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Capecitabine Induced Hand and Foot Syndrome and the Reproducibility of Friction Skin

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CAPECITABINE INDUCED HAND AND FOOT SYNDROME AND THE REPRODUCIBILITY OF FRICTION SKIN

By

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ABSTRACT

CAPECITABINE INDUCED HAND AND FOOT SYNDROME AND THE REPRODUCIBILITY OF FRICTION SKIN

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In 2008, a 62 year old male was detained by United States Customs and Immigration officials when attempting to enter the United States because his fingerprints were not detectable. It was later reported by his medical doctor in Singapore that the individual suffered from Hand and Foot Syndrome (palmar-plantar erythrodysaesthesia) as a result of his cancer treatment of capecitabine (N4-pentyloxycarbonyl-5-deoxy-5-fluorocytidine) which causes interruptions to the normal growth of keratinocytes in the friction skin. Capecitabine is a recently developed, orally administered fluoropyrimidine prodrug designed to generate 5-fluorouracil through a three-step enzymatic process giving it antineoplastic properties to combat cancerous tumor growth in a number of different cancers, including adjuvant colon cancer, metastatic colorectal cancer, and metastatic breast cancer. This study consisted of a 253-day evaluation of the physiological effects to the friction ridge skin from an individual undergoing capecitabine chemotherapy treatment. The results indicate the quality of the friction ridge skin impressions decreased by 32% and to a degree which may impair the ability to positively identify individuals using friction skin impressions alone while undergoing this type of treatment and experiencing hand and foot syndrome. Following cessation of capecitabine treatment, normal growth of keratinocytes resumed returning the skin to a normal state

with no indication of damage thus demonstrating the persistency of the friction ridge skin despite the temporary toxicity of capecitabine.

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CHAPTER I

INTRODUCTION

Friction Ridge Skin

Friction ridge skin is a specialized type of skin found primarily on the palmar surface of the hands and the plantar surface of the feet. This special layer of skin is comprised of two anatomical layers, the epidermis and the dermis. The layer of primary concern for means of personal identification is the epidermis as it is comprised of a series of furrows and ridges with embedded eccerine sweat glands. Although eccerine sweat glands are found in skin throughout the body, they are found in the highest concentrations in the friction skin. As a primary function, these eccerine sweat glands secrete sweat and exude waste covering the friction skin with a contaminate or "matrix." This matrix, when in contact with an adequate surface or substrate, can be transferred to that substrate in the same unique formation as the friction ridges on the fingers resulting in what is commonly referred to as a latent fingerprint or latent impression.

Fingerprints take on three general patterns: the *arch*, the *loop*, and the *whorl.* In the arch pattern, ridges enter one side of the pattern area, make a slight rise in the center and exit out the other side. In the loop pattern, ridges enter one side of the pattern area, loop around to form a recurve, and exit back out the same side. Whorls can take on many appearances but generally take on a "bull's eye" appearance. Within the pattern areas of loops and whorls are focal points called *cores* and *deltas*. The *core* is the approximate center of the pattern area. The *delta* is the area at which the ridges diverge or form a Y shape (Enforcement) (Figure 1). The recognition, development and preservation along with careful analysis, comparison and evaluation of the features captured within the

transferred matrix is what allows a trained individual to render an opinion if individualization.

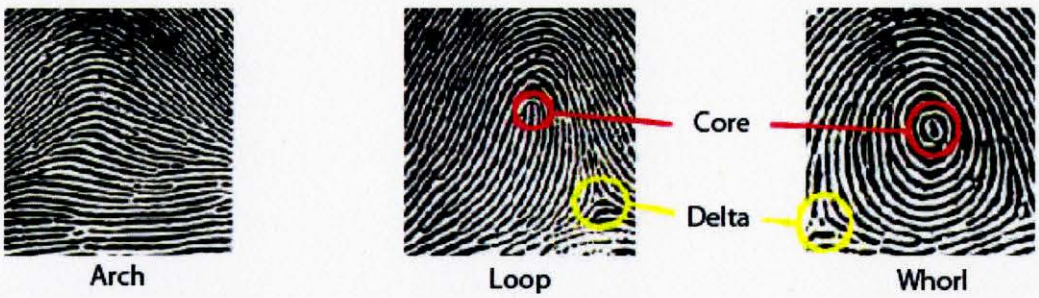


Figure 1. Fingerprint Patterns and Focal Points.

Friction ridge skin has been used as a means of personal identification throughout many cultures for thousands of years. Evidence shows the use of friction ridge skin as proof of an individual's identity in China dating as far back as 300 B.C. However, the modern day use of friction ridge skin as a means of personal identification has been used for well over a century with multiple purposes such as identity verification and forensic identification. International travel ports rely heavily on the use of fingerprints to ensure foreign visitors produce proper forms of identification and ensure these visitors do not pose a potential security threat. U.S. Customs and Border Patrol agents have the ability to reference a multitude of digitally captured biometric information databases in an attempt to conduct immediate and thorough security searches. Biometric information is captured and stored from individuals on a daily basis. Facial images, iris scans, and fingerprints are three of the primary means of biometrically enrolling an individual for later retrieval. While facial and iris recognition software are still somewhat in their infancy stages of development, the use of fingerprint identification has proven to be the mainstay of identification due to the low cost and quick results. One of the more frequently employed

techniques to enable personal identification is through the use of fingerprints via an Automated Fingerprint Identification System (AFIS). The use of fingerprints as a means of personal identification is dependent upon the reproducibility of the unique arrangements of friction ridge skin on the surface of the fingers. Due to the high volume of visitors processed each day in these international travel ports, officials rely heavily on automated systems to record and compare the fingerprints of foreign visitors prior to entry into the United States. Failure of the friction ridge skin to record properly will prevent this routine security process from occurring bringing into question a potential threat to national security.

Friction Ridge Skin Alteration

The idea behind using fingerprints as a means of personal identification is established on two basic premises: uniqueness and permanence. The first individual to recognize that friction skin was unique was German anatomist J. C. A. Mayer around the year 1788 while German anthropologist Hermann Welcker was the first to establish permanency in 1856. (U.S. Department of Justice, 2011).

Since this time, numerous attempts have been made by nefarious individuals to disguise or alter the unique arrangements of friction skin on the tips of the fingers in an attempt to avoid detection and/or fool automated systems. Some of the more notable attempts include that by the infamous mobster John Dillinger who used acid in an attempt to dissolve several layers of the epidermis (Figure 2).

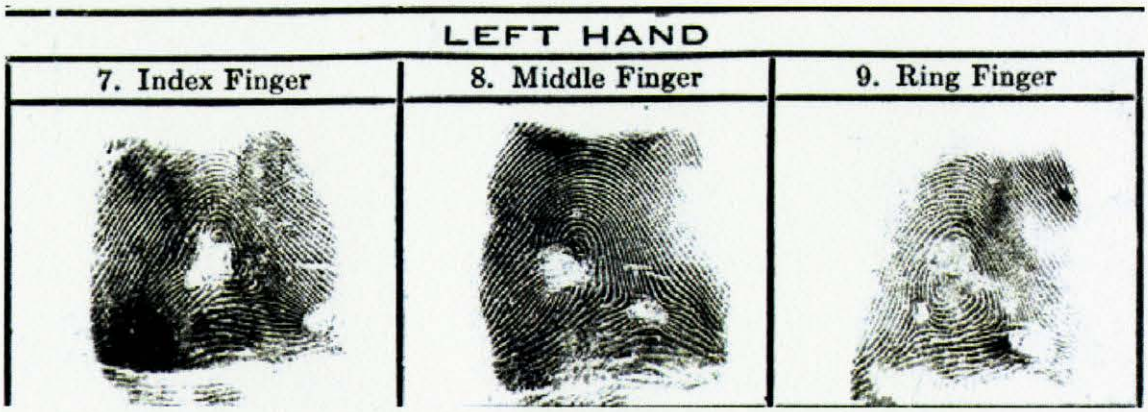


Figure 2. Postmortem record fingerprints of DILLINGER depicting acid damage (Wertheim, 2002).

