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# Sickle cell pain: a critical reappraisal.

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**Sickle Cell Pain: A Critical Reappraisal**

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## Abstract

Sickle cell pain includes three types: acute recurrent painful crises, chronic pain syndromes and neuropathic pain. The acute painful crisis is the hallmark of the disease and the most common cause of hospitalization and treatment in the Emergency Department. It evolves along four phases: prodromal, initial, established and resolving phases. Each acute painful episode is associated with inflammation that worsens with recurrent episodes and often culminates in serious complications and organ damage such as acute chest syndrome, multiorgan failure and sudden death. Aborting the acute painful episode at the prodromal phase could potentially prevent or minimize tissue damage. Three pathophysiologic events operate in unison at the prodromal phase of the crisis: Vaso-occlusion, inflammation and nociception. Managing these events with vasodilators, anti-inflammatory drugs and aggressive analgesia could abort the crisis and prevent or minimize further damage. Chronic pain syndromes include avascular necrosis and leg ulcers. Neuropathic pain is usually due to nerve damage following vaso-occlusion of blood vessels (*vasa vasorum*) feeding nerves. Management of sickle cell pain should be based on its own pathophysiologic mechanisms rather than borrowing guidelines from other non-sickle pain syndromes.

## Introduction

The proper study of mankind is Man.

*Alexander Pope*

Sickle cell disease (SCD) has been considered primarily a disease of children with a few patients surviving to adulthood. Thus, between 1910 and 1950 the median survival of patients with SCD was less than 20 years of age<sup>1</sup> and sudden death occurred in about 41% of the patients and in 29% death occurred within 24 hours after the onset of painful crises<sup>2</sup>. By 1980 50% of children survived to 20 years of age and by 2009 survival to age 20 years increased to 85% of children<sup>2</sup>.

If we rewind the clock of time by five scores and two years when SCD was first discovered in the US, however, we find that the first four patients were adults, not children and they all had leg ulcers<sup>3-6</sup>. Even before 1910 there were observations among adult African slaves suggestive of sickle cell disease. These included immunity to malaria and high prevalence of leg ulcers<sup>7</sup>.

Moreover autopsy on a slave with history of fever and respiratory illness in 1846 showed absence of the spleen<sup>8</sup>. The inevitable question then, is where were the children with SCD in the US before 1910? There must have been children with SCD. The patient reported by Cook and Meyer<sup>5</sup> gave family history of brothers and sisters who died in early life of a disease associated with grave anemia. Only our imagination describes the pain and suffering that affected infants and children with SCD. These innocent souls must have lived, suffered and died prematurely, invisible and hidden within the shrouds of the dark side of the discovery of sickle cell anemia in the US<sup>9</sup>. It was not until the early 1930's that children with SCD were recognized as the major victims of this disease.

## Sickle Cell Pain between 1930 and 1960

Between 1930 and 1960 the emphasis was on studying the basic science of SCD. This period witnessed quantum leaps in defining the specific molecular lesion of SCD and the advent of Hb electrophoresis<sup>10-12</sup>. Diggs and Ching<sup>13</sup> suggested that the painful sickle cell crises are the result of blockage of the small blood vessels by the abnormal red cells. The major therapeutic approach was to identify methods to prevent the blockage of small blood vessels by the sickled cells. Not much was written about specific pain management during this period partly because of the pre-occupation with the basics and partly because potent analgesics were not available then.

Nevertheless Diggs realized that pain was a major problem among patients with sickle cell anemia (SS) and used papaverine and acetaminophen to treat it<sup>14</sup>. Other futile therapeutic modalities included liver extract, whole liver diet, spleen diet, iron, arsenic, calcium, iodides, alkalis, blood transfusion, urea, cyanate and hyperbaric oxygen<sup>15-19</sup>.

We reviewed 398 charts of the patients seen by Diggs and Kraus at the University of Tennessee in Memphis. There were descriptions of severe anemia, leg ulcers, skeletal abnormalities, death, etc and pain. It seems the physicians were at loss how to treat the pain. They used whatever they thought might help including most of the methods mentioned above and enemas for patients with abdominal pain. Papaverine, a naturally occurring opioid derived from the opium poppy known for its anti-spasmodic effect, was the ideal analgesic for abdominal painful crises. What is most admirable about Diggs and Kraus is that they believed their patients and listened to them with great empathy and respect.

