PYREXIA IN CHILDREN WITH BURNS: INVESTIGATIONS INTO A NUMBER OF POSSIBLE AETIOLOGICAL FACTORS IN THE UNIVERSITY TEACHING HOSPITAL. LUSAKA. ZAMBIA

DR. LAMECK ZIMBA MD.

A DISSERTATION SUBMITTED TO THE UNIVERSITY OF ZAMBIA IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER IN MEDICINE (SURGERY)

SCHOOL OF MEDICINE
THE UNIVERSITY OF ZAMBIA
LUSAKA

1999.

TABLE OF CONTENTS

COPYRIGHT DECLARATION

I THE UNDERSIGNED DECLARE THAT THE DISSERTATION REPRESENTS MY OWN WORK AND THAT IT HAS NOT PREVIOUSLY BEEN SUBMITTED FOR A DEGREE AT THIS OR ANOTHER UNIVERSITY.

DATE: 7/11/2000 CANDIDATE'S SIGNATURE L. Zimba

I HAVE READ THIS DISSERTATION AND APPROVED IT FOR EXAMINATION.

DATE: 8/11/00 SIGNATURE .....

SUPERVISOR: PROF. ERZINGATSIAN KRIKOR FRCSI
PROFESSOR OF SURGERY AND HEAD,
DEPARTMENT OF SURGERY
SCHOOL OF MEDICINE
UNIVERSITY OF ZAMBIA

DATE: 14.NOV.'00 SIGNATURE .....

CO-SUPERVISOR: DR. JIM JEWELL MD, FACS, FCCP.
SENIOR LECTURER
DEPARTMENT OF SURGERY
SCHOOL OF MEDICINE
UNIVERSITY OF ZAMBIA

ABBREVIATIONS

AA	Amino acids
ADH	Antidiuretic hormone
BSA	Body surface area
D	Dermis
DIC	Disseminated intravascular coagulation
DP	Dermal papillae
EDTA	Ethylene diamine tetra-acetic acid
ESR	Erythrocyte sedimentation rate
FBC	Full blood count
HF	Hair follicles
iNOS	Inducible nitric oxide synthase
IL-1	Interleukin-1
IL-6	Interleukin-6
IL-8	Interleukin-8
LBP	LPS-binding protein
LPS	Lipopolysaccharide
MLN	Mesenteric lymph node
MSOF	Multiple System Organ Failure
PAF	Platelet activating factor
PBD	Postburn day
PD	Papillary dermis
PGE_2	Prostaglandin E_2

PUO	Pyrexia of unknown origin
RBC	Red blood cells
RD	Reticular layer of skin
SB	Stratum basalis
SS	Stratum spinosum
SGR	Stratum granulosum
SL	Stratum lucidum
SC	Stratum corneum
TBSA	Total body surface area
TNF	Tumor Necrosis Factor
TSS	Toxic Shock Syndrome
TxA2	Thromboxane A2
WBC	White blood cell

APPROVAL

This dissertation of Dr. Lameck Zimba is approved in partial fulfillment of requirements for the award of the Master of Medicine (Surgery) by the University of Zambia.

EXAMINERS

1. Signature:..... Date: 8/11/00

2. Signature:..... Date: 14 NOV 00

3. Signature:..... Date: 14. 11. 2000

4. Signature:..... Date:.....

ACKNOWLEDGEMENTS

I am grateful to Professor Erzingatsian who guided me through the preparation and writing up of this dissertation. He has been my role model of dedication, hard work and honesty to Surgery.

I am also thankful to Dr. Jewell and Dr. Labib for their contributions and guidance towards the completion of this study.

Special thanks to my wife M╣rta for the support and encouragement at every stage of this project.

Candidate's Signature:..... L. Zumba .....

ABSTRACT

Pyrexia is seen in 93 percent of all children with burns admitted to the University Teaching Hospital, Department of Surgery, Lusaka, Zambia. Sixty five percent of these had fever on the first day of admission. The cause could not be determined with certainty.

Pyrexia was a common feature in patients with burn wound sepsis. Culture studies from wounds in the first week of admission yielded gram positive organisms, the pattern changed in the subsequent weeks to include gram negative organisms. There was no statistically significant association between pyrexia and the presence of sepsis as determined by blood culture and wound swab culture. Malaria parasitaemia was seen in 5 percent of pyrexial children and 63 percent of all pyrexial children were treated by antimalarial medication.

LIST OF FIGURES

LIST OF TABLES

INTRODUCTION

Fever in children with burns is a major morbidity factor. The significance of pyrexia in the burnt child is often unclear. There are many causes for pyrexia in the burnt child, but in a significant proportion of patients the aetiology of fever and its contribution to morbidity and mortality is undetermined. This retrospective and prospective study was undertaken in the University Teaching Hospital, Department of Surgery to address the problem. Patients who had sustained burns and developed pyrexia at some stage during admission were included in this study with particular attention given to the role of bacteraemia and malarial parasitaemia as possible causative factors in the aetiology of pyrexia

SKIN

Anatomy and physiology

The skin is considered to be the largest organ of the body and has many different functions. Its functions include thermoregulation, protection, excretion, a sensory organ and production of vitamin D from ultraviolet light. The skin is divided into two main regions, the epidermis, and the dermis, each providing a distinct role in the overall function of the skin. The skin overlies subcutaneous connective tissue, which is a store of fat.

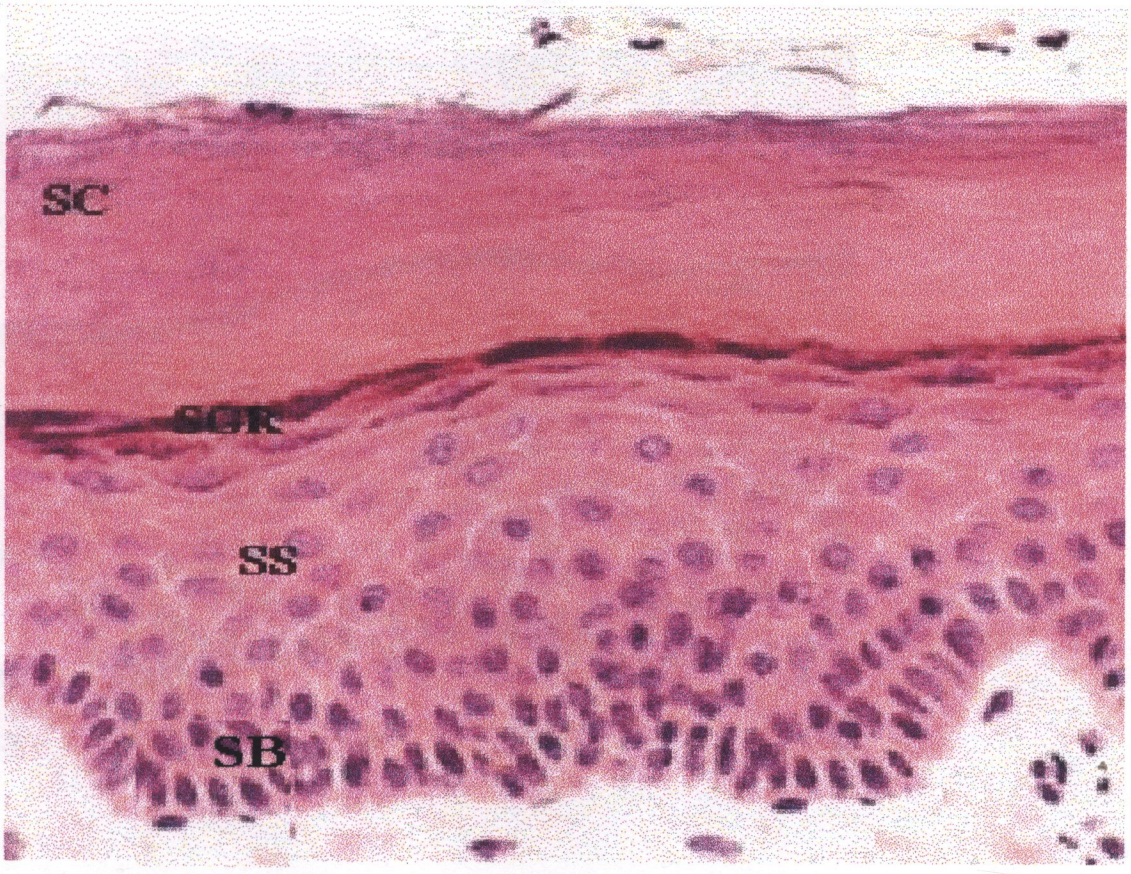


Figure 1. Skin , different layers of the epidermis

The epidermis is the most superficial layer of the skin and provides the first protective barrier. The principal cell of the epidermis is called a keratinocyte.

The epidermis is subdivided into five layers or strata:

- Stratum basalis (**SB**),
- Stratum spinosum(**SS**),
- Stratum granulosum(**SGR**),
- Stratum lucidum(not seen in the above photomicrograph) and
- Stratum corneum(**SC**) in which a keratinocyte gradually migrates to the surface and is sloughed off in a process called desquamation.

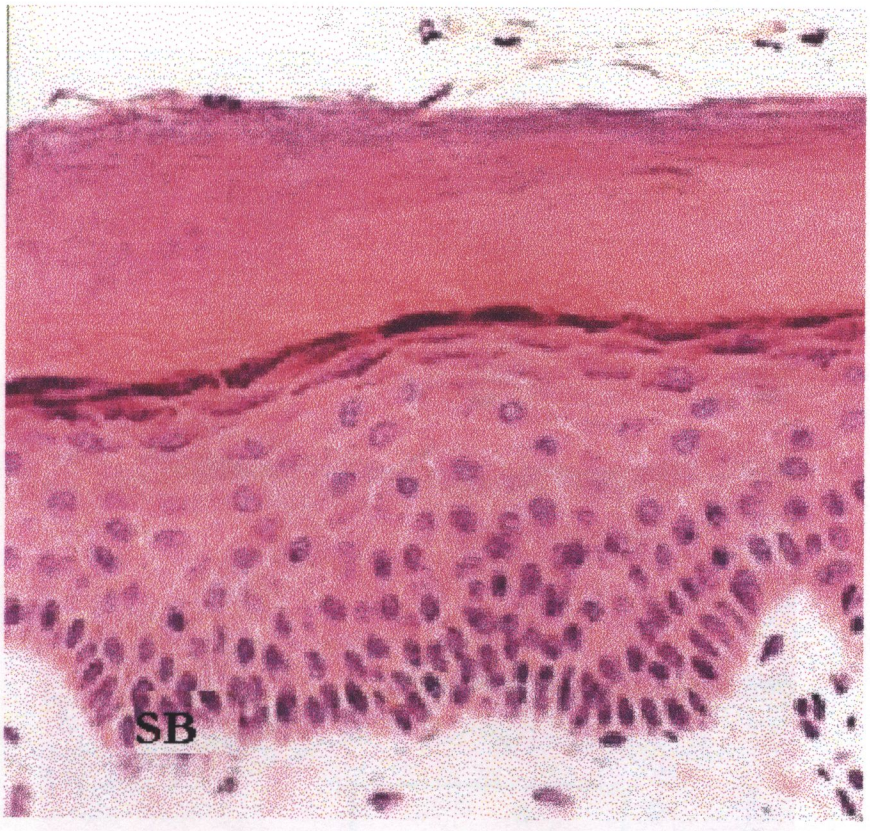


Figure 2. Skin, Stratum Basalis (SB)

The stratum basalis (**SB**) provides the germinal cells necessary for the regeneration of the layers of the epidermis. These germinal cells are separated from the dermis by a thin layer of basement membrane. After a mitotic division a newly formed cell will undergo a progressive maturation called keratinization as its migrates to the surface. Some of these cells also contain melanin and are called melanocytes.

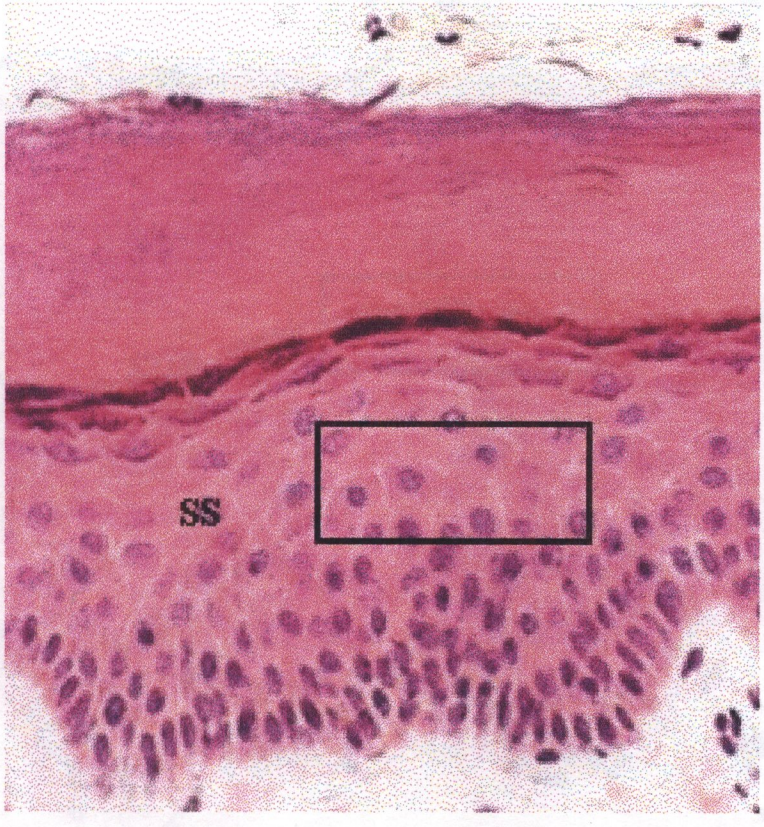


Figure 3. Skin, Stratum spinosum (**SS**) (Malpighian layer)

The cells that divide in the statum germinativum are located in the stratum basalis and stratum spinosum. These cells begin to accumulate many desmosomes on their outer surface that provide the characteristic "prickles" (seen on a close-up view) of the stratum spinosum (**SS**), which is often called the prickle-cell layer or Malpighian layer.