Other techniques involved the use of abrasive materials to brush away the friction ridges, the graphing of other friction ridge skin (Figure 3) or non-friction ridge skin (Figure 4) transplantation onto the tips of the fingers and a more recent "Z-flap" surgical technique designed to alter the pattern on the surface of the finger (Figure 5).

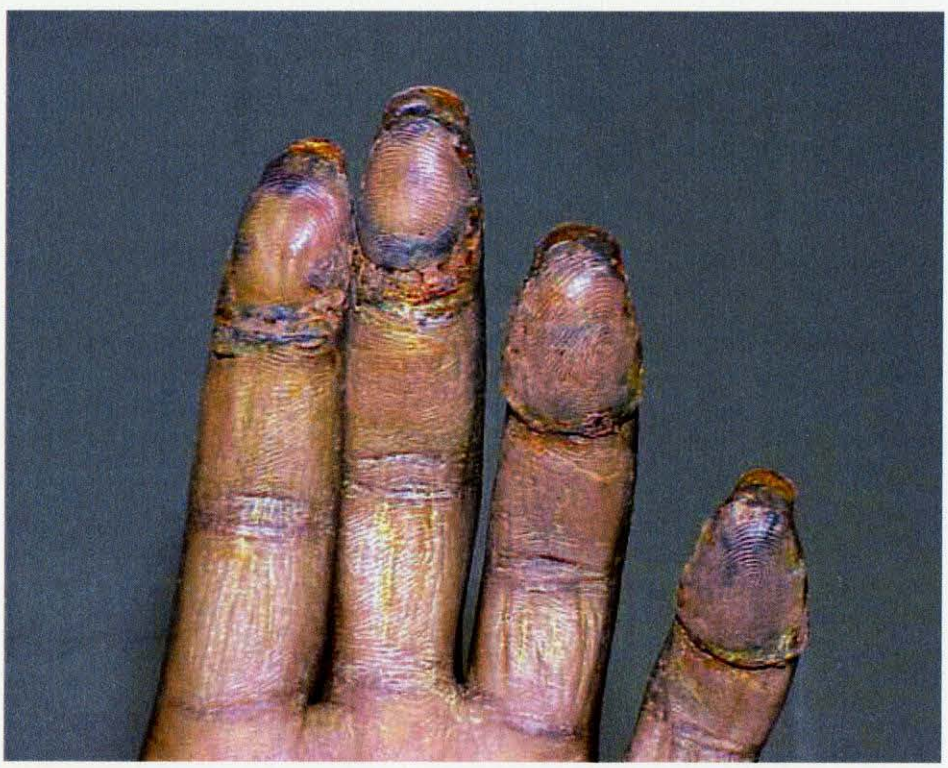


Figure 3. Transplantation of other Friction Ridge Skin onto the tips of the fingers.

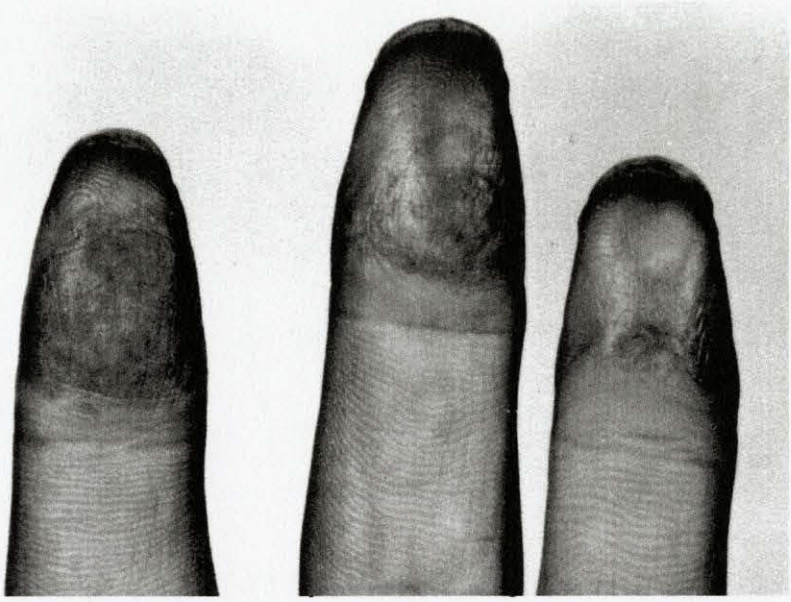


Figure 4. Transplantation of non-friction ridge skin onto the tips of the fingers.

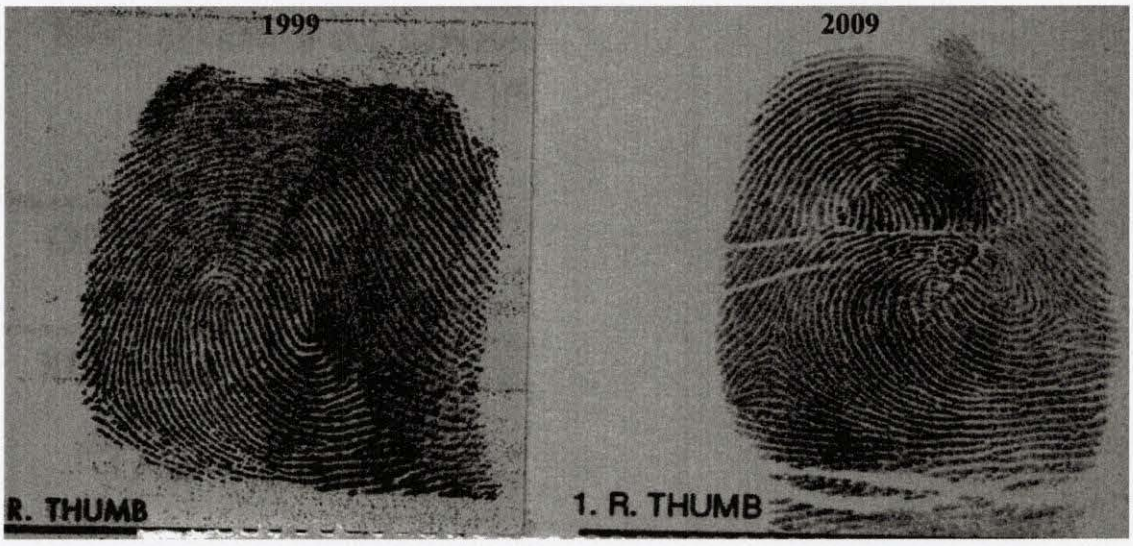


Figure 5. Right Thumb before (1999) and after (2009) Z-Flap alteration.