In the 1960's adult patients with SCD appeared on the scene again; but this time with severe pain that often did not respond to oral analgesics. Patients had to resort to the Emergency

Departments (ED) for help. At that time the only parenteral opioids approved by the FDA for pain management were meperidine (approved in 1942) and fentanyl citrate (approved in 1968). The latter, however, was approved for surgical use only and meperidine became the drug of choice to treat severe sickle cell pain. Follow-up studies of the Multicenter Study of Hydroxyurea (MSH) in SS showed that meperidine was most often used for painful crises in the ED and Hospital and short-acting oxycodone with acetaminophens most often used for pain at home.<sup>20, 21</sup>

## **Sickle Cell Pain and Opioids: Is Morphine the Ideal and only Opioid for Sickle Cell Pain?**

A shift in the management of sickle cell pain from meperidine to morphine occurred in the 1990's. Morphine sulfate was approved by the FDA in 1984 and was widely used in the management of cancer pain. Brookoff and Polomano<sup>22</sup> published a paper titled "Treating Sickle Cell Pain like Cancer Pain". This initiated a trend to treat sickle cell pain by borrowing methods from other disciplines rather than establish treatment based on the specific pathophysiology of the disease itself. Brookoff and Polomano<sup>22</sup> reported that using intravenous and controlled release oral morphine instead of meperidine reduced the frequency of hospital admissions of patients with painful crises and their length of stay. It turned out, however, that the decrease was probably because many of their patients transferred their care to other hospitals in the area after the institution of the morphine-only policy<sup>23</sup>. Unfortunately, this policy gave the wrong message to providers who thought that morphine is the only opioid to be used to treat acute painful crises. An ultimatum was created for the patients: "you will be treated with morphine or you go

somewhere else”, where the somewhere else often used the same ultimatum. Tragedies occurred. One patient told her provider she is allergic to morphine. This was not taken seriously and she was given morphine intravenously anyway. Within minutes she had an anaphylactic shock but luckily she could be managed successfully in the intensive care unit (Ballas, Unpublished data).

The meperidine phobia emerged because normeperidine, the major metabolite of meperidine is neurotoxic and may cause seizures especially in patients with impaired renal function. There are no controlled trials to compare meperidine with morphine in patients with sickle cell disease. The incidence of seizures related to the use of meperidine in patients with SCD varies between 1% and 12%<sup>24-26</sup>. There are a few patients to date for whom meperidine is the ideal analgesic for the acute painful crisis with no evidence of neurological complications.

Although there are no controlled trials to compare the safety and efficacy of different opioids in the management of acute sickle cell crises, patient safety can be maximized by obtaining a detailed history, understanding opioid pharmacology & their mechanism of action & side effects, carefully monitoring patients and individualizing care. Meperidine should not be used to treat acute sickle cell pain in patients who have impaired renal function, history of seizure disorder, or who are taking serotonergic medications. A sickle cell center that uses only one opioid to treat all patients with SCD all the time raises questions about the justifications and rationale for such a restricted policy.

Ironically it turned out that morphine is not a panacea after all. Like other medications it carries a load of problems associated with its use. Morphine also causes seizures with a reported prevalence of 1.2% if given in sufficiently large doses<sup>27</sup>. Morphine is the most histaminergic opioid<sup>28</sup> and is often associated with severe pruritus in some patients. Moreover, there have been

reports of death with the use of morphine in patients with sickle cell disease<sup>29,30</sup>. The use of morphine in patients with SCD seems to be associated with acute chest syndrome<sup>31-33</sup>. In addition morphine and morphine-6-glucuronide, a major metabolite of morphine, are both excreted in the urine and care has to be taken if given to patients with renal failure. Morphine induces expression of platelet derived growth factor-b (PDGF-BB) in human brain and umbilical vein endothelial cells<sup>34,35</sup>. Morphine also activates VEGFR2, PDGFR-b, SIP3R, MAPK/ERK and COX-2 in endothelial cells and the central nervous system<sup>35-39</sup>. Together, these growth factor-like activities of morphine stimulate vascular permeability, endothelial activation, vascular smooth muscle cell pathology, analgesic tolerance and kidney disease. Morphine induces kidney injury in transgenic sickle mice<sup>40</sup>. Studies in the transgenic sickle mouse showed that morphine amplifies renal pathology, stimulates albuminuria and impairs renal function. Morphine stimulates the proliferation of glomerular, mesangial and epithelial cells, but causes apoptosis at higher concentration, representing early and late lesions<sup>36,41,42</sup>. Thus morphine may contribute to both development and progression of renal lesions in SCD. These morphine-induced signaling mechanisms also support clinical observations of pulmonary edema in patients receiving morphine and hydrated or over-hydrated at the same time. Increased vascular permeability induced by morphine may be associated with hemorrhagic stroke in SCD. Considering the endothelial-specific effects of morphine, mechanism(s) of morphine signaling need to be critically evaluated for their contribution to organ disease while treating patients with SCD.