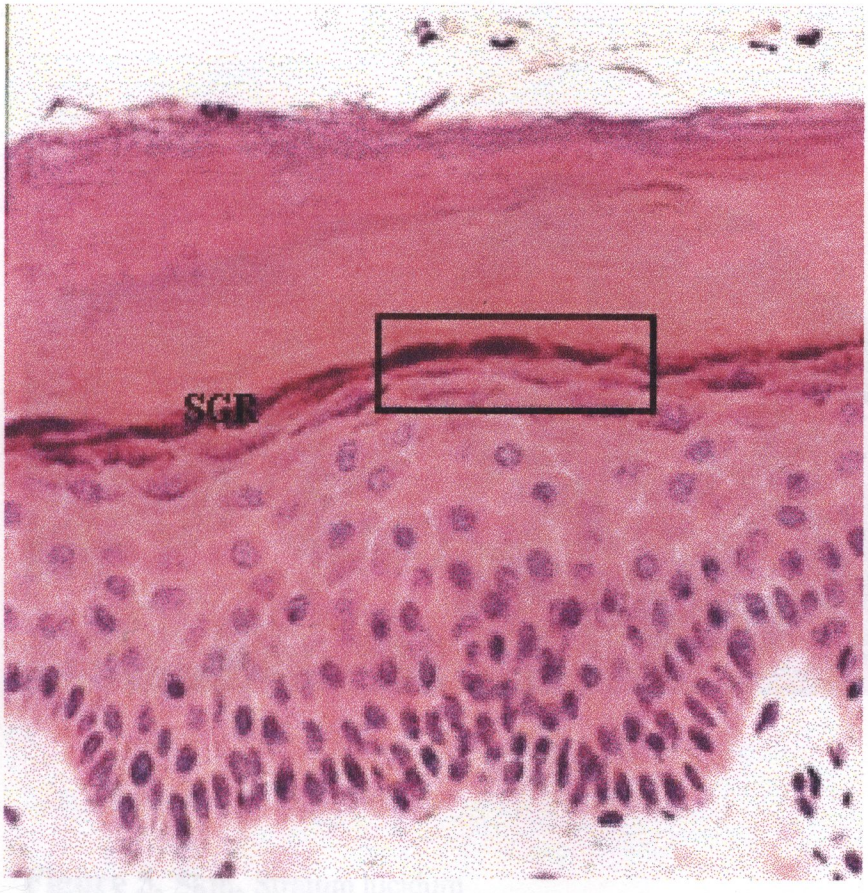


Figure 4. Skin, Stratum granulosum

The progressive maturation of a keratinocyte is characterized by the accumulation of keratin, called keratinization. The cells of the stratum granulosum (**SGR**) accumulate dense basophilic keratohyalin granules. These granules contain lipids, which along with the desmosomal connections, help to form a waterproof barrier that functions to prevent fluid loss from the body. Melanocytes - melanin-containing cells are also found in this layer.

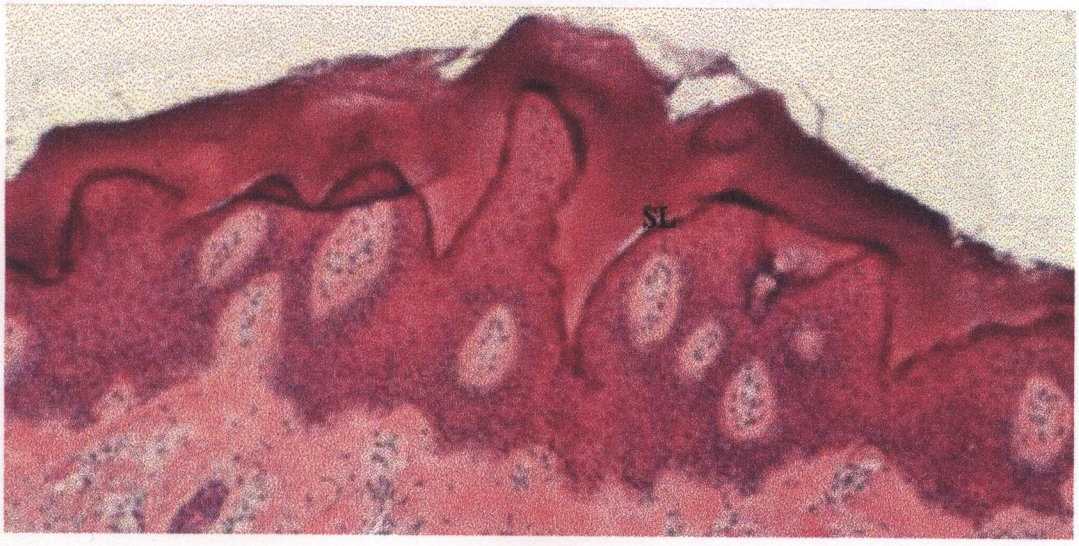


Figure 5. Skin, Stratum lucidum

Epidermis varies in thickness throughout the body depending mainly on frictional forces and is thickest on the palms of the hands and soles of the feet. The stratum lucidum is normally only well seen in thick epidermis and represents a transition from the stratum granulosum to the stratum corneum.

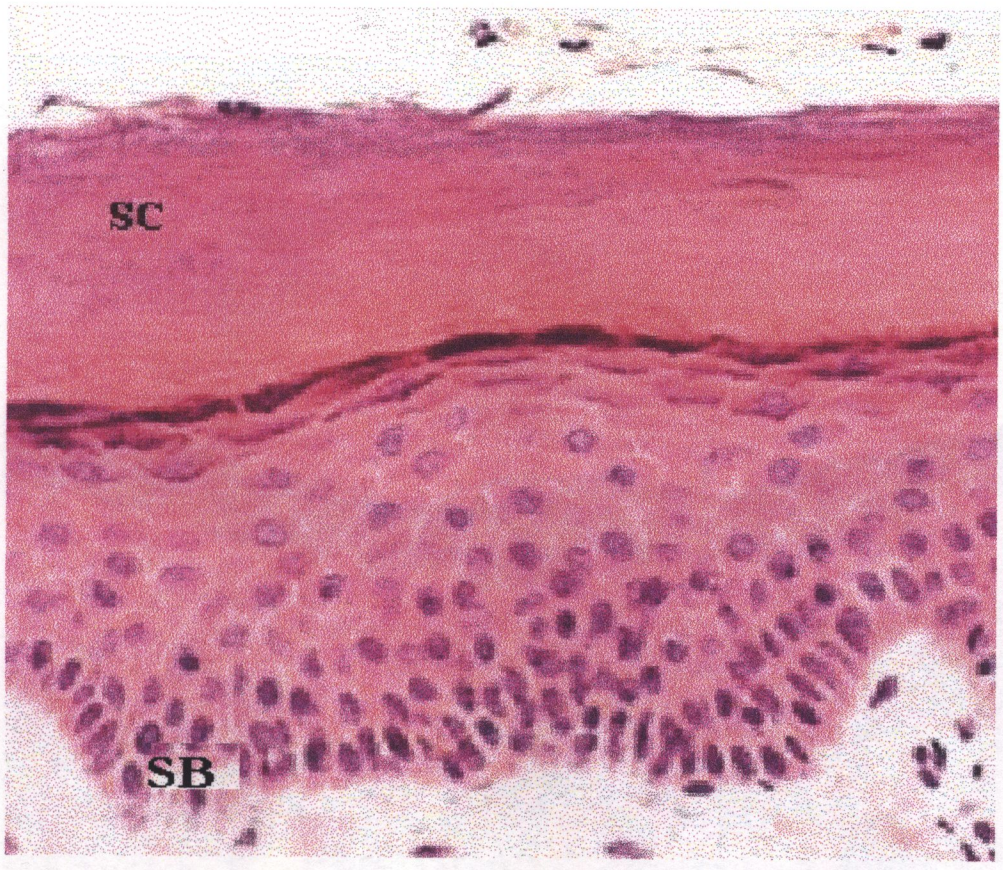


Figure 6.Skin Stratum corneum (**SC**).

As a cell accumulates keratinohyalin granules, it is thought that rupture of lysosomal membranes release lysosomal enzymes that eventually cause cell death. The dead and dying cells filled with mature keratin form the stratum corneum (**SC**). The deeper cells of the stratum corneum retain their desmosomal junctions, but as they are pushed to the surface by newly forming cells of the stratum basalis (**SB**), the dead cells gradually break apart and are lost, a process called desquamation.

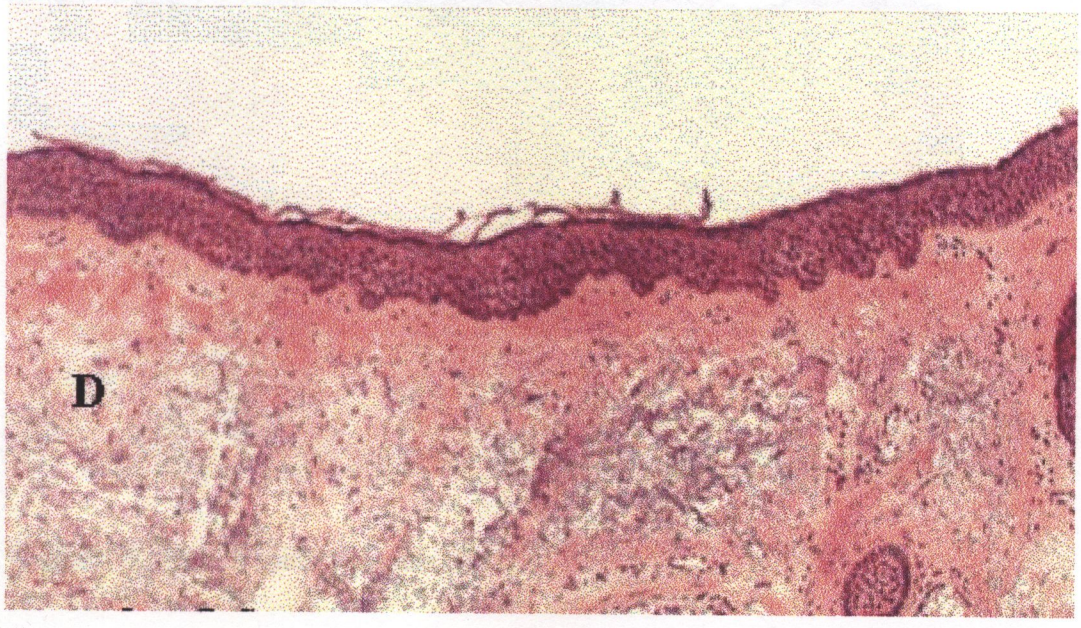


Figure 7. Skin, Dermis

The dermis **(D)** assumes the important functions of thermoregulation and supports the vascular network to supply the avascular epidermis with nutrients.

The dermis is typically subdivided into two zones,

- a papillary dermis and
- a reticular layer.

The dermis contains mostly fibroblasts that are responsible for secreting collagen, elastin and ground substance that give the support and elasticity of the skin. Also present are immune cells that are involved in defense against foreign invaders passing through the epidermis.

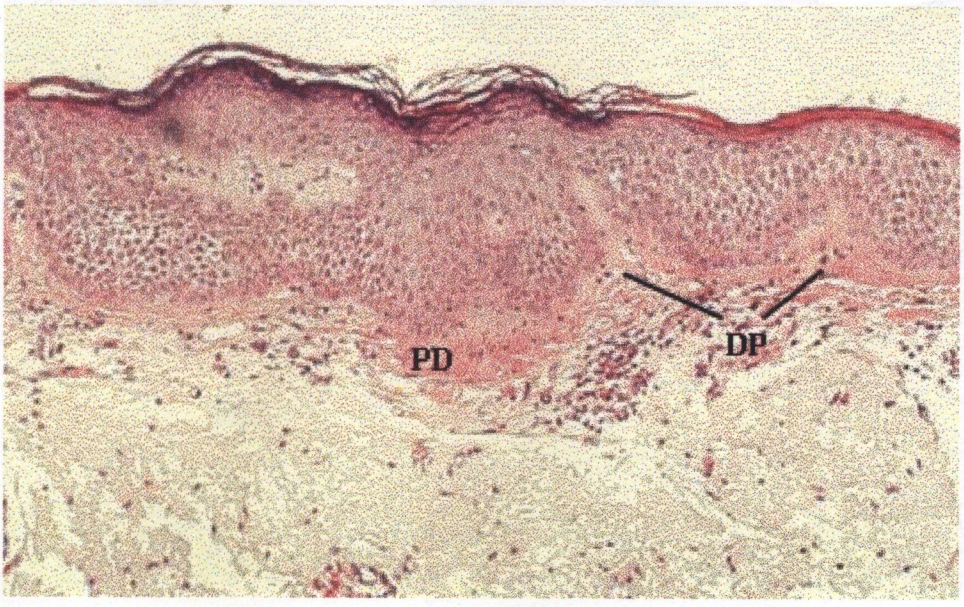


Figure 8. Skin, Papillary dermis (PD)

The papillary dermis (**PD**) contains vascular networks that have two important functions. The first being to support the avascular epidermis with vital nutrients and secondly to provide a network for thermoregulation. The vasculature is organized so that by increasing or decreasing blood flow, heat can either be conserved or dissipated. The vasculature interdigitates in areas called dermal papillae (**DP**). The papillary dermis also contains the free sensory nerve endings and structures called Meissner's corpuscles in highly sensitive areas.