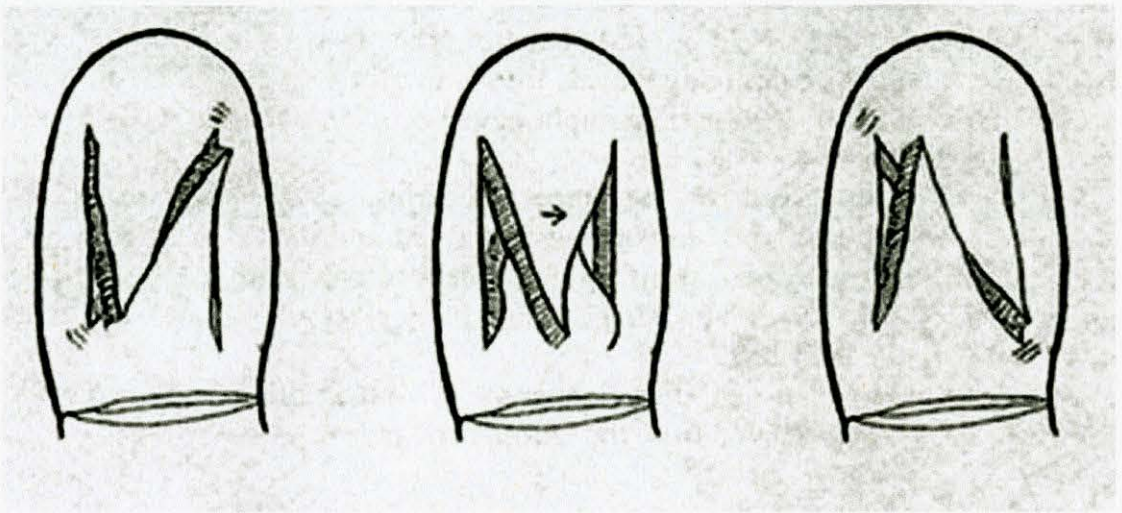


Figure 6. Diagram depicting method of Z-Flap alteration.

It is important to note here that all past attempts have been via either a deliberate topical application or physical alteration of the friction skin. Of more important notice is that despite the numerous attempts over the last 100 years, none have been successful. Recently, the author of this paper had the opportunity to observe the biochemical changes in friction ridge skin through an internal chemical application as an unintentional side effect of chemotherapy treatment medication. As a result, a study was conducted and the data referenced within this paper.

The focus of this study is two-fold: 1) To understand the association between capecitabine induced HFS and the reproducibility of friction ridge skin for forensic or other comparative purposes, and 2) To reinforce the basic premise behind friction ridge identification regarding permanency despite biochemical alteration. This will be accomplished by analyzing the previously recorded quality of record fingerprint impressions obtained from an individual diagnosed with metastatic breast cancer during the entire course of capecitabine treatment. While the changes in quality of captured ridge

detail throughout the course of chemotherapy treatment is the main scope of this project; the reemphasis of one of the key premises permanency behind friction ridge identification is a major contribution to the field of forensic science, particularly to the friction ridge identification discipline. The permanency of friction ridge skin after biochemical induced changes has not previously been explored in the literature available to the author.

CHAPTER II

LITERATURE REVIEW

The Skin

Friction ridge skin, like all skin on the human body has two outer layers: the *epidermis* and the *dermis* (Figure 7). The *epidermis* is the outermost layer of skin and is

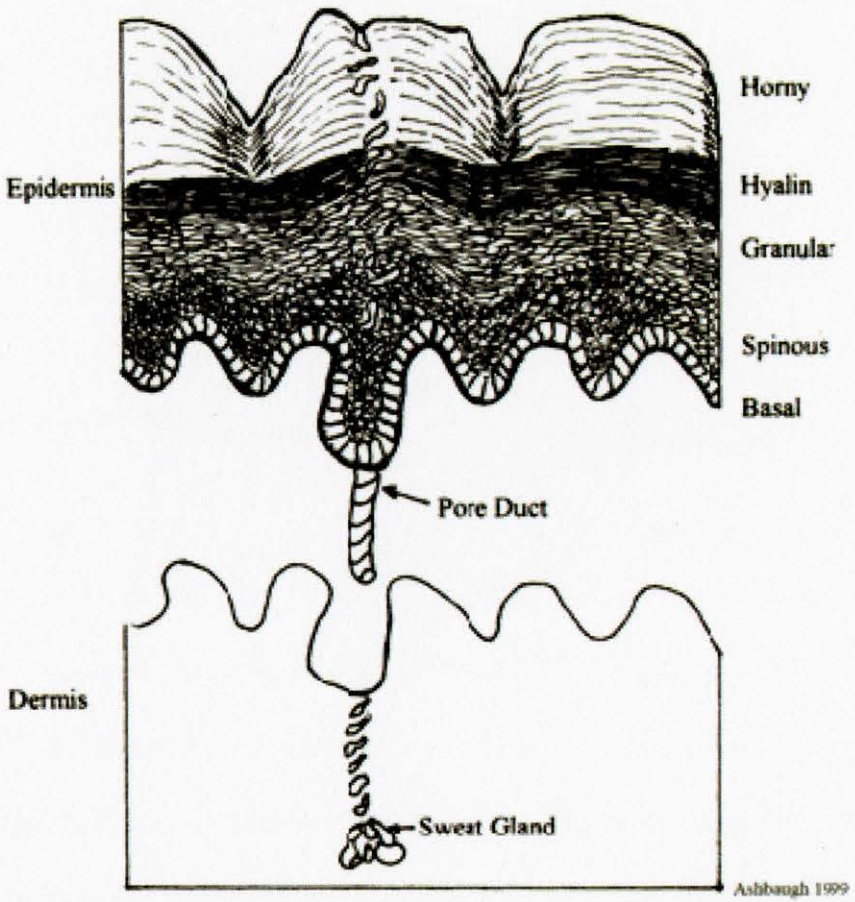


Figure 7. Dermis and Epidermis.

made up of several layers of skin cells, including the *horny layer* which is composed of dead skin cells at the skin surface. The *dermis* is made up of loose connective tissues and houses various blood vessels, tactile nerves, and glands, including sweat glands.

The lowest layer, or *basal layer*, of the epidermis is where new skin cells are generated (Ashbaugh, 1999) (Figure 8). Over the course of 30–45 days, as new cells are

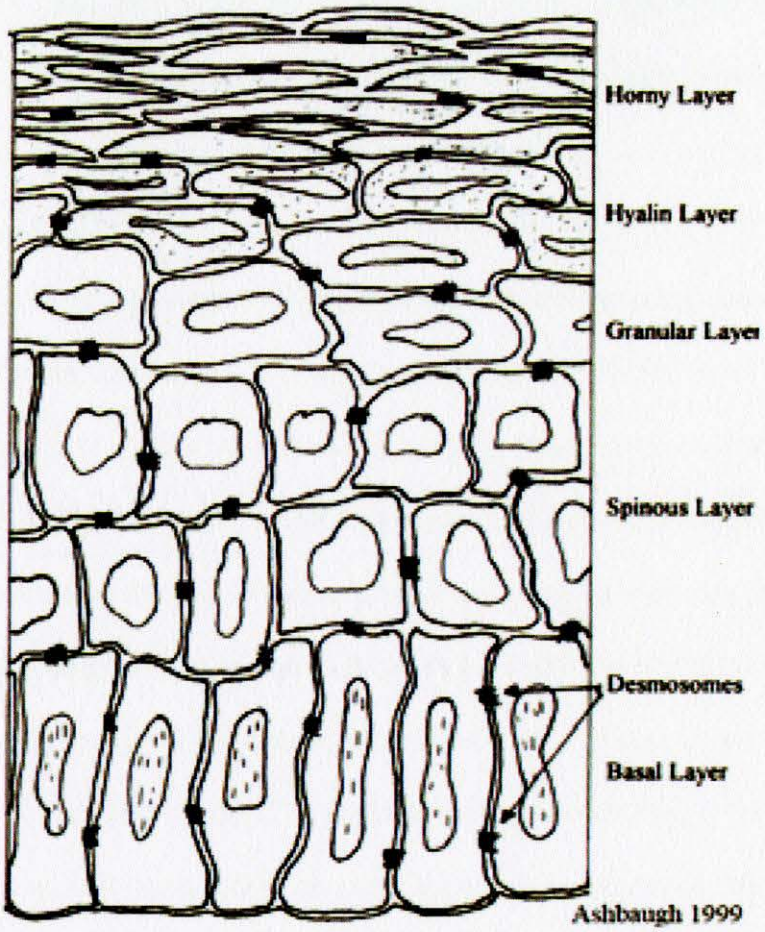


Figure 8. Cellular layers of the Epidermis.

generated, older cells migrate toward the skin surface. During the migration, the cells change in structure, gradually dehydrating and dying off as they reach the topmost or horny layer. Once at the horny layer, the dead skin cells will eventually be sloughed off, or shed, to make way for the newer cells. (Enforcement).