At the present several opioids are available for parenteral use as needed including morphine, codeine, meperidine, hydromorphone, oxymorphone, levorphanol, methadone, and fentanyl. The

choice of opioid, its dose and route of administration has to be individualized with frequent monitoring for possible side effects and to minimize risks of abuse, misuse or diversion.

## **The Acute Sickle Cell Painful Crisis**

The acute sickle cell painful crisis is the hallmark of SCD and the number-one cause of hospitalization<sup>43</sup>. It is unpredictable and may be precipitated by known or unknown risk factors and triggers<sup>44</sup>. Much of the devastation caused by the disease is due to the recurrent acute painful crises. Diggs<sup>45</sup> described the clinical features of a typical painful crisis accurately. He reported that “patients experience sudden onset of pain in the low back or in one or more joints or ones of the extremities. The pain may be localized or migratory and is continuous and throbbing. The severe pain causes patients to grunt, groan, cry, twist and turn and to assume abnormal postures in the futile attempt to obtain relief”. Descriptors of pain include, among other things, throbbing, sharp, pounding, dull, stabbing, cutting, and gnawing or like a generalized toothache<sup>44</sup>.

Extensive review of the literature pertinent to the clinical description of the painful crisis requiring hospitalization showed that it evolves along distinct phases. Ballas and Smith<sup>46</sup> and Akinola et al<sup>47</sup> independently and almost simultaneously described the presence of two phases of the uncomplicated painful crisis in prospective longitudinal studies of adults with SCD. Akinola et al<sup>47</sup> studied 20 patients over 16 months, and Ballas and Smith<sup>46</sup> studied 117 painful crises affecting 36 patients with sickle cell anemia over 6 years. Both studies indicated the presence of

two phases. The initial phase was associated with increasing pain, decreased RBC deformability, increase in the number of dense cells, red cell distribution width (RDW), hemoglobin distribution width (HDW), reticulocyte count, leukocytosis and relative thrombocytopenia. The second phase was characterized by established pain of maximum severity and gradual reversal of the abnormalities of the first phase. Later, Ballas<sup>48</sup> revised the description of the painful crisis and refined its evolution into four phases by including observation by several other investigators. For example Murray & May<sup>49</sup> reported a premonition of painful crisis in 59 out of 102 (58% patients with SCD) during a questionnaire study in the UK. Reported symptoms included numbness, parasthesia or aches in the areas that subsequently became painful. The duration of the prodromal phase was up to one or two days. The phases were called prodromal, initial, established, and resolving phases (Figure 1). Beyer et al<sup>50</sup> and Jacob et al<sup>51</sup> reported the evolution of painful crises along similar phases in children.

The presence of phases of the crises allows providers to monitor the progress of the crisis and manage it according to rational basis and avoid the conflicts that often arise about the authenticity of pain. As shown in Fig 1 and Table 1 a number of changes in objective signs occur during the evolution of the crisis. These changes, however, can be appreciated if the parameters are determined serially and, more importantly, if they are compared to steady state values<sup>52</sup>. The decrease in Hb level and the increase in the reticulocyte count, for example, suggest hyperhemolysis that occurs in some patients during uncomplicated painful crises<sup>53</sup>.

### **Consequences of the acute painful crisis**

The acute painful crisis is associated with serious complications of the disease. About 50% of reported cases of acute chest syndrome occur after admission to the hospital with a painful crisis<sup>54</sup>. Acute multiorgan failure<sup>55</sup> and sudden death<sup>56</sup> also have been reported during painful crises. Most of these serious complications usually occur during day 1-5 of the crisis.