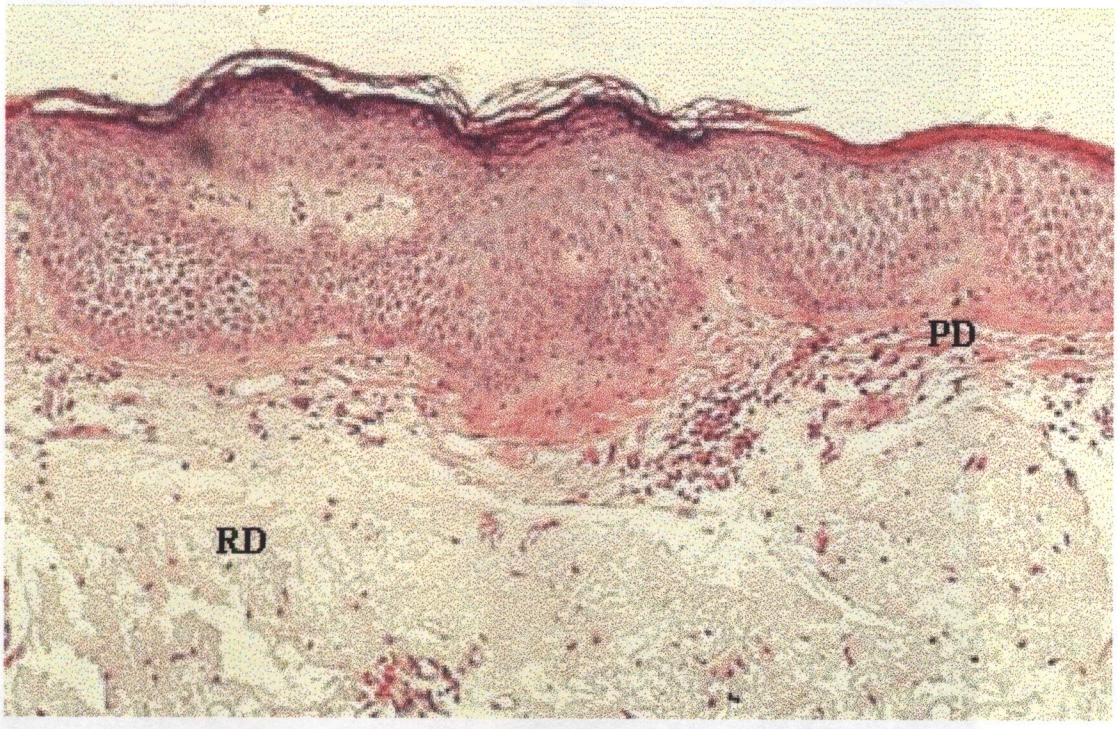


Figure 9. **Skin,** Reticular layer of the dermis **(RD)**

It consists of dense irregular connective tissue, which differs from the papillary layer (**PD**), which is made up of mainly loose connective tissue (note the difference in the number of cells). The reticular layer of the dermis is important in giving the skin its overall strength and elasticity, as well as housing other important epithelial derived structures such as glands and hair follicles.

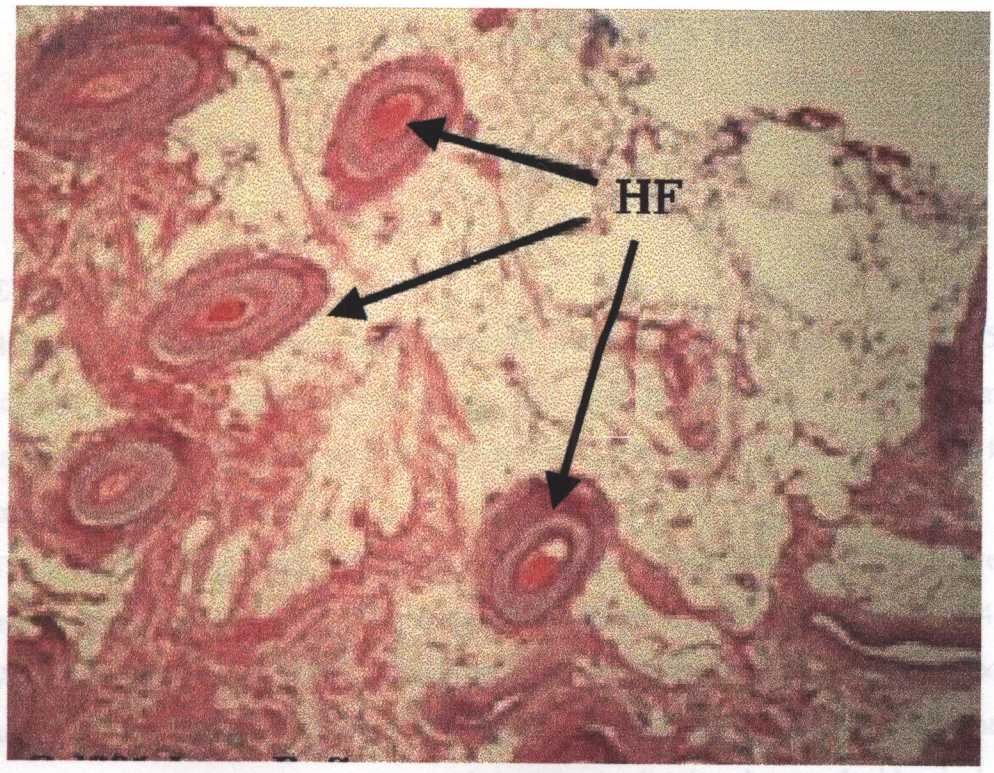


Figure 10. Skin Appendages

The skin contains a variety of appendages, mainly

- hair follicles (**HF**),
- sweat glands , and

sebaceous glands which are all embryologically epidermal in origin.

LITERATURE REVIEW

BURNS

EPIDEMIOLOGY

Burns are a common home accident world -wide with a peak age between 2-5years. The causative agent is normally hot water. The majority of burns are mild to moderate in severity, that is, first and second degree burns. The major cause of death is from sepsis and electrolyte imbalance[1] .

The mean age of patients with burns in the paediatric age group is 4.3+/- 0.2year, and the male :female ratio is 1.9:1. The majority of deaths occur under the age of 4yrs of age. With respect to large burns, defined as greater or equal to 30percent total body surface area (TBSA), the mortality rate for children under age 4 is significantly higher than that for older children. (46.9percent v 12.5percent), despite the nearly identical mean burn size of the two groups except for the incidence, there are no differences between the males and females[1].

Inhalation injuries are strongly associated with large burns. Scalds are the most common types of burn among children under 4 years; flame burns predominate in older children. Burn type, size and mortality rate does not differ between children from urban and rural communities. Large burn size is the strongest predictor of mortality, followed by (in order) age less than 4 and the presence of inhalation injury[1,2].

Burns in children are often preventable and result from inadequate supervision, curiosity, and the inability to escape a burning agent . A Child's skin is thinner and more susceptible to injury and because of thin skin and the inability to escape the burn source, the extent of injury is worsened[3].

AETIOLOGY

Burns can occur due to a variety of reasons, including exposure to fire or fluids at high temperature, chemicals such as acids, bases and oxidizing agents, high voltage electricity and exposure to the sun(in the light skinned).

PATHOGENESIS

Burns cause hyperaemia, capillary stasis and coagulation necrosis depending on the depth of injury. Because children have thinner epidermal layers, morbidity is higher in children[3].

Jackson has described three concentric zones of burn injury[4].

1. Zone of hyperaemia - it heals well with adequate care.
2. Zone of stasis, the blood flow is slowed down. This zone, if managed properly the damage can be minimized or even reversed
3. Central zone of coagulation indicates maximum damage to tissues and blood vessel resulting in death of the affected area.

General Microscopic Description

In the University Teaching Hospital some units classify burns as superficial, partial thickness or deep burns.

In full thickness burns, the entire epidermis, parts or all of the dermis, and the subcutaneous tissue may be injured. As with a partial thickness burn, the tissue involved is converted into a homogeneously staining material. The epidermis and part of the dermis is involved in partial thickness burns and in a superficial burn only the epidermis is damaged[5].

General Clinical Features

Definitive diagnosis is determined by histologic depth of tissue necrosis and there are 4 types:

CLASSIFICATION OF BURNS BY DEPTH-1ST DEGREE

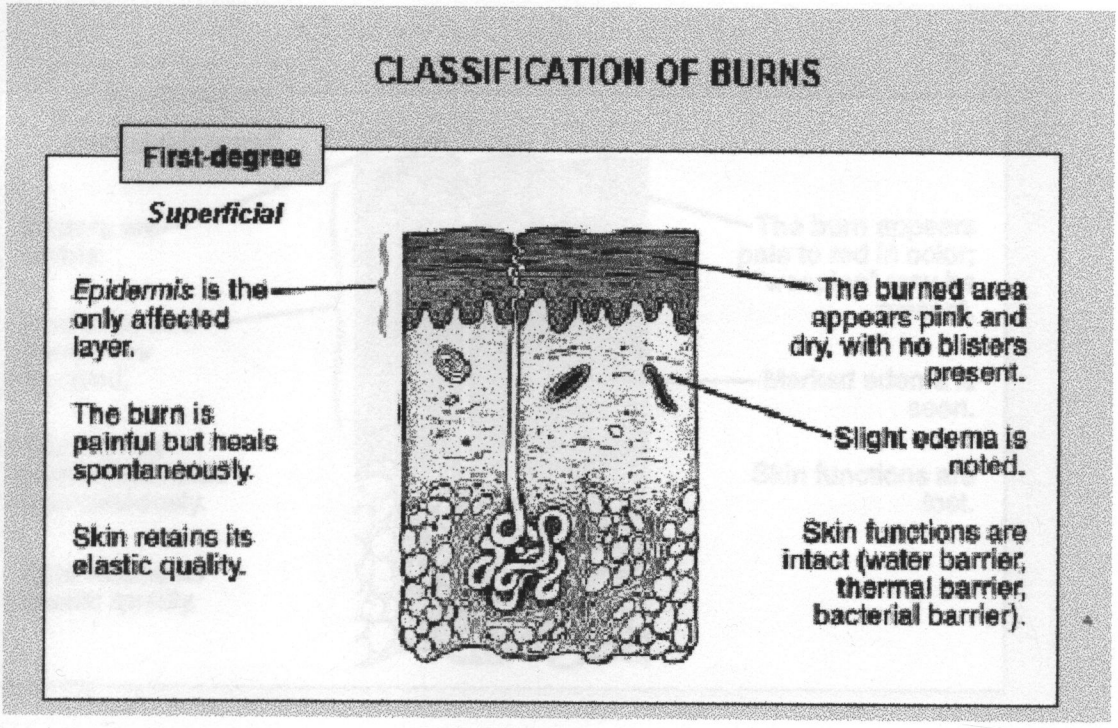


Figure 11. First degree burns

FIRST-DEGREE BURNS-PARTIAL THICKNESS INJURY: affects epidermis only without injury to underlying dermal or subcutaneous tissue. Skin maintains water vapor barrier and bacterial barrier functions. Most caused by sunburn. The symptoms are local pain and erythema and no blisters appear for 24 hours. Extensive first-degree may cause systemic response such as chills, headache, localized edema and nausea and vomiting[6].

CLASSIFICATION OF BURNS BY DEPTH-2ND DEGREE

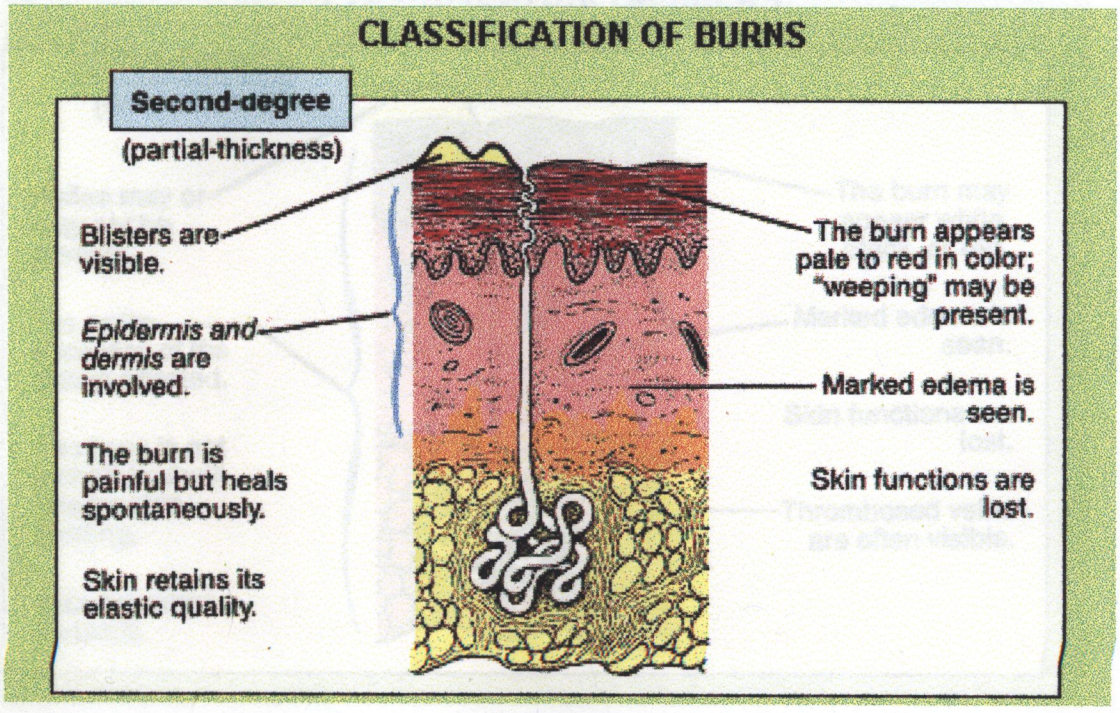


Figure 12. Second degree burns

SECOND-DEGREE BURNS: There are two subcategories in partial thickness burns with markedly different characteristics. In superficial partial thickness burns-thin-walled, fluid filled blisters develop within minutes and the dominant symptom is pain. As blisters break or are removed, nerve endings are exposed to air. In deep partial thickness burns the entire dermis is involved, the burn often looks waxy white and is surrounded by margins of superficial partial thickness injury. The injury is often indistinguishable from full-thickness injury[6].