The Problem

It was reported in a letter published in *Annals of Oncology* in early 2009 by Dr. Eng-Huat Tan, a Cancer Specialist in the Medical Oncology Department of the National Cancer Center in Singapore, that a 62 year old male diagnosed with metastatic nasopharyngeal carcinoma was detained by the United States Customs and Immigration Service in December 2008 (Wong, 2009). This individual, identified as Mr. S., was detained while attempting to enter the United States from Singapore because his fingerprints were not detectable. After four hours of detainment, officials were satisfied that Mr S. did not pose a threat to national security via other means of biometric and intelligence data and was released. It was later determined that the inability to detect Mr. S.' fingerprints was due to a side effect of his current chemotherapy treatment. Dr. Tan reported that following Mr. S.' previous treatment regimen of a cisplatin-5-fluorouracil (5FU) combination, he was administered capecitabine (N4-pentyloxycarbonyl-5-deoxy-5-fluorocytidine) from July 2005 (1750 mg twice a day, 2 weeks on, 1 week off) as maintenance treatment. Upon follow up of his capecitabine treatment, Mr. S was diagnosed with grade 2 hand and foot syndrome (HFS), also called palmar-plantar erythrodysaesthesia (Wong, 2009) which is histologically characterized as basal keratinocyte toxicity causing dyskeratosis (premature keratinization) with pronounced eosinophilia (high concentration of white blood cells) in the Stratum Spinosum and isolated keratinocyte necrobiosis (cellular death) (Janusch, 2006; Saini, 2007; Surjushe, 2009).

Palmar-Plantar Erthrodysesthesia (PPE) aka Hand and Foot Syndrome (HFS)

HFS is a distinctive and relatively common toxic reaction related to some chemotherapeutic agents that was initially described by Zuehlke in 1974 in association with mitone therapy for a hypernephroma (Baack, 1991). Symptomatically, HFS is characterized as numbness, dysaesthesia/paraesthesia (unpleasant/abnormal tingling, prickling, numbness feeling), erythema (redness of skin), painless swelling or discomfort and, in more severe cases; blisters, ulceration, desquamation (peeling of skin), or severe pain on the palms of the hands and soles of the feet. Severe cases of HFS can interfere with the normal daily activities of patients and is considered the major dose-limiting toxicity of capecitabine treatment necessitating dose reduction, treatment interruption, or in severe cases of HFS, withdrawal of treatment. It has been well documented that treatment interruption followed by dose reduction, if necessary, usually leads to rapid reversal of the symptoms with no long-term consequences. (Janusch, 2006; Milano, 2008). Although not life-threatening, PPE/HFS can develop into a painful and debilitating condition that interferes with patients' activities of daily living and quality of life. The mainstay of the PPE/HFE management appears to be a dose reduction or treatment interruptions coupled with supportive measures to reduce pain and discomfort and prevent secondary infections (Viale, 2006).

Grading systems for PPE/HFS have been established to assess the severity of conditions. These tools are instrumental in helping nurses recognize and assess both the objective and subjective symptoms of this toxicity and initiate the appropriate interventions. The grading systems used for PPE/HFE may vary per institution; however, the majority of systems are comprised of three basic categories. Grade 1 PPE/HFE

typically involves numbness, dysesthesia/paresthesia, tingling, painless swelling, or erythema of the hands and/or feet and basic discomfort that does not disrupt normal activities. Patients experiencing Grade 1 symptoms typically maintain their doe level during the course of treatment and are monitored closely to see if symptoms worsen. Grade 2 PPE/HFE typically involves painful erythema with swelling of the hands and/or feet and discomfort affecting daily activities. During the first, second, and third appearance of Grade 2 symptoms, capecitabine treatment is typically interrupted until symptoms are reduced down to Grade 1. Treatment is typically permanently discontinued on the fourth appearance of Grade 2 symptoms with a similar course of action upon the onset of Grade 3 PPE/HFS. Grade 3 involves moist desquamation coupled with ulceration, blistering, or severe pain of the hands and feet and severe discomfort that causes the patient to be unable to work or perform activities of daily living (Xeloda Prescribing Information, 2005).

Capecitabine and its Pathogenesis

Physicans and oncology nurses must continuously update their knowledge on current treatments and treatment-related side effects; and they must search for effective methods to prevent and/or manage the side effects that develop. Capecitabine is the recently developed, orally administered fluoropyrimidine prodrug designed to generate 5FU through a three step enzymatic process giving it antineoplastic properties to combat cancerous tumor growth in a number of different cancers, including adjuvant colon cancer, metastatic colorectal cancer, and metastatic breast cancer (Drug Information Online; Milano, 2008; Quinney, 2005; Saini, 2007). It should be noted that a number of other cancer treatment regimes have been reported to cause HFS. Chemotherapeutic

concoctions involving Capecitabine (Xeloda), Cytarabine (Cytosar-U), Floxuridine (FUDF), Fluorouracil (5-FU, Adrucil), Idarubicin (Idamycin), Liposomal doxorubicin (Doxil), Doxorubicin (Adriamycin), Sunitinib (Sutent), Sorafenib (Nexavar), Pazopanib (Votrient) and Vemurafenib (Zelboraf) are some of the more common producers of HFS. However, while HFS is observed at a greater frequency among patients undergoing capecitabine treatment as opposed to other treatments; the incidences of diarrhea, stomatitis (inflammation of the mouth), nausea/vomiting, alopecia (loss of hair), and nutropenia (decrease in white blood cells in neutrophils) associated with these other chemotherapeutic agents is markedly lower. In addition to the lower incidences of these symptoms, the benefit of reduced hospitalization time and associated costs related to capecitabine treatment as opposed to other methods has caused capecitabine treatment to become a superior treatment regimen for these types of cancers (Quinney, 2005).

The *in vivo* three-step enzymatic activation process of capecitabine to preferentially target 5FU production in tumor cells begins with its hydrolization by a 60kDa carboxylesterase (enzyme) in the liver converting capecitabine to the intermediate 5-DFCR (5-deoxy-5-fluorocytidine). In the second step 5-DFCR is converted to 5-DFUR (5-deoxy-5-fluorouridine) by cytidine deaminase which is an enzyme found in most tissues, including tumor tissues. The third step exploits the high concentrations of the enzyme thymidine phosphorylase (TP) in some human carcinomas compared to surrounding normal tissues. TP hydrolyzes 5-DFUR to the active drug 5-FU (Chua, Wei, Sham, & Au, 2008; Drug Information Online; Milano, 2008). The relative high concentration of TP in some human carcinomas acts to preferentially localize the continuous exposure of malignant cells to the cytotoxic effects of 5FU while reducing

exposure to normal tissues thus limiting systemic toxicity (Chua, Wei, Sham, & Au, 2008; Milano, 2008).