As shown in Fig 1 and Table 1 the resolution of the painful crisis is associated with rebound thrombocytosis, elevated levels of fibrinogen, orosmomucoid, RBC deformability and plasma viscosity indicating the presence of a hypercoagulable state that may cause recurrence of the crisis. Ballas and Smith<sup>46</sup> found that about 20% of the patients who were discharged from the hospital after the resolution of a crisis had recurrent crises that required treatment with parenteral opioids in the ED or hospital within one week after discharge (Table 2). A painful crisis seems to be a risk factor to precipitate another crisis. Some patients, especially children, however, do well after the resolution of a crisis with a pain-free-period of variable duration before the onset of another crisis (Fig2). Others continue to have pain. According to the Pain In Sickle Cell Epidemiology Study (PISCES) adult patients reported SCD pain at home in about 55% of the 31,017 days surveyed<sup>57</sup>. Similarly children reported SCD pain at home on about 9% of the 1515 days surveyed<sup>58, 59</sup>. In MSH at-home analgesics were used for SCD pain on 40% of diary days and 80% of two-week follow-up periods, with short-acting oxycodone and acetaminophen being the most frequently used analgesics<sup>21, 60</sup>. Descriptors and location of the pain at home were similar to those during hospitalization but milder. What is important about the pain experienced at home is that patients prefer to treat it with short-acting opioids rather than the controlled-release opioids. Moreover, those who take controlled release opioids with short acting opioids for breakthrough pain experience frequent attacks of breakthrough pain resulting in the consumption of relatively large amounts of short-acting opioids. In addition, patients prefer to be

treated in the day unit rather than the ED whenever possible in order to avoid long hours of waiting before they are treated. Treatment of patients in the day unit with parenteral short-acting opioids decreased the frequency of hospital admissions and ED visits<sup>61</sup>.

In order to determine the actual pattern of hospital admissions of patients with SS and the causes of frequent hospital readmissions and their prognostic significance a prospective longitudinal and observation cohort study of all adult patients with sickle cell anemia admitted to one institution between January 1998 and December 2002 was conducted<sup>43</sup>. Major outcome measures included the frequency, etiology, and prognostic significance of readmissions to the hospital within 1 week and 1 month after discharge. Analysis of the data showed the following: 1) about 95% of all the 1540 admissions of 136 patients were for acute painful crises; 2) the intensity of pain score decreased significantly during the first 4 days of hospital admission from an average of  $8.7 \pm 1.17$  to  $7.5 \pm 1.00$  ( $P < 0.001$ ) and then reached a plateau of 7.4 until discharge. (Fig. 3); 3) the mean score of pain intensity was  $>7$  throughout the hospital stay; 4) about 50% of hospital admissions for acute painful episodes were readmitted within 1 month after discharge, and about 16% of all admissions were readmitted within 1 week after discharge (Table 3). The major cause of hospital readmission was the same acute sickle cell pain that was not controlled with analgesics at home or in the ED. Withdrawal syndrome was the cause of readmission only in five patients who were readmitted collectively 46 times (about 7% of all readmissions) within one week after discharge. Readmission within 1 week after discharge was associated with higher mortality than otherwise.<sup>43</sup>

Jacob et al<sup>62</sup> showed similar pattern of pain score that plateaus about 5 days after hospital admission for painful crises in children. Moreover, the high frequency of hospital readmission was confirmed by other studies<sup>63-65</sup>. In a Retrospective cohort of sickle cell disease–related ED visits and hospitalizations from 8 states (Arizona, California, Florida, Massachusetts, Missouri, New York, South Carolina, and Tennessee) in the 2005 and 2006 Healthcare Cost and Utilization Project (HCUP) State Inpatient Databases and State Emergency Department Databases, Brousseau et al<sup>63</sup> found that the 30-day and 14-day readmission rates were 33.4% and 22.1% respectively. Readmissions were highest for the 18- to 30-year old patients and for the publicly insured patients. In another retrospective study in children with SCD, the most common admission and readmission (within 30 days) diagnosis was acute pain, 78 and 70% respectively<sup>64</sup>. The major risk factor for readmission was lack of outpatient hematology follow-up within 30 days after discharge; Asthma was another risk factor for readmission within 30 days. Sobota et al<sup>65</sup> performed a retrospective examination of 12,104 hospitalizations for sickle cell crisis from July 1, 2006 and December 31, 2008 at 33 freestanding children’s hospitals in the Pediatric Health Information System (PHIS) database. They identified 4,762 patients with 12,104 qualifying hospitalizations of which 2,074 hospitalizations (17%) were readmissions for sickle cell crisis within 30 days after discharge. Risk factors for readmission included older children, pain and treatment with steroids.