CLASSIFICATION OF BURNS BY DEPTH-3RD DEGREE

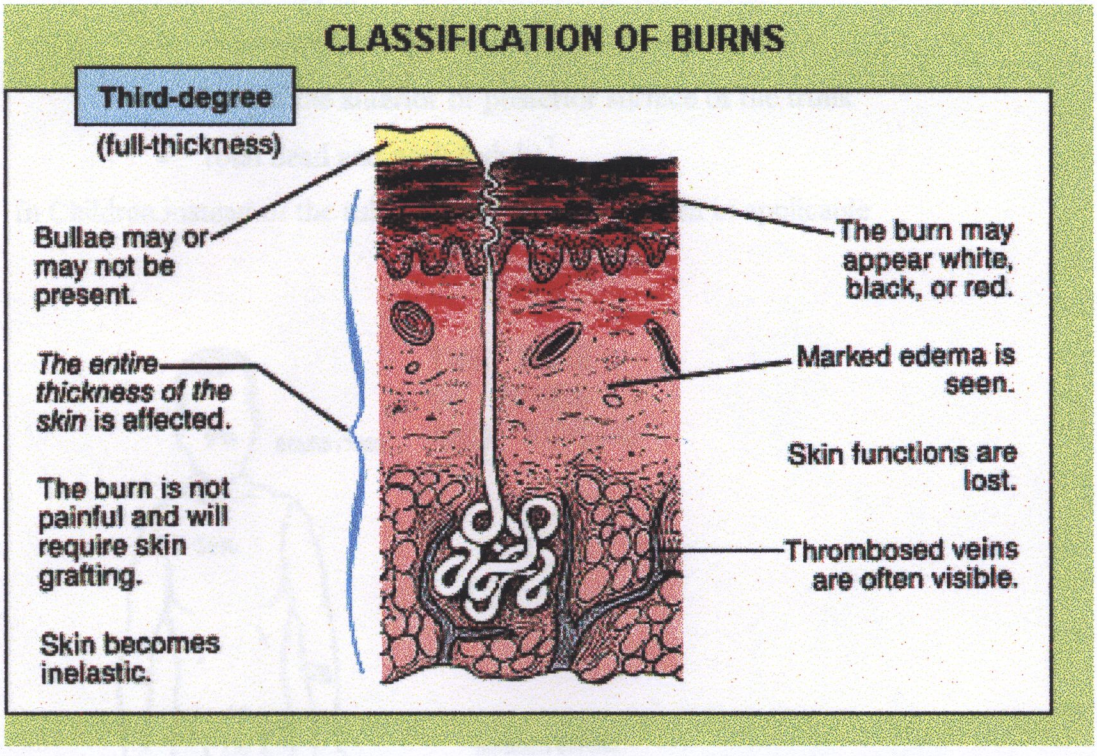


Figure13. Third degree burns

THIRD-DEGREE BURNS OR FULL THICKNESS-BURNS: destruction of epidermis, dermis, and often underlying tissues. Colour may be white and delineation between normal and burned skin may not be accompanied by marked colour change. The elasticity of the dermis is destroyed and wound has a dry, leathery appearance. Marked edema forms and distal circulation can be compromised in areas of circumferential burns requiring escharotomies (cutting through burned skin) to prevent compartment syndrome[6].

The burn extent is based on the percentage of Body Surface Area (BSA) which clinically has 2nd and 3rd degree burn, but 1st degree burn area is not included.

There are many methods for estimating burn extent, including:

- **Rule of Nine's** - in increments of 9 percent BSA
  - entire upper limb
  - anterior or posterior surface of one lower limb
  - half of the anterior or posterior surface of the trunk
  - total head and neck (adult)[7].

In Children instead of the rule of nine the rule of seven in applicable

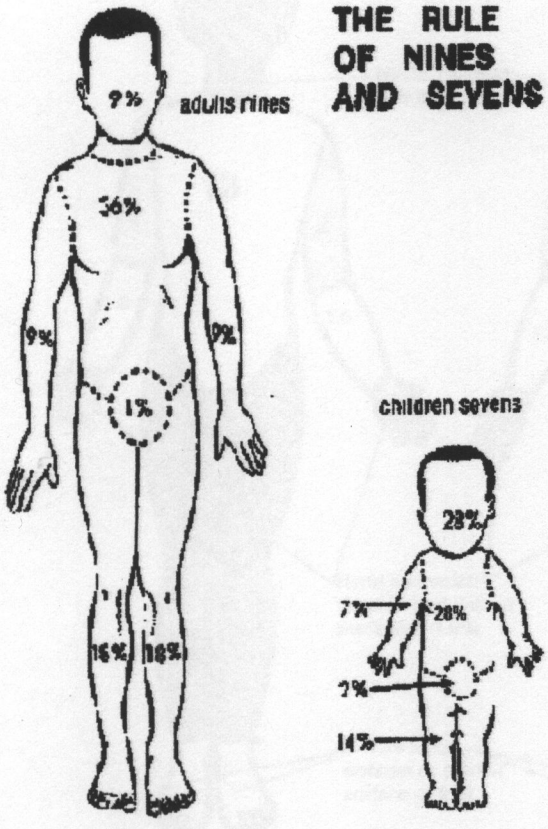


Figure 14. The Rule of Nines and Sevens. An adult's head and each of his arms make up 9percent of his surface area. The legs make up 18percent(2X9). In a child the unit is 7percent, but his proportionally larger head makes up 28percent

Lund & Browder Chart emphasizes the relatively larger head size in: (See also Appendix)

- infancy (largest)
- childhood (larger)
- adulthood (normal)

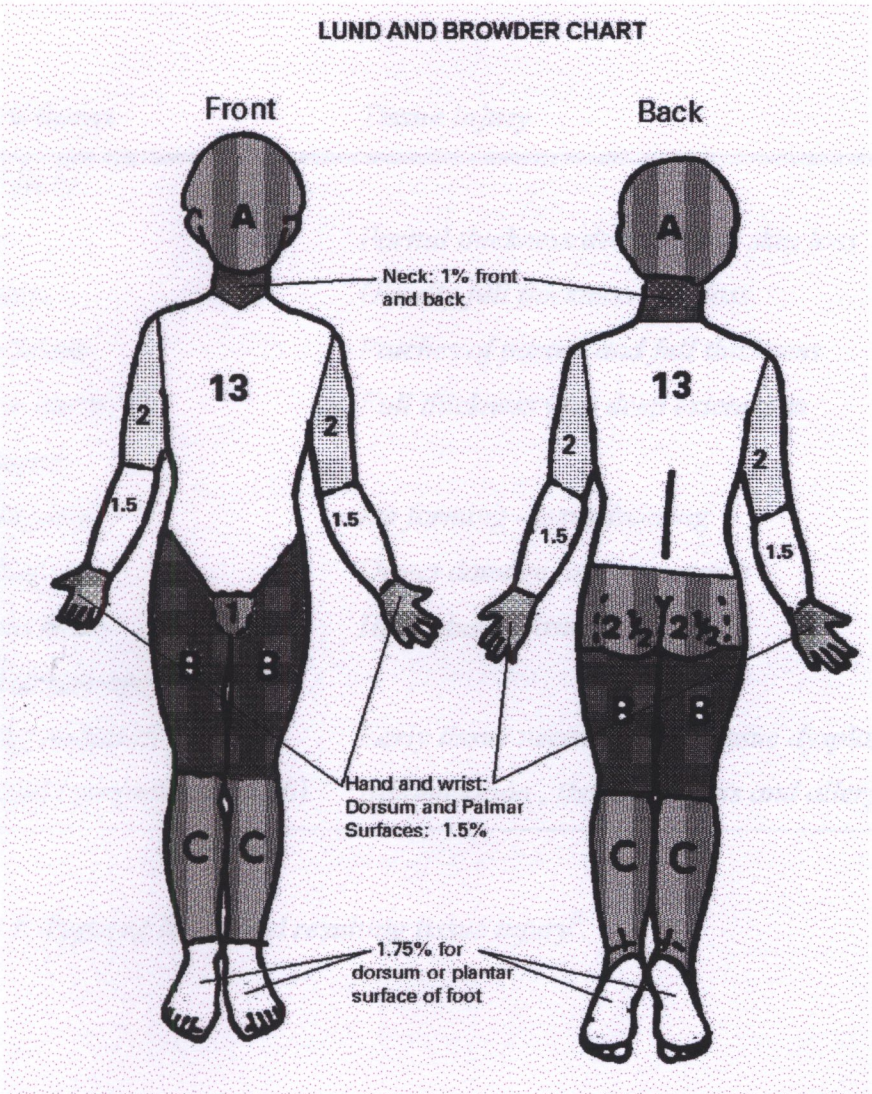


DIAGRAM AREA	AGE IN YEARS			
	0	*1*	*5*	*10*
A = ½ of Head	9.5	8.5	6.5	5.5
B= ½ of Thigh	2.75	3.25	4	4.25
C= ½ of Leg	2.5	2.5	2.75	3

Figure 15. Lund & Browder Chart applicable for both adults and children See also Appendix 1

- Patient's palm size in children represents 1 - 1.25percent

CLASSIFICATION OF TYPE OF BURN (Bailey and Love 1995)

TABLE 1.

Type of Burns	*Tissue injury*
Heat injury	
Scalds	*Partial thickness/deep dermal skin loss*
Fat burns	*Usually full thickness skin loss*
Flame burns	*Patches of partial and full thickness*
Electric burns	*Full thickness with deep extensions*
Cold injury	
Freezing injury	*Ice forming -tissue freezing*
Frostbite	*Direct damage and vasospasm*
Friction burns	*Heat plus abrasion*
Physical damage	
Ionising radiation	*Early tissue necrosis, later tissue dysplastic changes*
Chemical burn(acid or alkali)	*Inflammation , tissue necrosis and allergic response*

Table 1. *Types of burns and resulting tissue injury*[8].

CLASSIFICATION OF SEVERITY OF BURNS

TABLE 2.

American Burn Association classification of burn injury

Minor burn injury	***Moderate, uncomplicated burn injury***	***Major burn injury***
Second - degree burns of less than 15percent Total Body surface area in adults or less than 10percent Total Body surface area in children	*Second - degree burns of 15percent-25percent Total Body surface area in adults or 10percent to 20percent Total Body surface area in children*	*Second-degree burns of greater than 25percent Total Body surface area in adults or 20percent Total Body surface area in children*
Third -degree burns of less than 2percent Total Body surface area not involving special care areas(eyes, ears, face, hands, feet ,perineum)	*Third -degree burns of less than 10percent Total Body surface area not involving special care areas*	*All third-degree burns of 10percent Total Body surface area or greater*
Excludes electrical injury, inhalation injury, complicated injury(fractures), all poor-risk individuals(extremes of age, intercurrent disease,etc.)	*Excludes electrical injury, inhalation injury, complicated injury(fractures), all poor-risk individuals(extremes of age, intercurrent disease,etc.)*	*All burns involving hands, face, eyes, ears, feet, perineum* *All inhalation injury, electrical injury, complicated burn injury involving fractures or other major trauma.* *All poor risk individuals*

Table 2. *Classification of severity of burns - American Burn Association classification of burn injury*

PATHOPHYSIOLOGY

The body's general response to serious thermal injury is characterized by increased vascular permeability immediately after injury and subsequent hypovolaemic shock. Skeleto-muscular proteolysis, lipolysis, gluconeogenesis, increased metabolic rate, and a severe systemic inflammatory response induced by local infections or surgery[9]. The increased vascular permeability is mediated by histamine and numerous vasoactive substances, including serotonin, bradykinin, prostaglandins, leukotrienes, and platelet activating factor[9]. Hyper-metabolism is mediated by hormones such as catecholamines, glucagon, and particularly cortisol. In addition, among the putative mediators of the metabolic response to injury, attention has recently been focused on cytokines and lipid mediators which are mainly produced by activated reticuloendothelial cells[9]. Cytokines such as interleukin-1, interleukin-6 and tumor necrosis factor and cortisol responses are interrelated, since cytokines activate the hypothalamo-adrenal axis. The cytokine storm seen in burn patients may be associated with depression of the immune system and with susceptibility to infection[9]. Thermal injury can also lead to activation of the renin-angiotensin-aldosterone system, increased ADH production, and production of atrial natriuretic polypeptide to maintain the circulatory volume[9]. Burn wound infections or surgery can produce and perpetuate a mediator-induced systemic inflammatory response that may lead to multiple organ failure. Serum levels of interleukin-6 are very sensitive to surgical stress, and may be a useful indicator of the general condition of severely burned patients[9].