Once 5-FU is generated via the TP enzyme it is further metabolized by both normal and tumor cells into 5-fluoro-2 deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP) which inhibit deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis causing cell cycle arrest and apoptosis (cell death), thereby combating malignant cell growth by two different mechanisms: (1) FdUMP, in the presence of the folate cofactor 5, 10-methylenetetrahydrofolate, bind to thymidylate synthase (enzyme) thus inhibiting the formation of thymidylate which is a necessary precursor to thymidine triphosphate and essential for DNA synthesis thus inhibiting cell division, and (2) FUTP, which is structurally similar but chemically different to uridine triphosphate (a pyrimidine nucleotide necessary for RNA synthesis), is mistakenly incorporated by nuclear transcription enzymes in place of uridine triphosphate during RNA synthesis thus further preventing cell growth (Drug Information Online).

The exact pathogenesis of capecitabine induced HFS is unknown (Janusch, 2006; Milano, 2008; Surjushe, 2009); however, evidence suggests that the same mechanism in which capecitabine prevents malignant cell growth is thought to be the cause of capecitabine induced HFS exhibiting its cytotoxic effects not only on malignant cells, but also on basal keratinocytes. The pathophysiology of PPE/HFS is also not completely understood. It has been hypothesized that PPE/HFS is the result of small capillaries in the palm of the hands and soles of the feet rupturing under pressure causing small amounts of chemotherapeutic drugs to leak into tissues resulting in an inflammatory–type reaction. Another theory suggests that chemotherapeutic drugs are eliminated by sweating.

Because the hands and feet have an increased number of sweat glands, this theory postulates that these areas would be more prone to developing PPE/HFS (Webster-Gandy, 2007). TP has been found to also be expressed in a much higher concentration in friction ridge skin than other surrounding tissues (Milano, 2008) due to its association with keratinocyte hyperproliferation (high rate of keratinocyte division) (Schwartz, 1991). Thus, similar to the increased production and accumulation of 5-FU in malignant cells due to their higher proliferation rate and increased TP activity, the higher proliferation rate of keratinocytes and associated TP activity compared to other normal somatic cells (non-friction ridge skin cells) has been suggested to preferentially expose keratinocytes to the local cytotoxicity of 5-FU metabolites (Milano, 2008). Furthermore, the interrelationship between proliferating keratinocytes and thymidine metabolism has been demonstrated by Schwartz et al. (1991). This suggests that, in addition to nuclear transcription errors caused by FUTP, in the absence of thymidine due to the inhibition of thymidylate synthase to form thymidylate, proper basal keratinocyte proliferation is inhibited thus supporting the histological findings of dyskeratosis (premature keratinization) and isolated basal keratinocyte necrobiosis (cellular death) (Janusch, 2006; Saini, 2007; Surjushe, 2009) as well as the symptomatic desquamation (peeling of skin) associated with HFS previously noted. Due to the rapid proliferation rate of basal keratinocytes, upon a reduction in dosage or cessation of capecitabine treatment, concentrations of 5-FU decrease thus allowing for proper basal keratinocyte proliferation to resume resulting in a reversal of HFS related symptoms (Janusch, 2006; Milano, 2008).

The overall incidence of HFS observed with capecitabine in clinical trials of breast or colorectal cancer has been reported to be around 50% with 17% of patients reporting a severe form of HFS (grade 3) (Milano, 2008). Others studies by Hyun-Sook, et el report the prevalence of HFS to be as high at 77% with a severe form (grade 3) at 15.5% (Hyun-Sook, 2009). Because of the high incidence of HFS associated with capecitabine treatment coupled with the favorable chemotherapeutic factors compared to other methods for treating these types of cancers, it is suspected that the number of patients receiving capecitabine treatment will continue to increase.

Permanency and Forensic Science

Fordham Law Review has recognized that fingerprints are permanent by stating that fingerprints are contained in the epidermis (the outermost layer of human skin) but they are imprinted in, and generated from, the dermis (the thick layer of tissue underlying the epidermis). Thus, a fingerprint will not be destroyed unless damage to the skin reaches the dermis. Moreover, fingerprints remain unchanged from infancy until death; while they may expand or contract based on the weight of the individual, the pattern remains static. This characteristic is known as the permanency factor (Sombat). It has also been accepted in high profile court cases such *as United States v. Llera Plaza* (1998) where the court upheld that the government's expert could testify to the permanency and uniqueness of fingerprints (Sombat). Even in the controversial 2009 National Academy of Science (NAS) report entitled *Strengthening Forensic Science in the United States: A Path Forward,* the harshest of fingerprint critics state that the question is less a matter of whether each person's fingerprints are permanent and unique – uniqueness is commonly assumed – and more a matter of whether one can determine with adequate reliability that

the finger that left an imperfect impression at a crime scene is the same finger that left an impression with different imperfections in a file of fingerprints (Council, 2009)

As displayed in these stated proclamations by some renowned sources, the scientific basis of permanency regarding friction ridge skin identification is accepted throughout the scientific community. However, all previous research leading to these proclamations is based strictly on the idea of regeneration baring a healthy dermis. This project will explore the idea of permanency despite biochemical alteration and reinforce the premise behind the use of friction skin as a means of personal identification.

CHAPTER III

MATERIALS AND METHODS

Study Information

This study was designed to be completed as a case study to evaluate the reproducibility of friction skin from a single individual during the entire duration of capecitabine chemotherapy, beginning on the first day of treatment and ending approximately sixty days following the cessation of treatment. The study participant was initially diagnosed in May 2007 with invasive ductile carcinoma of the breast with a triple negative phenotype. Initial treatment consisted of three rounds each of Adriamycin/Cytoxan (administered together) and Taxol from July 2007 through November 2007. In November 2008, the study participant was diagnosed with metastatic breast cancer in the bones. Radiation and treatment with capecitabine (six rounds) showed success in clearing detectible cancerous activity according to positron emission tomography (PET) scans in May 2009. After a follow-up in August 2009 PET scans detected an increase in cancerous activity. The participant resumed capecitabine treatment on August 27, 2009, marking the first day of this case study evaluation. Informed consent was obtained prior to the study commencement. The treatment regimen of capecitabine consisted of multiple three week long cycles. During each cycle the participant is prescribed to take 2500mg/m^2 per day taken in two doses with a 12 hour lapse between each dose for two weeks and then no medication being prescribed for the third week. The duration of the treatment was contingent upon the therapeutic success and lasted a total of 188 days. The total duration of the study lasted 253 days.

Recording Medium

Multiple methods of capture were used in an attempt to record the friction ridge skin throughout the duration of the study to include digital imaging, powder, ink, and livescan. The digital imaging technique consisted of obtaining digital images under white light using a Nikon D2XS digital camera with and without black powder coating the friction skin for contrast purposes. The purpose of the general photography was two-fold: 1) To capture any friction ridge detail present through the use of traditional photography, and 2) to show the redness, irritation, and peeling of the skin as a result of the HFS. The powder technique consisted of coating the friction skin with a thin layer of traditional fingerprint powder. The powder was then removed from the ridges of the fingers through the use of the adhesive side of a white mailing label. This label was then placed adhesive side down, onto a clear piece of acetate similar to that of a fingerprint card. This technique is commonly known as the *powder/label* technique and is utilized when obtaining post mortem record fingerprints of deceased individuals. This technique has been shown to capture the faintest of friction ridge details from the most difficult of surfaces. The traditional ink method consisted of coating the friction skin with a thin layer of standard printers ink and rolling the fingers onto a white fingerprint card. This technique was incorporated as it is the most common method of obtaining record finger and palm prints in today's criminal justice system. While this technique is common, it typically does not provide as good detail as the post mortem technique previously mentioned. Two sets of record fingerprints were obtained utilizing this technique on a regular basis. In addition to the traditional inked sets of prints, a set of ten rolled prints strictly from the left index finger (study participant is left handed) on a standard white

8.5" by 11" sheet of printer paper were obtained. The set of ten were obtained in an attempt to ensure the highest quality impression was obtained despite possible movement or smudging. An additional set of record fingerprints utilizing the traditional ten-print card and ink were obtained following the application of *ID-Enhancer Spray* in order to evaluate the effectiveness of this product to determine its effectiveness for increasing the quality of the impressions. Limited access to Live Scan technology was available; however, several attempts were made which consisted of digitally recording the friction skin and saving the images according to the Electronic Fingerprint Transmission Specification (EFTS) using a Crossmatch Technologies ID500 livescan system.

