle (Williams, Kreider, and Branch. 1999). In the same year, Liebig (followed by Gregory in 1848, and Schlessberger in 1848) demonstrated that this molecule could be found in all mammals, birds and fish.

Before 1910, creatine had been, for the most part, connected primarily with muscle-related tissue, but there was still no clear consensus as to the 'richest' site of creatine accumulation, or why. Liebig's initial work in 1847, and those who followed, had produced evidence showing that a considerable amount of creatine could be found in 'dark muscle' tissue – such as the cardiac muscle. Cardiac muscle's contractions are involuntary and smooth in motion, in some respects like the action of the diaphragm muscle. A heart's muscle action is governed by the autonomic nervous system, and hence moves in a predictable pattern and speed (for the most part). This muscle undergoes few rapid pace changes, and no stops (except the final one!). Because of its physical behavior and its physiological role, the cardiac muscle's energy needs are significant but

relatively constant. However, in 1910, Pekelharing and Van Hoogenhuyze would provide the first real evidence for the richest site of creatine accumulation, and a glimpse into creatine's most important function as an energy delivery system or 'sink'. Pekelharing and Van Hoogenhuyze found that muscles which were involved in physically demanding (strenuous 'explosive' energy bursts, or prolonged aerobic) activity, harbored – by far, the most creatine. The richest site for creatine was actually discovered to be the rapidly contracting pale muscles, instead of the more slowly contracting dark muscles, as it had been believed (Pekelharing and van Hoogenhuyze. 1910).

During the early years, extraction of creatine from fresh muscle tissue was an expensive and labor-intense activity. Nevertheless, by the dawn of the 20th century the first creatine supplement had been produced in a laboratory and had been shown to increase muscle creatine content in experimental animals.

The phosphorylated form of creatine – phosphocreatine, was discovered in 1927 by Fisk and Subbarow. Through their research they were able to show that this unstable compound, found in fresh muscle tissue, disappears rapidly (in about 20 minutes) whether their tissue sample was let to stand on the lab bench, or was stimulated. Inorganic phosphate and creatine replaced this labile compound. However, when fresh muscle was collected after a 'rest from fatigue' they found that the compound had resynthesized itself. In the same year, an unstable ester of phosphoric acid, which was loosely associated with creatine, was also discovered (Eggleton and Eggleton. 1927). These discoveries helped bolster a hypothesis about creatine's potential significance in relation to where it was discovered, and why it was found in larger quantities. Prior to this work, creatine was believed to be nothing more than a simple metabolite or a

random by-product of muscle activity. However, the work of Fisk, Subbarow, and Eggleton(s) provide the first tangible evidence that creatine wasn't simply a metabolite, but a necessary component for normally functioning tissue.

Numerous additional milestones, during the early years of creatine's discovery, which are beyond the scope of this book, yet equally important, have been documented in a comprehensive review by Hunter (1928).

It's important in this treatise to note that, as knowledge concerning the functional purpose for creatine grew, the first potential uses for creatine proposed were not recreational (as a sports supplement), but medicinal. As early as the later part of the 19th century and into the 20th century, investigators had (and still do) looked at creatine for its potential to treat muscle wasting diseases. While creatine's use was confined to laboratory animal supplementation and experimentation, during the early part of the 20th century, it was hypothesized that, if large muscle-creatine 'stores' were an essential part of a healthy muscle tissue's profile, could various forms of muscle wasting diseases be reversed by the reintroduction of extra *synthesized* creatine? Unfortunately, this is a question which has stubbornly remained inconclusively answered to this day.

Initially, creatine's use as a test substance had been restricted to relatively short experiments in laboratory settings. Before a reliable, (reasonably) clean, and relatively inexpensive creatine syntheses protocol was developed, creatine had been isolated from fresh muscle tissue and even urine. This made it far too labor-intense and costly to be seriously considered for use in human test

subjects. Initial laboratory chemical reaction protocols, yielding high percentages of impurities were also impractical. Serious research work in human subject could not begin until a method of large-scale production was available. By 1903 papers began appearing in the American Chemistry Journal which described simple straightforward chemical reactions yielding methyl guanidine acetic acid (creatine). By 1930, a reliable method for preparing creatine had been described, which involved reacting sarcosine hydrochloride with potassium hydroxide and methylisothiocarbamide hydrochloride. Under controlled laboratory conditions, creatine could be made to crystallize out as woolly needles (synthesis of creatine today occurs by reacting potassium or sodium sarcosine with cyanamide).