SYSTEMIC RESPONSE TO BURNS

Thermal injury leads to a number of systemic responses :

- Hypovolaemia
- Hypermetabolism
- Protein catabolism
- Hyperglycaemia (insulin resistant)
- Myocardial depression

Bacterial translocation through the gut mucosa

- Villous atrophy and capillary leak
- Source of pathogens
- Cause of multisystem failure

BURN TOXAEMIA

Inspite of good care of the wound, administration of the best and the latest antibiotics and maintenance of fluid and electrolyte balance, the mortality still continues to be high. It is presumed that burnt skin elaborates specific toxins, enzymatic in nature which stimulate antibody formation.

Animals burnt a second time are said to have less clinical disturbance. Serum of patients convalescent after burns is claimed to transfer specific benefits to burnt patients. However, higher doses of such serum can be dangerous[10]. It is also observed that agglutinating antibodies are produced by the 8th day after burns against their own burnt skin. Early removal of burnt skin may remove antigenic stimuli thereby reducing antibody formation and consequent ill effects. Presence of such antibodies in high titre lead to repeated graft rejection.

Changes occur in various organs following extensive burns, they are summarized hereunder;

1. Liver : there is sinusoidal congestion and varying degree of hepatic cell degeneration and necrosis.
2. Kidneys : There is degeneration of cells lining tubules, which may lead to acute tubular necrosis and renal shut down.
3. Gastrointestinal system : Acute ulceration of the stomach, duodenum (Curlings ulcers) may occur in 15-20 percent of cases which may then lead to gastrointestinal bleeding.
4. Heart : There may be decreased cardiac output and increased systemic vascular resistance
5. Circulatory system : There may be haemoconcentration due to large fluid loss and *reduction in platelet count.*
6. Respiratory system : Respiratory rate increases. Pulmonary oedema may result if the patient is over transfused or the patient may develop Adult Respiratory *Distress Syndrome.*
7. Late eosinophilia may develop 4-6 weeks after burns associated with increase in the histamine content of the tissues.

Acute inflammatory mediators

- Immediate: histamine, C5a, AA metabolites cause local, systemic oedema and changes in microcirculation
- Cytokines (TNF-alpha, interleukin-1, interleukin-8) are associated with progressive tissue necrosis and immunosuppression secondary to endogenous response .

Endotoxaemia in severely burned patients commonly occurs and is closely related to the development of sepsis and multiple system organ failure (MSOF) after burn injury. Dynamic observation of the changes in circulating endotoxin concentration are valuable as a marker for predicting sepsis and multiple system organ failure (MSOF) in critically ill patients with burns[11].

Sepsis and multiple system organ failure (MSOF) are major causes of morbidity and mortality in burnt patients. Bacterial translocation induced by hypotension, endotoxaemia, or burns is a reproducible phenomenon in the laboratory. The classical progression of bacteria from the gut to the bloodstream via the mesenteric lymph nodes (MLNs) may require time and developing gut mucosal injury. The data suggest that bacterial translocation to the MLNs is not a common occurrence in acutely injured trauma patients[12,13].

Burn tissue endotoxin can stimulate local Thromboxane A2 production leading to distant lung dysfunction without the need for circulating endotoxin. The source of the Thromboxane A2 is the burn, whereas with endotoxaemia generally the source is the lung[14].

Gut-derived endotoxaemia could account, at least in part, for the inflammatory mediator formation and release of toxins, which might be involved in the pathogenesis of sepsis and multiple organ dysfunction following severe haemorrhage, trauma and burns[14].

The findings in one study showed that considerable amounts of myocardial protein degradation and release due to destruction of cardiac myocytes occurred early after severe burns. The inflammatory mediators released after burn injury may be involved in the pathogenesis of myocardial destruction[15].

PYREXIA

Pyrexia is an elevation of body temperature above the normal circadian range as the result of a change in the thermoregulatory center located in the anterior hypothalamus. A normal body temperature is ordinarily maintained, despite environmental variations, through the ability of the thermoregulatory center to balance heat production by the tissues (notably, muscles and the liver) with heat dissipation. With fever, the balance is shifted to increase the core temperature. **Hyperthermia** is an elevation of body temperature above the hypothalamic set point due to insufficient heat dissipation (e.g., in association with exercise, perspiration-inhibiting drugs, or a hot environment).

Whereas the "normal" temperature in humans has been said to be 37°C (98.6°F) on the basis of Wunderlich's original observations more than 120 years ago, the overall mean oral temperature for healthy individuals is actually 36.8 0.4° C (98.2 0.7°F), with a nadir at 6 A.M. and a zenith at 4 to 6 P.M. The maximum normal oral temperature at 6 A.M. is 37.2°C (98.9°F), and the maximum normal oral temperature at 4 P.M. is 37.7°C (99.9°F)--both values defining the 99th percentile for healthy individuals. Given these criteria, an am. temperature of greater than 37.2°C (98°F) or a pm temperature of grater than 37.7°C (99.9°F) would define a fever. Rectal temperatures are generally 0.6°C (1°F) higher. Lower oesophageal temperatures closely reflect core temperature. This morning-low and evening-high pattern is usually preserved in febrile diseases but not in hyperthermia[16].

Pyrogens

Substances that cause fever are called **pyrogens** and may be either exogenous or endogenous. **Exogenous pyrogens** come from outside the host, whereas endogenous pyrogens are produced by the host, generally in response to initiating stimuli that are usually triggered by infection or inflammation. The majority of exogenous pyrogens are microorganisms, their products, or toxins. The best-characterized type of exogenous pyrogen consists of a heterogeneous group of molecules that is common to all gram-negative bacteria and is referred to as **endotoxin** (lipopolysaccharide, LPS). LPS, which is found in the outer membrane of all gram-negative bacteria, comprises lipid A and a

polysaccharide core linked to an O-polysaccharide side chain composed of repeating units of sugars that vary with the gram-negative organism. Gram-positive organisms are also sources of potent pyrogens[16,17].
These include cell wall-derived lipoteichoic acid and peptidoglycans. Several exotoxins and enterotoxins produced by pathologic strains of streptococci and staphylococci act as bacterial superantigens--polyclonal T-lymphocyte activators that bind to the variable region of the T-cell receptor rather than in the antigen-binding pocket of the receptor. This binding leads to the activation of cells of many specificities, with resultant mediator release and tissue damage. These toxins are thought to contribute to both staphylococcal and streptococcal toxic shock. In vivo, as little as 1 ng of LPS/kg is capable of producing fever in humans; although there are no in vivo data for humans, gram-positive cell-wall constituents generally require a larger amount of material by weight to induce the production of endogenous pyrogens in vitro'[18].

In general, exogenous pyrogens act primarily by inducing the formation of endogenous pyrogens through stimulation of the host's cells--usually monocytes and macrophages. However, the distinction between exogenous and endogenous pyrogens is sometimes blurred. For example, LPS may act directly on endothelial cells in the brain to generate fever, whereas many exogenous products result in the release of endogenous pyrogens, thereby causing fever. Such endogenous substances include antigen-antibody complexes with complement, complement cleavage products, steroid hormone metabolites, bile acids, and some cytokines[18].

Endogenous pyrogens are polypeptides produced by a variety of host cells, particularly monocytes/macrophages. Endogenous pyrogens, produced either systemically or locally, gain entrance to the circulation and produce fever at the level of the thermoregulatory center of the hypothalamus[18,19]

It was originally thought that there was a single endogenous pyrogen, but it was later realized that there are two leukocyte endogenous pyrogens: interleukin (IL) 1α and IL-1β.

These two interleukins have a common molecular weight of approximately 17.5 kDa, have only 26 percent amino acid sequence homology, and bind to the same receptors. Originally thought to be produced only by phagocytic cells, IL-1α or IL-1β are also produced by endothelial cells, B lymphocytes, natural killer cells, fibroblasts, smooth-muscle cells, keratinocytes, and glial cells. Because of the ubiquitous production of these and other interleukins, cell-derived inflammatory polypeptides, and growth-promoting peptides, the more general term **cytokine** has been adopted to refer to these substances. Cytokines are regulatory polypeptides produced by a large variety of nucleated cells. Specifically, monocytes/macrophages, lymphocytes, endothelial cells, hepatocytes, epithelial cells, keratinocytes and fibroblasts as well as other cells produce cytokines. Cytokines typically act locally, initiating autocrine (self-stimulating) or paracrine (nearby-stimulating) effects. When found in the circulation, cytokines are usually present in picogram-per-milliliter concentrations[18,19,20].

The major fever-inducing cytokines appear to be IL-1α, IL-1β, tumor necrosis factor (TNF), interferon (IFN) , and IL-6. When any of these cytokines are administered intravenously to humans, chills and fever develop within 1 hour IL-1α and -1β are the most pyrogenic, with temperatures of 39°C developing in response to doses of 1 to 10 ng/kg of body weight. Doses of 100 ng/kg have caused higher fevers and rigors. TNF produces chills and a temperature of 39°C at somewhat higher doses (50 to 100 ng/kg). IL-6 is the least pyrogenic of these cytokines, producing a temperature of 39°C at 10 g/kg[19,20]. IFN and IFN have been administered primarily by the subcutaneous route; therefore, chills and fever develop after 3 to 4 h. On a weight basis, the interferons are less potent than IL-1 or TNF and similar to IL-6. Moreover, the degree of fever elicited decreases with repeated injections of interferon. Studies with genetically altered mice have revealed that IL-1 and TNF cause fever by inducing IL-6 in the brain[19].

Hypothalamic Control Of Temperature

Body temperature is controlled by the hypothalamus. Neurons in both the preoptic anterior hypothalamus and the posterior hypothalamus receive two kinds of signals--one from peripheral nerves that reflect receptors for warmth and cold and the other from the

temperature of the blood bathing the region. These two signals are integrated by the thermoregulatory center of the hypothalamus to maintain normal temperature. In a neutral environment, the metabolic rate of humans consistently produces more heat than is necessary to maintain the core body temperature at 37°C. Therefore, the hypothalamus controls temperature by mechanisms of heat loss[16,21].

Clusters of neurons in the preoptic/anterior hypothalamus are supplied by a rich and permeable vascular network with limited blood-brain barrier function. The specialized vascular network is called the **organum vasculosum laminae terminalis**. It is likely that the endothelial cells of this network release arachidonic acid metabolites when exposed to endogenous pyrogenic cytokines from the circulation[21]. The arachidonic acid metabolites--mainly prostaglandin E_2 (PGE_2)--then presumably diffuse into the preoptic/anterior hypothalamic region and initiate fever. It is also possible that PGE_2 or other arachidonic acid products induce a second messenger such as cyclic AMP, which in turn raises the thermoregulatory set point. PGE_2 is the most potent of the fever-producing arachidonic acid derivatives when injected directly into the hypothalamus and is believed to mediate the rise in the thermoregulatory set point[21]. With the new, higher "thermostatic setting," signals go to various efferent nerves, particularly those sympathetic fibers innervating the peripheral blood vessels, which in turn initiate vasoconstriction and promote heat conservation[21]. The thermoregulatory center also sends signals to the cerebral cortex, initiating behavioural changes such as seeking a warm environment, putting on more clothes, and special posturing. With the shunting of blood from the periphery and these behavioural changes, the body temperature usually rises by 2 to 3°C; if the hypothalamus calls for more heat, shivering (involuntary muscle contraction) is triggered to increase heat production. The combination of heat conservation and increased heat production continues until the temperature of the blood bathing the anterior hypothalamic neurons matches the new "setting." At that point, the hypothalamus maintains the new febrile temperature[21].

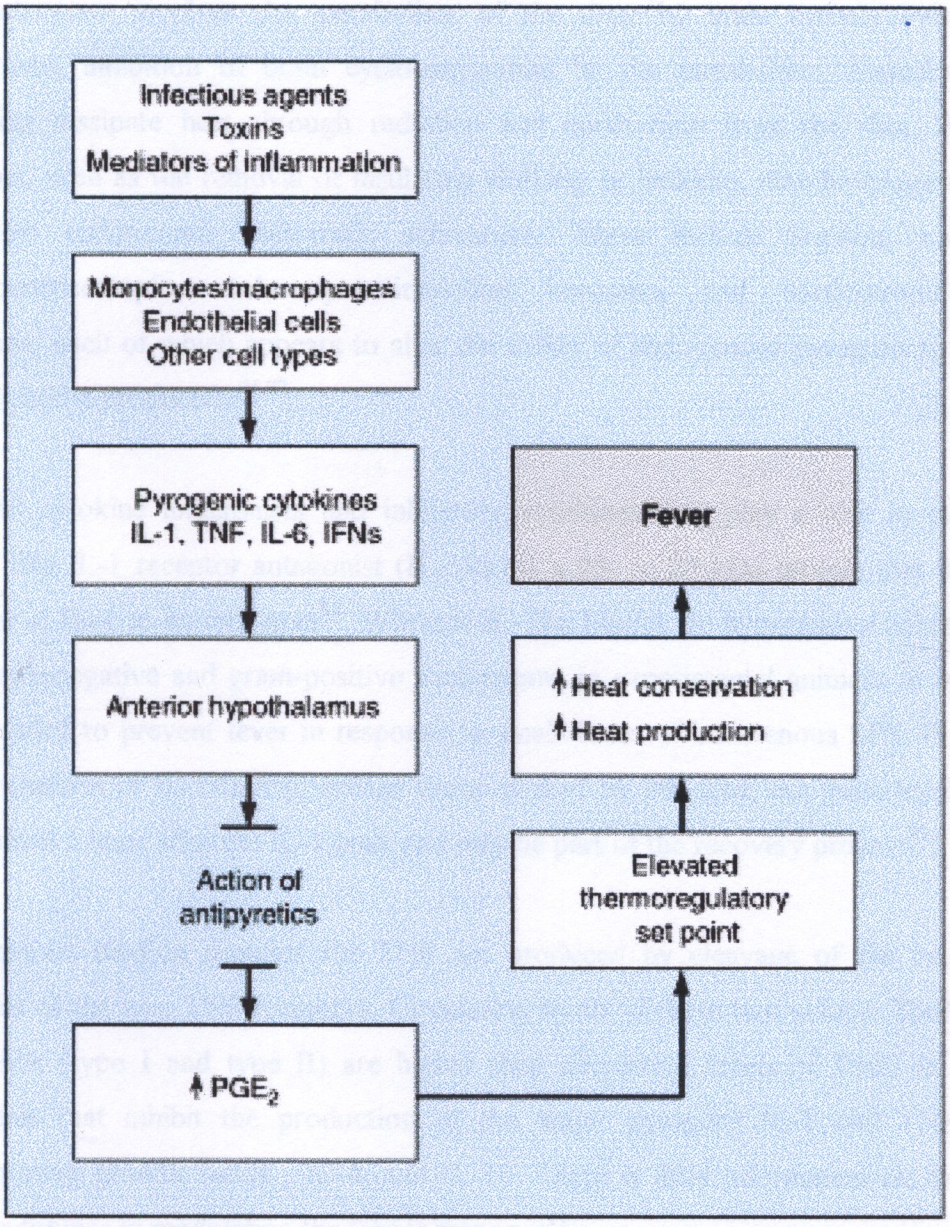


Figure 16. The mechanism of induction of fever[16].