The Procedure

A baseline set of record fingerprints were obtained at the beginning of the study on the first day of capecitabine treatment. This set of record fingerprints serves as the basis for which the quality of all friction skin should not surpass during the duration of the study. Throughout the course of the study, record fingerprints were obtained using the traditional ink technique on a weekly basis. In additional to the weekly traditional ink technique, one set of record fingerprints were obtained upon treatment with the ID Enhancer Spray. Approximately every four weeks throughout the course of the study additional record fingerprints were obtained using digital imaging and powder techniques. Record fingerprints using livescan were obtained on three separate occasions throughout the study due to the lack of availability to live scan equipment.

The quality of all record fingerprints were evaluated using the AFIX Tracker Automated Fingerprint Identification System (AFIS) automated quantitative scoring system with no digital enhancements. The AFIX Tracker ratings were used to evaluate

the quality of the impressions (reproducibility of the friction skin) over the course of treatment, as well as, to facilitate a comparison of the effectiveness of the various recording techniques and the ability of *ID Enhancer* to increase the quality of the impressions coming from damaged areas of friction skin.

A statistical analysis was carried out in an attempt to determine any statistical significance among the quality of the friction ridge skin recorded before and during capecitabine induced HFS (actual effect); the quality of the friction ridge skin recorded before and after capecitabine induced HFS (overall effect); the success amongst the methods used for capturing friction ridge skin (which technique is better) and; whether the *ID Enhancer* played a significant role in the enhancement of any friction ridge skin captured throughout any point in the study.

CHAPTER IV

ANALYSIS OF DATA

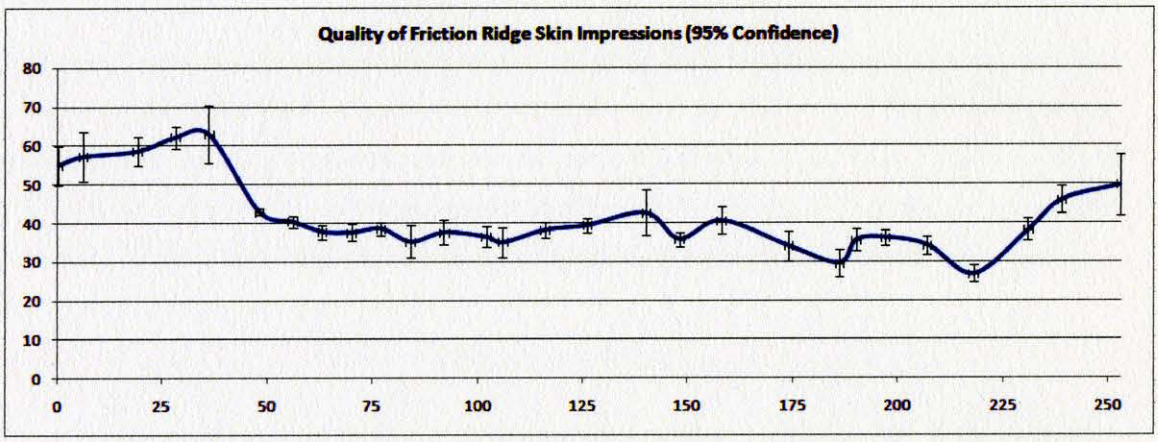
Reliability Measurements

Observations of the quality of the friction skin using the AFIX Tracker throughout the course of this study indicate that the average quality score, at 95% confidence, for the fifty impressions on each the first and last day of the study using the ink method was 55.0 +/- 5.1 and 49.8 +/- 7.8, respectively. The average quality score on the first day was considered the baseline reference score. The average quality over the course of the entire study using the ink method with and without the application of ID Enhancer was 43.1 +/- 3.4 and 41.6 +/- 1.6, respectively. The average quality score over the course of the entire study using the powder method was 42.4 +/- 10.7 and the average quality score on the three occasions over the course of the study in which the friction skin was recorded using livescan was 37.3 +/- 7.6. These results suggest that the powder method as well as the ink method with the application of ID Enhancer spray did appear to result in increased levels of quality compared to the other methods while the livescan method consistently yielded the least quality impressions. These differences between the two methods yielding the highest and lowest quality impressions (ink method with the application of ID Enhancer spray and the livescan method), however, did not differ to a statistically significant degree ($p=0.44$) assuming a significance level of $p=0.05$ using the student's t-test. Under this assumption of statistical significance, in order for one method to be considered as out-performing the other based on the quality of the impressions resulting from that method, the 'p' value would need to be less than 0.05.

The average quality of the friction skin rapidly decreased by 32% between approximately 36 to 48 days into the study. The quality of the friction skin remained at the decreased level throughout the course of treatment until approximately 30 days following the cessation of treatment at 218 days into the study at which point the quality of the friction skin began to rapidly improve returning approximately to the baseline level that was established on the first day of treatment (Tables 1 and 2).

Table 1

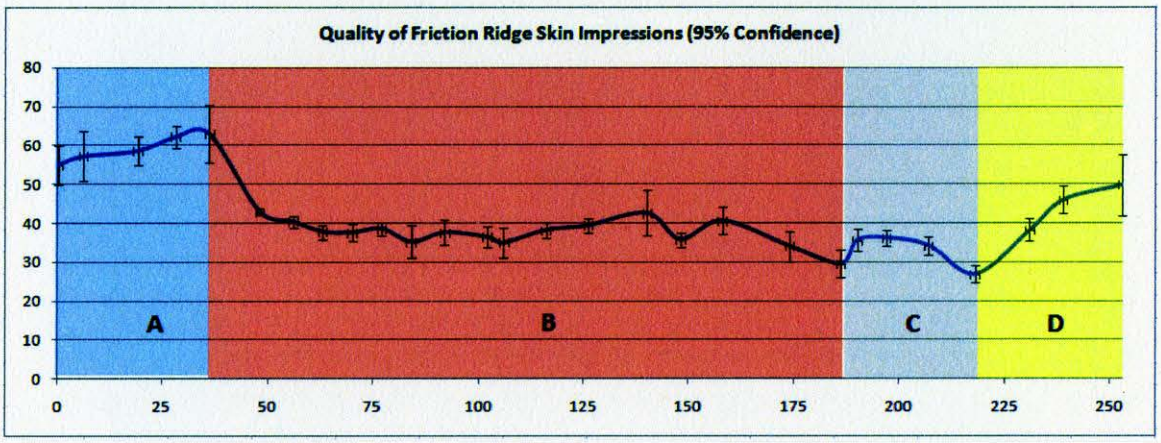
Friction Ridge Skin Quality Throughout Duration of Study



Graph representing the quality of the friction ridge skin impressions using the AFIX Tracker Automated Quality Score during the course of the 253 day evaluation. The graph represents the quality of the impressions recorded using the ink method.