Available data about the evolution of the sickle cell painful crisis show that about 10% of children and about 50% of adults with sickle cell disease continue to have pain between painful episodes. The severity of the pain between crises varies among individuals and in the same individual with time. Thus the hallmark of sickle cell disease seems to be continuous acute pain the severity of which varies from severe to mild or moderate. When the pain is severe it requires

treatment in the ED or in the hospital with parenteral opioids and when it is mild or moderate it is treated at home with oral analgesics. The transition from acute painful crises with no pain in between to acute painful crises with mild or moderate pain in between is age dependent. Thus the majority of children are pain free between recurrent painful episodes (Fig 2) and about 50% of adult continue to have mild to moderate pain between relapsing crises (Fig 4). The descriptors of the pain are mostly the same and short acting opioids are the preferred analgesics by the majority of adult patients.

### **Pathophysiology of acute pain**

Vaso-occlusion is the most important pathophysiologic event in sickle cell disease that explains most of its clinical manifestations. Tissue damage due to vaso-occlusion initiates complex biochemical, neurological, electrochemical and inflammatory sequence of events collectively referred to as nociception that culminates in the perception of acute pain. It is the combination of ischemic tissue damage and secondary inflammatory response that makes the pain of sickle cell disease unique in its acuteness and severity (Fig 5). Tissue injury generates several pain mediators<sup>66-69</sup> that bind to and activate or sensitize specific receptors at the peripheral nerve ending where biochemical energy is transformed into electrical energy that facilitates the transmission of the electric impulse of pain along peripheral nerves to the dorsal horn of the spinal cord via the dorsal root ganglion. Each neuron has multiple receptors and the more

receptors activated the faster and the more intense the transmission of the painful impulse would be. From the dorsal horn of the spinal cord the electrical impulse of pain ascends along the contralateral spinothalamic tract to the thalamus that interconnects reversibly with other centers, most notably the limbic system (mediator of memory and emotion) and the reward system (mediator of pleasure and addiction). The pathway of pain stimuli is subject not only to activators, sensitizers and facilitators, but also to inhibitors. Serotonin, norepinephrine, enkephalin,  $\beta$ -endorphin and dynorphin are endogenous central pain inhibitors. Thus, in a given patient, the net outcome of tissue ischemia may be severe or mild pain, depending on the extent of tissue damage and the net balance of pain stimulators versus pain inhibitors. This may explain, in part, the considerable variation in the frequency and severity of painful sickle crises among patients, and longitudinally in the same patient. Moreover, psychological, social, cultural and spiritual factors often unite and conspire with vaso-occlusion to initiate the unique nature of sickle cell pain.

## **Central Sensitization and Neuroplasticity**

Painful stimuli that originate peripherally are subject to modification once they reach the central nervous system both at the level of the spinal cord and the brain. This modification depends on the nature and frequency of transmission of the painful impulse. Repetitive and severe painful impulses from the periphery cause changes in excitability of the neurons in the spinal cord. This increase in neuronal excitability in the spinal cord is termed central sensitization<sup>70, 71</sup>. It explains the persistence of pain at the primary site of tissue damage and its spread to sites beyond the primary site of tissue damage. Another type of modification of the repetitive and severe painful impulse occurs at the level of the brain<sup>72, 73</sup>. The main function of the brain is message

transmission. To do this, it has 100 billion neurons and each neuron connects to 10,000 other neurons via synapses resulting in one million billion connections<sup>74</sup>. Thus the severe and repetitive pain impulse that reaches the brain will excite an enormous number of neurons that stimulate other neurons in a progressive manner resulting in the perception of severe pain. Neuroscientists describe this mass transit of information as “cells that fire together wire together”<sup>74</sup>. Moreover, the brain is neuroplastic; it has the ability to change functionally in response to experiences<sup>74</sup>. This is often referred to as “Rewiring” of the brain of patients who have persistent severe pain. Alternative circuits of pain transmission and remapping of functional connections<sup>74</sup> occur in the brains of these patients. The best example of this phenomenon in patients with SCD is that severe pain persisted for several weeks or months in those patients who were cured from sickle cell after successful bone marrow transplantation<sup>75</sup>. It took relatively long time to reset the “wiring” of the brain back to normal in these patients.

## **Chronic Pain**

Chronic pain is pain that does not go away. It is often defined as pain that persists for 3 or more months. Sources of chronic pain in sickle cell disease include bone infarction, avascular necrosis of joints, back pain from disk protrusion into vertebral bodies, leg ulcers, and chronic osteomyelitis.<sup>76</sup> The descriptors of the pain of these conditions are different from the pain associated with the acute painful crisis or the pain that persists between crises. The pain of these syndromes is usually treated with long-acting or control-release opioids and short-acting opioids for breakthrough pain are not used as often as is the case in the persistent pain between acute painful crises.<sup>77</sup> Moreover, these pain syndromes rarely require hospital admission except when a

painful crisis is superimposed on the chronic pain or if the underlying condition is associated with severe infection that requires parenteral antibiotics as may happen in leg ulcers.