The hypothalamic set point is reset downward by the disappearance of stimulating pyrogenic cytokines or by the inhibition of local prostaglandin synthesis by cyclo-oxygenase inhibitors such as aspirin and ibuprofen[20]. The reduction of fever by acetaminophen involves the metabolism of the drug by brain cytochromes and the subsequent inhibition of brain cyclo-oxygenase by the metabolites. Vasodilation and sweating dissipate heat through radiation and conduction from the skin. Behavioral changes, such as the removal of insulating clothing or bedding, may be triggered. There are also endogenous antipyretic substances. These include arginine vasopressin, adrenocorticotropin, melanocyte-stimulating hormone, and corticotropin-releasing hormone, each of which appears to alter the ability of endogenous pyrogens to stimulate prostaglandin production[21,22].

Specific cytokine antagonists and inhibitory cytokines may play a role in modulating fever. The IL-1 receptor antagonist (IL-1Ra) is a 23- to 25-kDa protein that blocks the binding of IL-1 to its receptors[16]. Whereas IL-1Ra blocks the hypotensive effects of IL-1 and gram-negative and gram-positive bacteraemia in experimental animals, in volunteers it has failed to prevent fever in response to small doses of intravenous LPS. Peak molar concentrations of IL-1Ra may exceed those of IL-1 by 100-fold, but these levels tend to be reached 1 hour after the IL-1 peak and may be part of the recovery process[21].

Endogenous binding proteins for TNF are produced by cleavage of the extracellular domains of the two TNF receptors. Circulating levels of these two soluble TNF receptor fragments (type I and type II) are higher than circulating levels of TNF. In addition, cytokines that inhibit the production of the major pyrogens IL-1 and TNF include transforming growth factor , IL-4, and IL-10. There is little information on the role of these cytokines in modulating the febrile response[21].

Biologic Activities of IL-1, TNF, And IL-6

It is important to distinguish between the critical physiologic roles of local IL-1 and TNF and the high systemic blood levels of these cytokines that are often seen with severe and life-threatening diseases[21]. IL-1 and TNF mediate local phagocytic-cell emigration and activation as well as the release of lipid-derived mediators such as PGE_2, thromboxane, and platelet-activating factor[21]. IL-1 induces the synthesis of IL-8, which in turn is a potent neutrophil and monocyte chemotactic factor. IL-8 stimulates the release of enzymes from neutrophils, further enhancing the host's attack on invading microbes[21]. Vasodilation, the induction of adhesive glycoproteins, the activation of T and B lymphocytes, and the enhancement of killing by phagocytic cells are directly or indirectly mediated by these pyrogenic cytokines[21]. The acute-phase response is stimulated, resulting in changes in protein synthesis in the liver. Serum albumin levels decrease, and the production of acute-phase proteins, including antiproteases, complement components, fibrinogen, ceruloplasmin, ferritin, and haptoglobin, is increased[21]. Levels of C-reactive protein, which binds to damaged and necrotic cells and to some microorganisms, may increase by 1000-fold. Concentrations of serum amyloid A protein also may increase markedly, with the protein deposited in various organs to cause secondary amyloidosis[21]. Decreases in serum iron and zinc levels deprive invading microbes of these critical growth factors[21]. Although IL-1 and TNF can induce these hepatic changes, IL-6 is thought to be the prime mediator of the acute-phase response[21].

IL-1 and TNF act synergistically to mediate local and systemic inflammatory effects[21]. Amounts of each cytokine that cause little inflammation individually produce refractory hypotension and the failure of multiple organ systems in combination[21]. Suppression of either of these two cytokines may have a significant therapeutic effect by blocking this synergistic toxicity. Furthermore, IL-1-induced activation of T and B cells is greater at 39°C than at 37°C[21]. Both IL-1 and TNF increase the loss of mean body mass and cause anorexia, contributing to the cachexia of chronic febrile states[21]. IL-1 and TNF are found in the circulation only briefly but nevertheless induce IL-6. Levels of IL-6 correlate better with the degree of fever and other pathologic findings in a variety of infectious diseases

than do levels of IL-1 or TNF because of the persistence of IL-6 in the circulation. However, there is little or no evidence that IL-6 is--like IL-1 and TNF--a lethal cytokine[19,20].

Reason for fever

In many situations, the elevation of body temperature increases chances for survival. The growth and virulence of several bacterial species are impaired at high temperatures; thus, for example, fever therapy was used in neurosyphilis before antibiotics became available. Type III pneumococci are particularly sensitive to high temperature and at 41°C grow poorly and may autolyze[17]. Inhibition of fever in rabbits infected with type III pneumococci increases the mortality rate. Temperatures in the febrile range appear to increase the phagocytic and bactericidal activity of neutrophils and the cytotoxic effects of lymphocytes[23]. Thus fever probably enhances the ability to survive infection. Redundancies among the pyrogens (IL-1, IL-1, TNF, IL-6, interferons) suggest that it is beneficial to preserve a number of pathways for eliciting this response[21].

However, fever involves considerable "costs" to the host in addition to discomfort. For each elevation of body temperature by 1°C, there is an increase in O_2 consumption of 13 percent and an increase in caloric and fluid requirements. IL-1 and TNF accelerate muscle catabolism, an effect leading to a loss of body weight and a negative nitrogen balance[20]. Essentially, skeletal muscle is utilized as an energy source, with liberation of amino acids for gluconeogenesis and for the synthesis of acute-phase proteins and formation of clones of immune cells[21]. Fever reduces mental acuity and can produce delirium and stupor. Children are prone to develop seizures with fevers, particularly if they have a history of seizures[16].

Patterns of Fever

The widespread use of antipyretics, glucocorticoids, and antibiotics can alter the course of fever so that "classic" fever patterns are not seen. Some patterns are clinically informative, however. Whereas the circadian temperature pattern is preserved and in fact exaggerated in most fevers, it may be reversed in typhoid fever and disseminated

tuberculosis[16]. Temperature-pulse dissociation (relative bradycardia) is seen in typhoid fever as well as in brucellosis, leptospirosis, some drug-associated fevers, and many factitious fevers. Bradycardia in the presence of fever also may signify cardiac conduction abnormalities, as it does in acute rheumatic fever, Lyme disease, viral myocarditis, or valve-ring abscess complicating bacterial endocarditis[16].

Fever may be sustained, intermittent, remittent, or relapsing. A **sustained** fever is one in which temperature elevation is persistent, with minimal variation. With **intermittent** fever, there is an exaggeration of the normal circadian rhythm; when this variation is extremely large, the fever is termed **hectic** or **septic**. Intermittent, hectic, and septic patterns are common in deep-seated or systemic infections, malignancy, and drug fevers. When hectic fevers occur daily, they are sometimes termed **quotidian**[16].

Remittent fever, in which the temperature falls each day but not to normal, is typical for tuberculosis, viral diseases, many bacterial infections, and noninfectious conditions. It should be emphasized that newborns, the elderly, patients with chronic renal or hepatic failure, patients taking glucocorticoids, or patients with bacteraemic shock may fail to generate fever altogether; in these individuals, **hypothermia** may be a sign of severe infection[16].

With **relapsing** fevers, febrile episodes are separated by intervals of normal temperature; when paroxysms occur on the first and third days, the fever is called **tertian**. *Plasmodium vivax* causes tertian fevers. **Quartan** fevers are associated with paroxysms on the first and fourth days and are seen with *Plasmodium malariae*. Other relapsing fevers are related to *Borrelia* infections and rat-bite fever, which are both associated with days of fever followed by a several-day afebrile period and then a relapse of days of fever. Pel-Ebstein fever, with fevers lasting 3 to 10 days followed by afebrile periods of 3 to 10 days, is classic for Hodgkin's disease and other lymphomas. Another characteristic fever is that of cyclic neutropenia, in which fevers occur every 21 days and accompany the neutropenia[16].

PYREXIA OF UNKNOWN ORIGIN

Pyrexia of unknown origin (PUO) was defined by Petersdorf and Beeson in 1961 as

1. temperatures higher than 38.3°C (101°F) on several occasions,
2. a duration of fever of more than 3 weeks, and
3. failure to reach a diagnosis despite 1 week of in-patient investigation. While this classification has stood for more than 30 years, Durack and Street have proposed a new system for classification of Pyrexia of unknown origin[24]:
4. classic Pyrexia of unknown origin,
5. nosocomial Pyrexia of unknown origin,
6. neutropaenic Pyrexia of unknown origin, and
7. PUO associated with human immunodeficiency virus (HIV) infection.

Categories of PUO*

TABLE 3

Feature	Nosocomial	Neutropenic	HIV-Associated	Classic
Patient's situation	Hospitalized, acute care, no infection when admitted	Neutrophil count either less than 500/L or expected to reach that level in 1–2 days	Confirmed HIV-positive	All others with fevers for 3 weeks
Duration of illness while under investigation	3 days†	3 days†	3 days† (or 4 weeks as outpatient)	3 days† or three outpatient visits
Examples of cause	Septic thrombophlebitis, sinusitis, *Clostridium difficile* colitis, drug fever	Perianal infection, aspergillosis, candidaemia	MAI‡ infection, tuberculosis, non-Hodgkin's lymphoma, drug fever	Infections, malignancy, inflammatory diseases, drug fever

* All require temperatures of 38.3°C (101°F) on several occasions.
† Includes at least 2 days' incubation of microbiology cultures.
‡ *M. avium/M. intracellulare.*

Table 3. Classification of Pyrexia of unknown origin

Table 3. summarizes the findings of a number of large studies of Pyrexia of unknown origin carried out since the advent of the antibiotic era[25]. Coincident with the widespread use of antibiotics, increasingly useful diagnostic technologies--both noninvasive and invasive--have been developed. Newer studies reflect not only changing patterns of disease but also the impact of diagnostic techniques that make it possible to eliminate many patients with specific illness from the Pyrexia of unknown origin category[24]. The ubiquitous use of microbiologic cultures and the widespread use of potent broad-spectrum antibiotics may have decreased the number of infections causing Pyrexia of unknown origin. The wide availability of ultrasonography, CT, and magnetic resonance imaging (MRI) has enhanced the detection of occult neoplasms and lymphomas in patients previously thought to have Pyrexia of Unknown Origin[25]. Likewise, the widespread availability of highly specific and sensitive immunologic testing has reduced the number of undetected cases of systemic lupus erythematosus (SLE) and other autoimmune diseases[24].

Several generalizations can be made. Infections, especially extrapulmonary tuberculosis, remain the leading cause of Pyrexia of unknown origin. Prolonged mononucleosis syndromes caused by Epstein-Barr virus, CMV, or HIV are conditions whose consideration as a cause of Pyrexia of unknown origin is sometimes confounded by delayed antibody responses[24]. Intraabdominal abscesses (sometimes poorly localized) and renal, retroperitoneal, and paraspinal abscesses continue to be difficult to diagnose. Renal malacoplakia, with submucosal plaques or nodules involving the urinary tract, may cause Pyrexia of unknown origin and is often fatal if untreated. It is associated with coliform infection, is seen most often in patients with defects of intracellular bacterial killing, and is treated with fluoroquinolones or trimethoprim-sulfamethoxazole[25].

Undetected fungal disease, most notably histoplasmosis involving the reticuloendothelial system, may cause Pyrexia of unknown origin[25,26]. Pyrexia of unknown origin with headache should prompt examination of spinal fluid for Cryptococcus neoformans. Malaria (which may result from transfusion, the failure to take a prescribed prophylactic agent, or infection with a drug-resistant strain) continues to be a cause, particularly of nonsynchronized Pyrexia of Unknown Origin[25].