Table 2

Friction Ridge Skin Quality Throughout Duration of Study with Time Explanation



Graph representing the same information in Table 1, except with the addition of sectioned time periods. The section labeled "A" indicates the 36 day time period prior to the decline in friction ridge skin quality due to the onset of HFS. The section labeled "B" indicates the sustained time period in which the participant continued normal treatment with capecitabine. The section labeled "C" indicates the 30 days time period in which the participant had ceased treatment, but the quality of the friction skin remained at the decreased quality state. The section labeled "D" indicates the time period in which the quality of the friction ridge skin rapidly improved (30 days post cessation of treatment).

Discussion of Results

The results of this study indicate that the decrease in the quality of the friction skin is directly related to the capecitabine treatment. The intervals of significant decrease and increase observed in the quality of the friction skin is consistent with previous literature suggesting that full keratinocyte maturation lasts approximately 30 to 40 days for the keratinocytes to migrate from the basal layer to the outer most layer of the epidermis (Stratum Corneum) (Wertheim K. M., 2002).

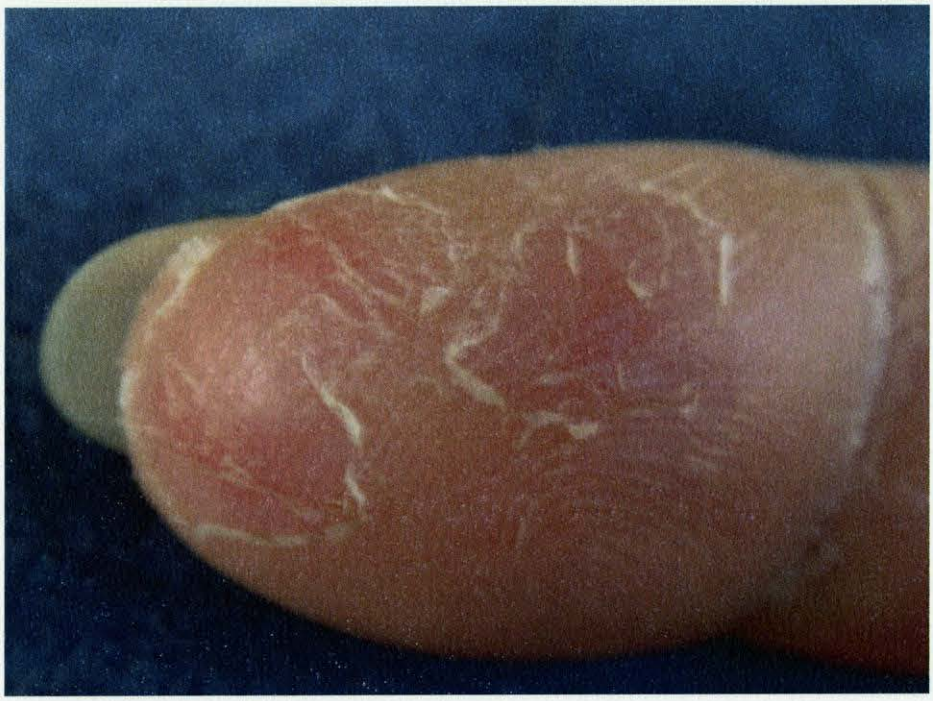


Figure 9. Friction skin of the study participant on the 89th day of the study

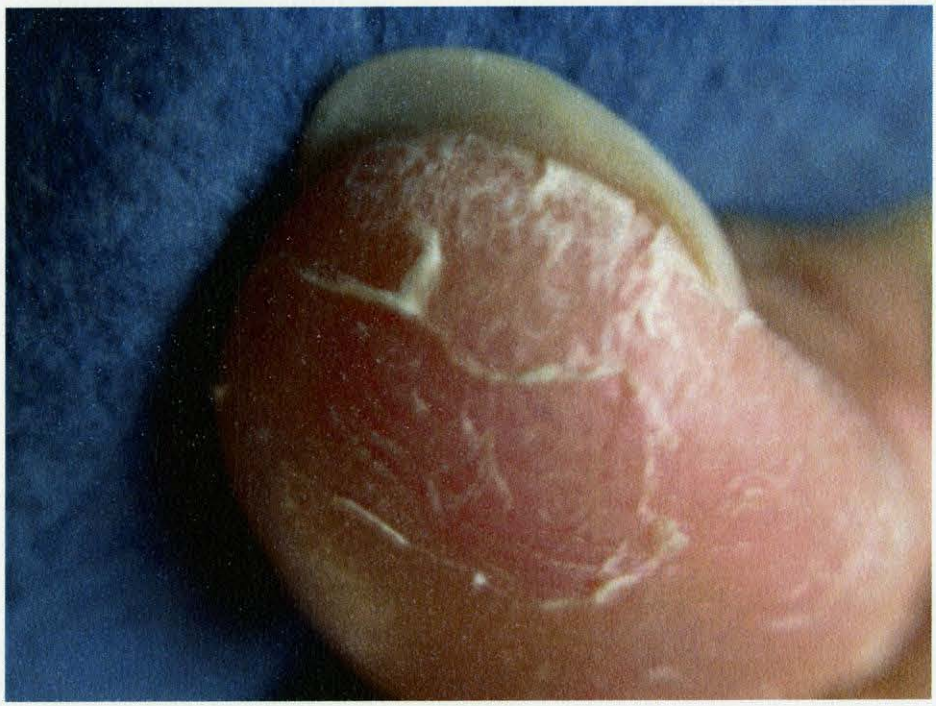


Figure 10. Friction skin of the study participant on the 89th day of the study

Because only those keratinocytes that are present on the outer most layer of the epidermis were observed in this study, this delay in observed decrease and increase of quality thus supports the literature suggesting that the pathogenesis of capecitabine induced HFS is the result of the exposure of the basal layer of keratinocytes to the cytotoxic effects of 5-FU and its metabolites thus preventing proper basal keratinocyte proliferation. Traditional symptoms of capecitabine induced HFS were both reported by the participant and observed throughout the course of treatment, which include general discomfort, mild to severe pain in the palms of the hands and soles of the feet, erythema, and pronounced desquamation which is illustrated in Figures 9, 10, and 11. The pain experienced by the study participant as a result of the HFS was mitigated through treatment with various pain medications as prescribed by the physician, which included Lyrica and Gabapentin. These pain medications were prescribed around the 130 day mark which is consistent with the graph in Table 2. As pain increased, the study participant was less likely to engage in normal daily activities. As a result, the severity of the HFS lessened and is represented as a short increase in friction ridge skin quality prior to the 130 day mark. However, as pain medication was prescribed, the study participant was able to carry on with regular daily activities. The constant abrasive forces and contact with the palmar side of the hand during routine activities resulted in an increased severity of HFS primarily due to the study participants inability to detect discomfort due to pain medication. The severe HFS was a result of decreased friction skin quality as depicted in the 175 to 180 day mark in Table 2. The particular time period also represents one of the lowest points in friction skin quality and the cessation of the capecitabine treatment. The 220 day time period clearly depicts the point where new friction skin is

given the opportunity to regenerate 30 days after the cessation of capecitabine treatment and is the cornerstone of establishing the permanency of friction ridge skin after biochemical manipulation/alteration.