Between the discovery of creatine kinase – an enzyme that catalyzes phosphocreatine, in 1934 and 1940, a slow shift in what investigators were hypothesizing that this substance could be used for, had already begun taking shape. In 1940, investigators had begun to theorize that creatine could possibly be used as an ergogenic aid, based on preliminary data obtained from early gelatin supplementation research. Because gelatin and creatine both contains the glycine building block (approximately 25%), it was reasoned that supplementation with glycine or gelatin should be ergogenic in nature. Though studies with both substances continued into the early 1960s, consistently conclusive evidence for their ergogenic potential remained lacking (Williams. 1985).

By the early 1960s (sited in anecdotal reports), creatine use by competitive athletes had already been quietly undertaken in Eastern European block countries (Plisk and Kreider. 1999). However it wasn't until almost the

beginning of the 1990s that creatine found its way into the world-wide sports arena and on the nutritional store shelves as a mass-marketed product.

An Ergo-Economic Bonanza

Today, synthetic creatine (creatine monohydrate) in various forms and packaging is routinely mass produced. With sales approaching almost 3 million kilograms annually, this synthetic energy-bearing supplement is enjoying estimated sales revenue of $100 million per year (Strauss and Mihoces. 1998). As of this writing, hundreds of reports, both pro and con, have been generated on its effectiveness as an ergogenic aid in all areas of sports fitness. Biologically produced creatine is both a natural and very essential substance – normally in metabolically high demand. It would be expected that reports on the impact of creatine monohydrate, on the users' health, would end with either a 'unanimous cheer', or at least – a 'neutral resign'. Instead, a few '*Boos'* have now been heard. Isolated reports have been trickling in, pointing to a potential 'dark side' of this synthetic substance, and casting a thin cloud of concern on the horizon.

Summary

Unraveling the intricate biochemical processes responsible for corporeal motion – from the briefest of cellular contraction to the dynamic perpetuation of life itself, has been one of the greatest sought after secrets. With the discovery of creatine, a natural biochemically produced substance, more than 170 years ago, science has slowly added another chapter to this quest. Beginning with a basic understanding of creatine synthesis from a few amino acid building blocks,

creatine is now acknowledged as vitally necessary for normally functioning tissues. With the finding of the richest site of creatine accumulation in rapidly contracting 'pale' muscle tissue in 1910 (Pekelharing and Van Hoogenhuyze) and enzymatic transformation into a high-energy carrier, the elucidation of its true function suddenly came to light. Creatine was a substance, which acted reversible – as an energy storage, transfer system and buffer to maintain a positive energy equilibrium, perpetuating dynamic motion.

Lis and Bijan (1970) concluded that there was approximately 30 kilograms of muscle in an average adult male (proportionally less in the female due to secondary-sex characteristics which are hormonally related). An average of 5g/kg phosphocreatine exists in resting (male) skeletal muscle. This gives a total potential energy reservoir of about 150 grams of phosphocreatine per (male) human 'frame'. So at any given time, phosphocreatine and creatine can total approximately 400 mg/gram of muscle tissue.

Though creatine was initially framed as a potential medicinal substance, once a reliable method for preparing creatine came into existence, creatine quickly found its way into the sports arena as a potential ergogenic sports-nutrition. Today, a voluminous number of reports have described creatine monohydrate use in all aspects of exercise science and in several corners of medical therapy as well. While reports of its positive influence on human athletic performance have generally pointed to its potential safety, a scattered and growing number of reports have revealed emerging health concerns. Beneath the enormous shadow of preexisting (and often undiagnosed) kidney disease, professionals question the wisdom of the unbridled use of supplements.

This book exposes the dangers of the bio-waste creatinine and its connection to Chronic Kidney Disease and related maladies. The book educates from a medical standpoint how to avoid potential renal problems by avoiding creatine-dense foods and over-the-counter creatine monohydrate.

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