In most early series neoplasms were the next most common cause of pyrexia of unknown origin after infections. In a series of 199 patients studied between 1980 and 1989, a decrease in the percentage of Pyrexia of unknown origin cases due to malignancy was attributed to the improvement in diagnostic technologies[27]. This observation does not diminish the importance of considering neoplasia in the initial diagnostic evaluation of a patient with fever. A large number of patients in this series had diseases such as temporal arteritis, adult Still's disease, drug-related fever, and factitious fever. In most series, approximately 10 percent of cases of Pyrexia of unknown origin remained undiagnosed. The general term "collagen vascular diseases" is used somewhat loosely to apply not only to SLE and temporal arteritis but also to systemic rheumatologic or vasculitic diseases such as polymyalgia rheumatica and adult Still's disease [25,27].

Many diseases have been grouped in the various studies as "miscellaneous." At the top of this list are the granulomatous diseases, including sarcoidosis, Crohn's disease, and granulomatous hepatitis. Additional diagnoses include drug fever, erythema multiforme, pulmonary embolism, factitious fever, familial Mediterranean fever, Behçet's syndrome, Fabry's disease, and Whipple's disease (now attributed to the bacillus Tropheryma Whippelii)[27].

A drug-related aetiology must be considered in any case of prolonged fever[27]. Any febrile pattern may be elicited by a drug, and both relative bradycardia and hypotension are uncommon. Eosinophilia and/or rash is found in only one-fifth of patients with drug fever. Fever usually begins 1 to 3 weeks after the start of therapy and remits 2 to 3 days after therapy is stopped. Virtually all classes of drugs cause fever, but antimicrobials (especially -lactam antibiotics), cardiovascular drugs (e.g., quinidine), antineoplastic drugs, and drugs acting on the central nervous system (e.g., phenytoin) are particularly common causes[27].

It is axiomatic that, as the duration of fever increases, the likelihood of an infectious cause decreases[27].

SEPSIS & SEPTIC SHOCK

Definitions

The host's reaction to invading microbes involves a rapidly amplifying polyphony of signals and responses that may spread beyond the invaded tissue. Fever or hypothermia, tachypnoea, and tachycardia often herald the onset of **sepsis**, the systemic inflammatory response to microbial invasion. When counterregulatory control mechanisms are overwhelmed, often as the microbe moves from a local site to invade the bloodstream, homeostasis may fail, and dysfunction of major organs may supervene (**severe sepsis**)[17]. Further failure of counterregulatory control leads to **septic shock**, which is characterized by hypotension as well as organ dysfunction. As sepsis progresses to septic shock, the risk of dying increases substantially. Early sepsis is usually reversible, whereas patients with septic shock often succumb despite aggressive therapy[17].

Aetiology

Sepsis can be a response to any class of microorganism. Microbial invasion of the bloodstream is not essential for the development of sepsis; local or systemic spread of microbial signal molecules or toxins can also elicit the response[17],. Blood cultures yield bacteria or fungi in approximately 20 to 40 percent of cases of severe sepsis and 40 to 70 percent of cases of septic shock[17]. Individual gram-negative or gram-positive bacteria account for approximately 75 to 85 percent of these isolates; the remainder are fungi or a mixture of microorganisms. In patients whose blood cultures are negative, the aetiologic agent is often established by culture or microscopic examination of infected material from a local site. In some case series, a majority of patients with a clinical picture of severe sepsis or septic shock have had negative microbiological results[17].

Pathophysiology

The septic response is usually triggered when microorganisms spread from the gastrointestinal tract or skin into contiguous tissues[17]. Localized tissue infection may then

lead to bacteraemia or fungaemia. Alternatively, microorganisms may be introduced directly into the bloodstream (for example, via intravenous catheters). In a minority of cases, no primary site of infection is apparent[17]. In general, the septic response occurs when an invading microbe has circumvented the host's innate and acquired immune defenses. Host factors that allow microbial growth (such as deficiencies of antibody, complement factors, or cell-mediated immunity) are therefore critical[17].

Microbial Signals

Animals recognize certain microbial molecules as signals that microorganisms have invaded[29]. Lipopolysaccharide (LPS, also called endotoxin) is the most potent and best-studied gram-negative bacterial signal molecule. A plasma protein (LPS-binding protein, or LBP) transfers LPS to CD14 on the surfaces of monocytes, macrophages, and neutrophils[29]. This interaction rapidly triggers the production and release of mediators, such as tumor necrosis factor (TNF) , that amplify the LPS signal and transmit it to other cells and tissues[29]. Soluble CD14 may also bind LPS in plasma and transfer it to vascular endothelial cells, which lack cell-surface CD14[29]. The peptidoglycan and lipoteichoic acids of gram-positive bacteria, certain polysaccharides, extracellular enzymes, and toxins elicit responses in animals that are similar to those induced by LPS[29]. The molecular basis for the stimulatory potency of these molecules is poorly understood, although some of them may also bind cell-surface or soluble CD14 before activating cells. CD14 may therefore be a receptor that facilitates responses to many microbial signals[29]. Other innate immune mechanisms that recognize microbial molecules include complement (principally the alternative pathway; mannose-binding protein, and C-reactive protein[29].

Host Responses

The septic response involves complex interactions among microbial signal molecules, leukocytes, humoral mediators, and the vascular endothelium[29].

Cytokines

Inflammatory cytokines amplify and diversify the response[17]. These proteins can exert endocrine, paracrine, and autocrine TNF stimulates leukocytes and vascular endothelial cells to release other cytokines (as well as additional TNF), to express cell-surface adhesion molecules, and to increase arachidonic acid turnover. Blood levels of TNF are high in most patients with severe sepsis[30]. Moreover, intravenous infusion of TNF can elicit many of the characteristic abnormalities of sepsis, including fever, tachycardia, tachypnoea, leukocytosis, myalgias, and somnolence. In animals, large doses of TNF induce shock, disseminated intravascular coagulation (DIC), and death[30]. Specific TNF antagonists can abrogate the septic response and prevent the deaths of experimental animals challenged with endotoxin[30,17].

Although TNF is a central mediator, it is only one of many cytokines that contribute to the septic process. Interleukin (IL)-1, for example, which exhibits many of the same activities as TNF, seems to play an increasingly significant role as the septic process intensifies [17,30]. TNF, IL-1, interferon , IL-8, and other cytokines probably interact synergistically with one another and with additional mediators[30]. Moreover, some mediators (such as IL-1 and TNF) may enhance their own rates of synthesis by positive feedback. As sepsis progresses, the mixture of cytokines and other mediators becomes very complex: elevated blood levels of more than 30 pro- and anti-inflammatory molecules have been found in patients with septic shock. In animal models, the septic response can be interrupted by early interventions that neutralize one or another of its many components; this observation testifies to the importance of mediator interactions in the overall outcome[30]. Unfortunately, it has been much more difficult to rescue animals from severe sepsis and septic shock[30].

Phospholipid-Derived Mediators

Arachidonic acid, released from membrane phospholipids by phospholipase A_2, is converted by the cyclo-oxygenase pathway into prostaglandins and thromboxanes[30]. Prostaglandin E_2 and prostacyclin cause peripheral vasodilatation, whereas thromboxane

is a vasoconstrictor and promotes platelet aggregation[30]. Leukotrienes are also potent mediators of ischaemia and shock; the fact that the reaction to endotoxin challenge is normal in mice that lack the 5-lipoxygenase gene, however, casts doubt on the role of leukotrienes in the septic response[30].

Another important phospholipid-derived mediator is platelet-activating factor (PAF, or 1-*O*-alkyl-2-acetyl-*sn*-glycerol-3-phosphocholine). PAF potently stimulates neutrophil aggregation and degranulation, promotes platelet aggregation, and may contribute to tissue injury[30].

Coagulation Factors

Intravascular fibrin deposition, thrombosis, and DIC are important features of the septic response[31]. TNF promotes intravascular coagulation initially by inducing blood monocytes to express tissue factor[31]. When tissue factor is expressed on monocytes, it binds to factor VIIa to form an active complex that can convert factors X and IX to enzymatically active forms[31]. The result is activation of both extrinsic and intrinsic clotting pathways, culminating in the generation of fibrin[31]. Clotting is also favored by impaired function of the protein C-protein S inhibitory pathway, while fibrinolysis is prevented by increased plasma levels of plasminogen activator inhibitor 1[31]. Thus, there may be a striking propensity for intravascular fibrin deposition, thrombosis, and bleeding. Contact-system activation occurs during sepsis but contributes more to the development of hypotension than to DIC[31].

Complement

C5a and other products of complement activation may promote neutrophil reactions such as chemotaxis, aggregation, degranulation, and oxygen-radical production. When administered to animals, C5a induces hypotension, pulmonary vasoconstriction, neutropaenia, and vascular leakiness due in part to endothelial damage[32].

Activation of The Vascular Endothelium

Many tissues may be damaged by sepsis. The probable underlying mechanism is widespread vascular endothelial injury, with fluid extravasation and microthrombosis that decrease oxygen and substrate utilization by the affected tissues[32]. Leukocyte-derived mediators and platelet-leukocyte-fibrin thrombi contribute to this injury, but the vascular endothelium itself seems to play an active role[32]. Stimuli such as TNF induce vascular endothelial cells to produce and release cytokines, procoagulant molecules, PAF, endothelium-derived relaxing factor (nitric oxide), and other mediators. In addition, regulated cell-adhesion molecules promote the adherence of leukocytes to endothelial cells[33]. While these responses may attract phagocytes to infected sites and activate their antimicrobial arsenals, endothelial cell activation can also promote increased vascular permeability, microvascular thrombosis, DIC, and hypotension[33]. Moreover, vascular integrity may be damaged by neutrophil enzymes (such as elastase) and toxic oxygen metabolites so that local haemorrhage ensues[33]. Blocking the adhesion of leukocytes to endothelial cell surfaces, as with monoclonal antibodies to intercellular adhesion molecule 1, can prevent tissue necrosis in response to endotoxin administration in animals[33].

Septic Shock

Much evidence now implicates nitric oxide, produced by inducible nitric oxide synthase (**iNOS**), as a mediator of septic shock in experimental animals and probably in humans[34]. Mice that lack the **iNOS** gene may not be resistant to endotoxic shock however[34]. Other prominent hypotensive molecules are -endorphin, bradykinin, PAF, and prostacyclin. Agents that inhibit the synthesis or action of each of these mediators can prevent or reverse endotoxic shock in animals.

Control Mechanisms

Elaborate host mechanisms regulate both microbial signals and the inflammatory response. While plasma LBP promotes the inflammatory response by facilitating the interaction of LPS with monocyte cell-surface CD14, LBP and soluble CD14 can also prevent LPS signaling by transferring LPS molecules into plasma lipoprotein particles[30]. The relative plasma concentrations of LPS, LBP, CD14, and lipoprotein therefore may determine LPS signal intensity. The mechanisms that control the inflammatory response

are complex, overlapping, and poorly understood[30]. Glucocorticoids inhibit cytokine synthesis by monocytes in vitro and, when administered with or shortly after an inflammatory stimulus, may protect animals from septic shock[35]. The increase in blood cortisol levels early in the septic response presumably plays a similar inhibitory role. Certain cytokine antagonists also may contribute. Blood levels of IL-1 receptor antagonist often greatly exceed those of circulating IL-1, and this excess may result in inhibition of the binding of IL-1 to its receptors. Transforming growth factor (TGF) and IL-10 also can inhibit LPS-induced responses of human monocytes in vitro and prevent endotoxic death in animals. Blood and tissue levels of prostaglandin E_2, TGF, -melanocyte-stimulating hormone, cortisol, IL-1 receptor antagonist, soluble TNF receptors, and IL-10 increase during the septic response, and these molecules probably act in concert to diminish its intensity[36]. Indeed, blood leukocytes from patients with severe sepsis may be hyporesponsive to agonists such as LPS[36]. The fact that plasma concentrations of many of these anti-inflammatory molecules may be very high in the patient with septic shock, however, indicates that they are unable to control the inflammatory response when it is most severe[36].

Clinical Manifestations

The systemic inflammatory response often intensifies over time from mild (sepsis) to extremely severe (septic shock). The rate at which the response increases may differ from patient to patient, and there are striking individual variations in its manifestations[17]. For example, some septic patients have a normal temperature or are hypothermic; the absence of fever is most common among neonates, elderly patients, and persons with uraemia or alcoholism. Hyperventilation is often an early sign. Disorientation, confusion, and other manifestations of encephalopathy may also develop early in the septic response, particularly in the elderly and in individuals with preexisting neurologic impairment. Focal neurologic signs are uncommon, although preexisting focal deficits may become more prominent[17].

Hypotension and DIC predispose to acrocyanosis and ischaemic necrosis of peripheral tissues, most commonly the digits. Cellulitis, pustules, bullae, or haemorrhagic lesions may develop when haematogenous bacteria or fungi seed the skin or underlying soft

tissue[17]. Bacterial toxins may also be distributed haematogenously, eliciting diffuse cutaneous reactions. On occasion, skin lesions may be suggestive of specific pathogens. When sepsis is accompanied by cutaneous petechiae or purpura, infection with *Neisseria meningitidis* (or, less commonly, *Haemophilus influenzae*) should be suspected; in a patient who has been bitten by a tick while in an endemic area, petechial lesions also suggest Rocky Mountain spotted fever[17]. A cutaneous lesion seen almost exclusively in neutropenic patients is ecthyma gangrenosum, usually caused by *Pseudomonas aeruginosa* or *Aeromonas hydrophila*. It is a bullous lesion, surrounded by edema, that undergoes central hemorrhage and necrosis. Histopathologic examination shows bacteria in and around the wall of a small vessel, with little or no neutrophilic response[17]. Hemorrhagic or bullous lesions in a septic patient who has, recently suffered a dog bite may indicate bloodstream infection due to *Capnocytophaga canimorsus* or *Capnocytophaga cynodegmi*. Generalized erythroderma in a septic patient suggests the toxic shock syndrome due to *Staphylococcus aureus* or *Streptococcus pyogenes*[17].