We and others previously described a second type of chronic pain in SCD.<sup>76, 78-80</sup> It is intractable chronic pain without obvious pathology where the only complaint is the patient's self-report of pain that does not go away. I think we were adopting and borrowing concepts from other pain disciplines. We need to reconsider this. SCD does have obvious pathology documented by the presence of the sickle gene and sickle Hb which are pathologic. It seems we were referring to the persistent pain between crises as chronic pain without pathology.

## **Neuropathic pain**

Neuropathic Pain is usually described as numb, tingling, lancinating, spontaneous, shooting or paroxysmal in nature associated with a sensation of pins and needles, hyperalgesia and allodynia (pain due to ambient non-noxious stimuli).<sup>76, 79</sup> Its severity is also enhanced by exposure to either cold or heat. This pain could be secondary to nerve injury or nerve dysfunction whether peripherally or centrally. Neuropathic pain in SCD could be due to tissue damage following vaso-occlusion of blood vessels of nerves (vasa vasorum). These include mental nerve neuropathy,<sup>81, 82</sup> trigeminal neuralgia<sup>83</sup>, acute proximal median mononeuropathy<sup>84</sup>, entrapment neuropathy<sup>85</sup> acute demyelinating polyneuropathy<sup>85</sup>, ischemic optic neuropathy<sup>86</sup>, orbital infarction<sup>87</sup>, orbital apex syndrome<sup>88</sup>, and spinal cord infarction.<sup>89</sup> Neuropathic pain that is often associated with persistent acute or chronic pain has not been well studied in SCD to date.

## **Redefining Sickle Cell Pain**

We wish to paraphrase Alexander Pope's quotation by saying: "the proper study of sickle cell pain is patients with SCD". Although the molecular pathophysiology of SCD is well understood, the management of sickle cell pain, its hallmark, is an embarrassing failure. Neglect, disparity, prejudice, disinterest and faulty assumptions & accusations punctuate the treatment of patients, especially adults, with sickle cell pain. Our perspectives redefine sickle cell pain and its unique features based on available data and the experience of experts in the field that accumulated since 1910. This redefinition may reveal new avenues to improve our understanding and management of this complex pain syndrome. Our knowledge of sickle cell pain that evolved over the last 102 years suggests that the hallmark of SCD is acute pain that waxes and wanes, relapses and remits in a recurrent and unpredictable fashion. When severe it is the acute painful crisis that requires treatment with parenteral analgesics in the ED or Hospital. When mild or moderated it is the residual or persistent acute pain between two subsequent acute painful episodes. This explains why patients are often readmitted after discharge, why they prefer using short-acting analgesics and why they are treated in the day unit frequently with short acting opioids between hospital admissions. It is tempting to call the persistent pain between two crises "chronic acute pain", but such terminology is confusing and it is better to use the persistent or residual nomenclature. The use of "chronic sickle cell pain" should be limited to the chronic pain syndromes mentioned above.

The emerging picture of the acute sickle cell pain is that early in life the pain is episodic with periods of acute pain alternating with pain free intervals in between (Fig. 2) but as they age mild or moderate acute pain persists between episodes of painful crises (Fig, 4) The severity of the residual pain between crises varies in intensity among patients and in the same patient with time. The pattern of pain shown in Fig 4 occurs in about 50% of adult patients with SCD.<sup>21, 57, 60</sup>