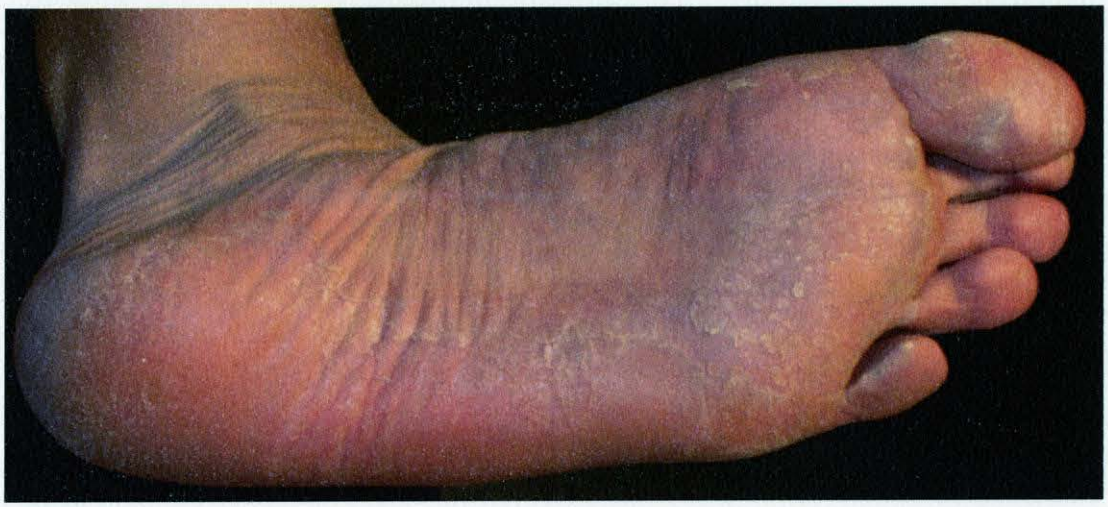


Figure 11. Friction skin on the foot of the study participant on the 106th day of the study.

Once the quality of the friction skin improved and returned to the baseline level, approximately 65 days following the cessation of treatment, it was noted that the arrangement of the friction skin characteristics were not altered in their location, orientation, or relative spatial relationship. This observation again supports the persistency of the arrangements of the friction skin characteristics despite this temporary toxic exposure to the basal keratinocytes throughout the treatment (Figure 12). The middle image in Figure 12 demonstrates the poor quality of the friction skin impression obtained using the ink method while undergoing treatment of capecitabine and experiencing HFS. The poor quality of the friction skin impression in Figure 12 (middle) illustrates the severity of which capecitabine induced HFS can interfere with the friction ridge skin examination process.

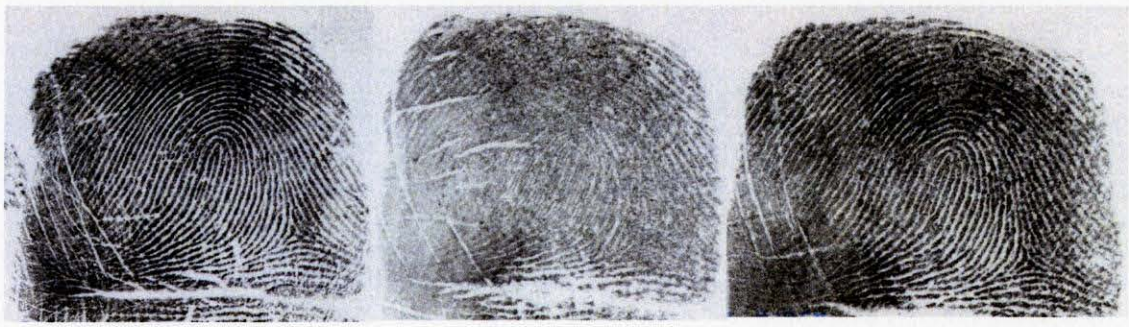


Figure 12 - Each image represents the appearance of the friction skin of the left index of the study participant recorded using the ink method on (left) the first day of the study, (middle) the 84th day of the study, and (right) the 253rd (last) day of the study. Note that the arrangement of the friction ridges and ridge characteristics were not altered between the first and last days of the study (left and right respectively) despite the temporary toxicity to the keratinocytes. The middle image demonstrates the poor quality of the friction skin impression obtained using the ink method while undergoing treatment of capecitabine and experiencing HFS.

CHAPTER V

SUMMARY

This study focused on evaluating the negative effects that capacitabine induced HFS has on the quality of friction skin for forensic and other comparative purposes. The results of this study show that capecitabine induced HFS caused a significant decrease in the quality of the friction skin which may impair the ability to positively identify an individual using friction skin impressions alone. The results of this study support previous literature suggesting that capecitabine induced HFS, which is responsible for the negative effects to the friction skin, is caused by the exposure of the basal keratinocytes to the cytotoxic effects of 5-FU and its metabolites thus preventing proper basal keratinocyte proliferation. Despite this temporary toxicity to the basal keratinocytes, persistency of friction ridge characteristics was noted during the former and latter portions of the study. The results obtained from this study provide insight into the effects that capecitabine induced HFS has on the quality of friction skin from a forensic or other comparative perspective; however, this study was limited to evaluating the effects to the friction skin on one individual during the course of capecitabine treatment. Further research is needed to more fully understand the potential effects that capecitabine treatment, with various dosage regimens, may have on other individuals as well as the effects other methods of chemotherapy may have on the quality of friction skin and to what level of severity.

Of major concern for those within the criminal justice community is the ability to temporarily obliterate ones identity via the oral ingestion of several pills. Communications with research oncologists and law enforcement officials indicate that

capecitabine is not a very common drug of choice on the street simply due to its overall effects. Street drugs are typically focused around obtaining a euphoric high or an adrenaline rush with almost negligent consequences depending on the amount and frequency of ingestion. These drugs typically do not cause as much discomfort as that which is attributed to capecitabine. Individuals looking to partake in common street drugs in a social environment would typically shy away from those causing blisters, ulceration, and desquamation. However, those individual not necessarily after the social high and are in need of concealing their identity for short periods of time for one reason or another may consider the capecitabine route if available. Rather than undergoing the painstaking techniques previously mentioned in this study such as the Z-Flap incision, acid etching, and transplantation; popping a few pills with the occasional diarrhea and skin peeling side effects doesn't sound like such a bad idea.

APPENDIX A

IRB FORM

THE UNIVERSITY OF
SOUTHERN MISSISSIPPI

INSTITUTIONAL REVIEW BOARD
118 College Drive #5147 | Hattiesburg, MS 39406-0001
Phone: 601.266.6820 | Fax: 601.266.4377 | www.usm.edu/irb

NOTICE OF COMMITTEE ACTION

The project has been reviewed by The University of Southern Mississippi Institutional Review Board in accordance with Federal Drug Administration regulations (21 CFR 26, 111), Department of Health and Human Services (45 CFR Part 46), and university guidelines to ensure adherence to the following criteria:

- The risks to subjects are minimized.
- The risks to subjects are reasonable in relation to the anticipated benefits.
- The selection of subjects is equitable.
- Informed consent is adequate and appropriately documented.
- Where appropriate, the research plan makes adequate provisions for monitoring the data collected to ensure the safety of the subjects.
- Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of all data.
- Appropriate additional safeguards have been included to protect vulnerable subjects.
- Any unanticipated, serious, or continuing problems encountered regarding risks to subjects must be reported immediately, but not later than 10 days following the event. This should be reported to the IRB Office via the "Adverse Effect Report Form".
- If approved, the maximum period of approval is limited to twelve months. Projects that exceed this period must submit an application for renewal or continuation.

PROTOCOL NUMBER: **12021408**
PROJECT TITLE: **Capecitabine Induced Hand and Foot Syndrome and the Reproducibility of Friction Skin**
PROJECT TYPE: **Thesis**
RESEARCHER/S: **Rodney A. Schenck**
COLLEGE/DIVISION: **College of Science & Technology**
DEPARTMENT: **Forensic Science**
FUNDING AGENCY: **N/A**
IRB COMMITTEE ACTION: **Exempt Approval**
PERIOD OF PROJECT APPROVAL: **02/14/2012 to 02/12/2013**

Lawrence A. Hosman, Ph.D.
Institutional Review Board Chair

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