## **New Approach to Therapy**

Aegeus Euripides (484 BC-404 BC) said: “A bad beginning makes a bad ending”. Thus if the acute painful crisis is treated aggressively at its beginning, its end would be of short duration with little or no complications. Unfortunately, the end of an acute sickle cell painful crisis at the present is a fuzzy point in time. Discharge from the ED or Hospital does not necessarily indicate the end of the crisis. It is an arbitrary point that depends on several factors that are not based on the individual status of the patient but subscribes to insurance coverage, Hospital policy and the attitude of the providers. Table 4 lists the approaches for the treatment of SCD and its complications. The ultimate goal is to achieve a cure. Short of that preventing the painful crisis with agents that induce the production of Hb F is possible and short of that aborting the painful crisis is highly desirable. A triad of pathophysiologic factors initiates the acute painful crisis: vaso-occlusion, inflammation and nociception. Each painful crisis is associated with residual inflammatory damage that accumulates with recurrent crises culminating in organ dysfunction and organ failure. The rational approach to abort a crisis is to treat it early at the prodromal phase where tissue ischemia and inflammation are in their early stages<sup>90</sup> (Fig 5). The goal of management at this phase is anti-vasoocclusive therapy akin to therapy of ischemic stroke in adults in the general population<sup>91, 92</sup> and to the treatment of acute myocardial infarction (MI)<sup>93, 94</sup>. The standard of care of ischemic stroke and MI is to give tPA within a few hours after the onset of signs and symptoms in order to restore perfusion. Beyond that tPA will not be as effective. Anti-vasoocclusive therapy to abort a crisis at the prodromal stage should include vasodilators, anti-inflammatories and analgesics. Diabetics determine their blood glucose level at home and treat themselves with antiglycemic agents accordingly. Patients with SCD could be counseled and trained to treat themselves at home as soon as they feel an impending crisis. Nitric

oxide would be the ideal vasodilator for self-administration at home. Gladwin et al showed that NO in the hospital is not effective in reducing the hospital length of stay of patients with painful crises.<sup>95</sup> Administration of NO in the ED, however, was effective in aborting crisis in some patients.<sup>96, 97</sup> It is probable that shifting the utilization of NO to the left (at home) rather than to the right (Hospital) is the right way to go. Moreover blood transfusion or vigorous hydration at the prodromal phase may be effective in aborting the crisis. Sobota et al reported that transfused pediatric patients with crisis were readmitted less frequently to the hospital than otherwise.<sup>65</sup> The combination of NO and blood transfusion/hydration in the prodromal phase would restore perfusion and prevent or minimize damage due to hypoxia, the addition of anti-inflammatories would prevent or minimize damage due to inflammation and, most importantly, aggressive management of pain would prevent the barrage of painful impulses from reaching the brain thus avoiding its “rewiring”.

According to the current state of affairs patients with acute painful crisis receive treatment about 2-3 days after the onset of the early prodromal signs and symptoms of the crisis. By that time irreversible tissue damage is well established and difficult to reverse. This has to change. The rational therapy of acute sickle cell pain must be actively based on its own mechanistic pathophysiology and not by the passive adoption of guidelines of other pain syndromes.

## **Authorship**

SKB designed and wrote the manuscript. KG wrote the section that pertains to the systemic effects of morphine in the transgenic sickle cell mouse. PEA reviewed and summarized data

from the charts of the patients that were treated by Drs. Diggs and Kraus between 1930 and 1960. All authors contributed comments, and revised the manuscript for critical content.

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**Table 1. Changes in objective signs during the evolution of the sickle cell painful crisis**

Podromal Phase	Initial Phase	Established Phase	Resolving Phase
<i>Decreasing</i>	<i>Decreasing</i>	<i>Peak</i>	<i>Peak</i>
RBC deformability	RBC deformability	Temperature	Fibrinogen
	Platelets	WBC count	Orosomuroid
<i>Increasing</i>		Dense Cells	ESR
Dense RBC	<i>Increasing</i>	ISC	
	Temperature	RDW	<i>Decreasing</i>
	WBC count	HDW	Temperature
	Dense cells	Reticulocytes	WBC Count
	ISC	LDH	Dense Cells
	RDW	CRP	ISC
	HDW	SAA	RDW
	ESR		HDW
	LDH	<i>Nadir</i>	CRP
	CRP	RBC deformability	
	Fibrinogen	Hb	<i>Increasing</i>
	Orosomuroid		RBC deformability
	SAA	<i>Increasing</i>	Plasma viscosity
		Fibrinogen	Platelets
		Orosomuroid	
		Plasma viscosity	
		ESR	

Note: Parameters shown are those reported at least twice by different investigators. ISC, irreversibly sickled cells; WBC, white blood cells; RDW, red cell distribution width; HDW, hemoglobin distribution width; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; CRP, C-reactive protein; SAA, serum amyloid A; Hb, hemoglobin. From Ballas SK. Sickle Cell Pain<sup>44</sup>. Progress in Pain Research and Management, Vol.11; Seattle, WA, IASP Press, 1998; with permission

**Table 2 Incidence of Recurrent Painful crises (1985-1989)**

Year	Admissions* n	Recurrent Crises After Discharge†	
		Within 1 wk n (%)	Within 1 mon n (%)
1985	209	31(14.8)	127(60.8)
1986	266	73(27.4)	155(58.3)
1987	246	67(27.2)	157(63.8)
1988	307	61(20.0)	154(50.2)
1989	427	59(13.5)	214(50.0)
Total	1465	291 (19.8)	807 (26.1)

\*Represents crisis-related admissions only.

†Recurrent crises are those which required treatment with parenteral

Opioid analgesics in the emergency room or during rehospitalization.

Values in parentheses are percentages. Adapted from Ballas SK and Smith ED,<sup>46</sup> Red Blood Cell Changes During the Evolution of the Sickle Cell Painful Crisis. *Blood*, 1992;79:2154-2163.

**Table 3. Incidence of Hospital Readmissions for Acute Painful Episodes in 1998-2002**

	<u>Hospital Readmissions after Discharge</u>	
	Within 1 Week	Within 1 Month
Patients, n		
Males, n (%)	27/55 (49)	36/55(66)
Females, n (%)	28/62 (45)	37/62 (60)
Total, n (%)	55/117 (47)	73/117 (62)
Readmissions		
Males, n (%)	148/871 (17)	516/871 (59)
Females, n (%)	80/586 (14)	210/586 (36)
Total, n (%)	228/1457 (16)	726/1457 (50)

The numerator of each fraction represents the number of readmissions and the denominator represents the total number of hospital admissions before discharge. Values in parentheses are percentages. About 16% of readmissions occur one week after discharge and 50% of readmissions occur after one month after discharge. Adapted from Ballas and Lusardi <sup>43</sup> with permission.

**Table 4. Approaches to the Management of Sickle Cell Disease and its Complications**

Approach	Definition
1. Supportive Management	Management intended to maintain the essential requirements for good health such balanced diet, sleep, hydration, folic acid, etc.
2. Symptomatic Management	Management targeted to alleviate the symptoms of the disease as they occur. These include blood transfusion for symptomatic anemia, analgesics for pain, antibiotics for infections, etc.
3. Preventative management	Approaches to prevent the occurrence of complications of the disease. These include things like vaccination, avoidance of stressful situations, Hb F induction with hydroxyurea or other agents, transfusion to prevent the recurrence of stroke, etc
4. Abortive management	Major purpose of this approach is to abort painful crisis thus preventing them from getting worse or precipitating other complication. The only promising abortive approach has been nitric oxide.
5. Curative therapy	This is the ultimate goal of all inherited disorders. This has already been achieved in SCD by stem cell transplantation. Gene therapy is another challenging goal.

## Legends to Figures

**Figure 1.** A typical profile of the events that develop during the evolution of a severe sickle cell painful crisis in an adult in the absence of overt infection or other complications. Such events are usually treated in the hospital with an average stay of 9-11 days. Pain becomes most severe by day 3 of the crisis and starts decreasing by day 6 or 7. The Roman numerals refer to the phase of the crisis: I, prodromal phase; II, initial phase; III, established phase; and IV, resolving phase. Dots on the X axis indicate the time when changes became apparent and dots on the Y axis indicate the relative value of change in comparison to the steady state indicated by the horizontal dashed line. Arrows indicate the time when certain clinical signs and symptoms may become apparent. Values shown are those reported at least twice by different investigators; values that were anecdotal, unconfirmed, or that were not reported to occur on a specific day of the crisis are not shown. Abbreviations: ISC, irreversibly sickled cells; RDW, red cell distribution width; HDW, hemoglobin distribution width; RBC DI, red cell deformability index; CRP, C-reactive protein; SAA, serum amyloid A; LDH, lactate dehydrogenase; CPK, creatinine phosphokinase; Hb, hemoglobin; ESR, erythrocyte sedimentation rate. Reproduced from Ballas SK. The sickle cell painful crisis in adults: phases and objective signs. *Hemoglobin* <sup>48</sup> 1995; 19:327; with permission.

**Figure 2.** Two sequential painful crises with no pain during the time in between them.

**Figure 3.** Pain intensity scores during hospitalization for acute painful episodes in 1998 –2002.

Adapted from Ballas & Lusardi <sup>43</sup> with permission.

**Figure 4.** Two sequential painful crises with residual pain during the time in between them.

Severity of the residual pain between crises varies among patients and in the same patient with time as indicated by the arrows.

**Figure 5.** Sequence of events during the evolution of the prodromal phase of the painful crisis.

Tissue necrosis consequent to ischemia elicits an inflammatory response that is associated with an increase in the serum level of acute phase reactants. Adopted from Ballas.<sup>90</sup>