Gastrointestinal manifestations such as nausea, vomiting, diarrhoea, and ileus may be indicative of acute gastroenteritis. Stress ulceration can lead to upper gastrointestinal bleeding[17]. Cholestatic jaundice, with elevated levels of serum bilirubin (mostly conjugated) and alkaline phosphatase, may precede other signs of sepsis. Hepatocellular or canalicular dysfunction appears to underlie most cases, and the results of hepatic function tests return to normal with resolution of the infection. Prolonged or severe hypotension may induce acute hepatic injury or ischaemic bowel necrosis[17].

Blood lactate levels rise early, in part because of increased glycolysis with impaired clearance of the resulting lactate and pyruvate by the liver and kidneys. As hypoperfusion develops, tissue hypoxia generates more lactic acid, contributing to metabolic acidosis. The blood glucose concentration often increases, particularly in diabetics, although impaired gluconeogenesis and excessive insulin release on occasion produce hypoglycaemia. The cytokine-driven acute-phase response inhibits the synthesis of albumin and transthyretin while enhancing the production of C-reactive protein, LBP, fibrinogen, and complement components. Protein catabolism is often markedly accelerated[17].

BURN WOUND INFECTION

Bacterial

A study on wound sepsis reveal that while 96.7 per cent of burn wounds are sterile on admission, bacterial colonization reach 80.6percent within the first week after admission. Although the Gram-negative organisms, as a group, are predominant, staphylococcus aureus(38.2percent) was the most prevalent organism in the first week. It is however surpassed by pseudomonas aeruginosa from the second week onwards. Anaerobes were conspicuous by their absence. Similarly, beta-haemolytic strepococcus was not isolated from any patient. Proteus mirabilis was unusally preponderant, forming 19.4 percent of all isolates. The antibiotic sensitivity pattern showed resistance of most of the organisms to ampicillin. Only 15percent of staphyloccocci were sensitive to cloxacillin. Most of the organism cultured (93.5percent)were sensitive to ceftazidime[37].

Fungal

Sepsis due to candida infection can be a major cause of morbidity and mortality in patients with burns. Factors known to predispose to fungal sepsis are large burns (14-98percent total body surface area - TBSA) with a mean of 48.3percent. Central venous line and respiratory problems requiring ventilator support. The major type of fungus is Candida albicans and others are Candida parapsilosis and Candida tropicalis. The drugs of choice for treatment are Amphotericin B and Fluconazole[38].

Nosocomial infections

Seriously burned patients are clearly at increased risk for nosocomial infection due to the nature of the burn injury itself, the uncompromising effects of the burn injury, prolonged hospital stays, and invasive diagnostic and therapeutic procedures. Infections include pneumonias, urinary tract infections, bacteraemias and cellulitis. Intubation is strongly associated with nosocomial infection, particularly with pneumonia and bacteraemia[39].

TOXIC SHOCK SYNDROME

TSS is an acute, noncontiguous systemic illness characterised by high fever, hypotension, rash, multi-organ dysfunction, and cutaneous desquamation during the early convalescent period[40]. In resent years several papers have been written about its association with burns, especially in children[40].

It is caused by any of several related staphylococcal exotoxins. The exotoxins of *S. aureus* are proteinaceous compounds that are secreted at certain times during bacterial growth. The most common TSS toxins are toxic shock syndrome toxin-1 (TSST-1; ~75 percent of cases) and staphylococcal enterotoxin B (SEB; 20-25 percent of cases)[40].

The pathogenesis of TSS proceeds as follows:

(1) human colonisation or infection by a strain of *S. aureus* capable of producing a TSS toxin ("toxigenic strain"),

(2) toxin production,

(3) toxin absorption,

(4) intoxication.

About 25 percent of all *S. aureus* strains are toxigenic[40]. Roughly 4-10 percent of normal people harbour toxigenic strains at any given time[40]. Although toxigenic strains have the genetic potential to produce toxins, they actually do so only at limited times, times when toxin production serves the bacterium's survival needs. The exact nature of the environmental signals that cue the bacterium to produce toxin in vivo are not fully understood. Even less is known about the requirements and mechanisms for toxin uptake, but circulating toxin can be demonstrated in human TSS patients[40,41]. Intoxication by the TSS toxins is a very complex process. The toxins affect the host immune system, causing an exuberant and pathological host inflammatory response. Antibodies directed at the TSS toxins protect against TSS, and develop by early adolescence in the majority of people[41,42].

Laboratory findings consistent with TSS include leukocytosis, elevated prothrombin time, hypoalbuminaemia, hypocalcaemia, and pyuria. Each is present in greater than 70 percent of patients. In the less ill patient with suggestive symptoms who fails to meet diagnostic criteria, but who is in an epidemiological risk group, consider the possibility of mild systemic staphylococcal intoxication[40,43].

Diagnostic Criteria for TSS

TABLE 4

I.	**Fever:** temperature ≥ 38.9 C
II.	**Rash:** diffuse macular erythroderma ("sunburn")
III.	**Hypotension:** systolic blood pressure ≤ 90 mm Hg (adults) or ≤ 5th percentile for age (children under 16 years of age), or orthostatic hypotension, dizziness or syncope
IV.	**Multisystem dysfunction:** at least three:
	*A. **Gastrointestinal:** vomiting or diarrhoea at onset of illness* *B. **Muscular:** severe myalgias, or serum creatine phosphokinase level (CPK) ≥ twice the upper limit of normal* *C. **Mucous membranes:** vaginal, oropharyngeal, or Conjuctival hyperaemia* *D. **Renal:** blood urea nitrogen (BUN) or creatinine ≥ twice the upper limit of normal, or pyuria (≥ 5 leukocytes per high-power field), in the absence of urinary tract infection* *E. **Hepatic:** total serum bilirubin or transaminase level ≥ twice the upper limit of normal* *F. **Haematologic:** platelets ≤ 100,000 per L* *G. **Central nervous system:** disorientation or alteration in consciousness but no focal neurological signs at a time when fever and hypotension are absent*
V.	***Desquamation:** 1 to 2 weeks after the onset of illness (typically palms and soles)*
VI.	***Evidence against an alternative diagnosis:** If obtained: negative cultures of blood, throat, or cerebrospinal fluid; absence of a rise in antibody titres to the agents of, leptospirosis, measles or Rocky Mountain spotted fever.*

"Confirmed" cases meet all six criteria; "probable" cases meet 5 of the 6. Blood culture may be positive for *S. aureus*[40].

Table 4. Criteria for the diagnosis of Toxic Shock Syndrome

AIMS AND OBJECTIVES

To shed light on possible factors which cause pyrexia in children with burns admitted to the University Teaching Hospital , Department of Surgery, Lusaka.

RATIONALE

The study is intended to improve patient care, demystify the treatment of fever in these children and help in the formulation or modification of guidelines in the management of burns in children.

PATIENTS AND METHODS

Study group: Sixty two patients were recruited in the University Teaching Hospital at different stages of their hospital stay. The criteria of inclusion to the study were

a) Child 0-16 years.
b) Admitted with burns.
c) Signed consent by guardian.
d) Fever during hospital stay

Patients from different surgical units who fulfilled the first three of the above criteria and presented with fever on admission were included in the study. Those subsequently developing fever were also included after fulfilling the a-c criteria.

For the study **fever was defined as temperature above 37.5°C**

Ethical considerations: Written consent was signed by the guardian of the patient for inclusion of the patient in to the study. Approval for the study had gone through the Ethics committee of the University of Zambia, School of Medicine.

Methods: Wound swabs, blood culture, blood slides for malaria parasites, full blood and differential counts were collected at different stages of the patient's hospital stay and were categorized as follows:

- Admission samples
- First week samples
- Second week samples
- Third week samples

Morning temperatures were taken from the time of inclusion into the study. Temperatures were taken by the ward nurses or the investigator if the nurses had failed to record it.

One hundred and twenty files were reviewed retrospectively to distinguish those with fever, those with no fever and mortality (see Figs. 24, 37 and 38). The University Teaching Hospital's Department of Surgery audits for the period 1992-1998 were also reviewed as part of the study.

Timeframe: Six months, between October 1998 and March 1999.

Age: Age group 0-16years.

Wound Swabs

Wound swabs were collected from the wounds on admission from 18 patients (see figs. 26 and 27) before application of Flamazine on burn wound. Samples were taken a few days after admission, and later samples were taken before patients were taken for baths in the 2^{nd} and 3^{rd} weeks. A total of 131 samples were taken in the 62 patients recruited. Some patients had more samples taken depending on the time when fever peaked-hence these were also included in the series. (See table 5 and Figs 26 and 27)

Blood Culture: Blood cultures were generally taken at the same time as the pus swabs and were sent for bateriology studies. However due to lengthy preparatory process for culture media, fewer blood cultures than wound swabs were done. A total of 93 samples were taken (see Figs 28 and tables 6 and 7) As for the pus swabs they were taken at different times of the patients hospital stay.

Blood slides for Malarial parasites were done once at the beginning of their inclusion in the study. A total of 62 samples were taken.

Full Blood and differential counts and erythrocyte sedimentation rates were take at different times as pus swabs (see figures in APPENDIX III).

During their hospital stay obvious morbidity (for example pneumonia and diarrhoea) were recorded at the time of collection of samples and follow up(see figures 35 and 36).

BACTERIOLOGY.

Pus swabs:

Culture: The swabs were inoculated onto culture media, Blood, Maconkey and Chocolate agar and incubated at 37°C for 48 hours.

The incubated plates were then examined for possible growth which went under identification tests and antibiotic sensitivity tests.

Blood culture:

Trypticase soya broth medium was used . Each container had 70ml medium into which 7ml of blood was inoculated. It was incubated at 37°C for 18 to 24 hours after which the specimen bottles were examined for visible signs of bacterial growth - turbidity, particles of bacterial colonies and haemolysis. Specimens with no growth were reincubated and those with growth were subcultured onto Blood , Maconkey and Chocolate agars. Mueller Hinton agar was used for diffusion sensitivities. The ones with no growth were re-examined at 72hours and 144hours (6days) before being considered as negative growths.

HAEMATOLOGY

A coulter counter was used to determine the full blood count. Differential counts and erythrocyte sedimentation rates were done manually.

PARASITOLOGY

Blood slides were stained and examined for Malaria Parasite slides.

Management of Burns

- **Initial Care**

The management of admitted burnt children in the University Teaching Hospital included:

Attention to airway

After the airway was stabilized when necessary, the extent and depth of the burn injury was assessed. Intubation was considered early on in those patients who showed signs of inhalation injury, such as singed nasal hairs, facial burns, oral burns, sooty sputum or respiratory difficulty manifested by stridor or wheezes, however, this step was rarely required.

Fluid resuscitation.

Fluid replacement was started according to the Leeds formula: percent x wt/2=Xml (fluids). Given in the form of Crystalloids over the period of 4:4:4:6:6:12 hours.

Colloids were not used in this study as they are not generally available.

Wound treatment

Both open and closed wound management was practiced. The open was the most common method in casualty and the closed was usually used for deeper burns and joint areas with splintage for inpatients. Flamazine was the topical antibacterial cream commonly used.

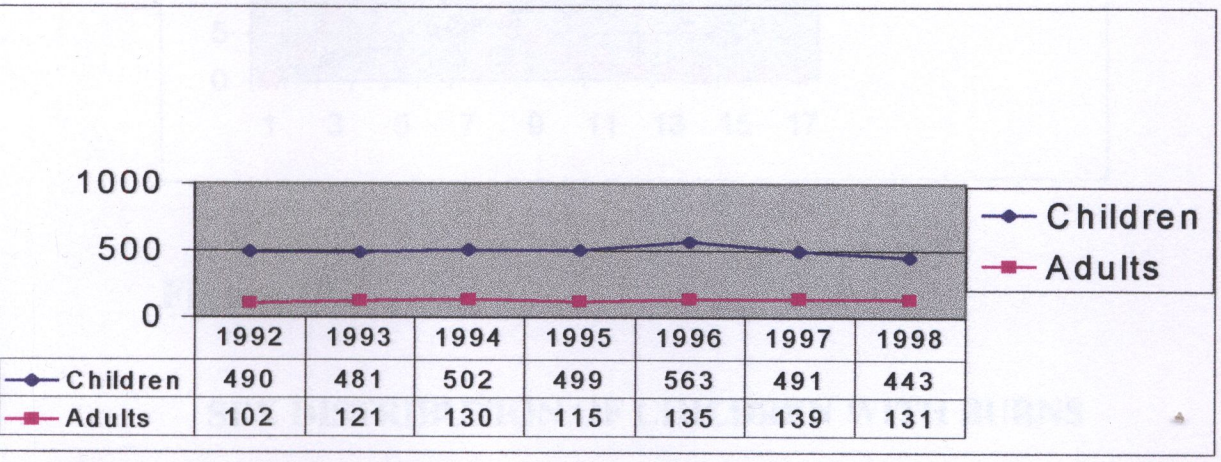
Escharotomy

When circumferential full thickness burns involving the extremities or chest were present, escharotomy was occasionally necessary. Early burn excision and closure was not practiced in the patients included in this study.

RESULTS

Data analysis (spreadsheets and graphs) was done with Microsoft Excel versions 5.0, 97.)

EPIDEMIOLOGY OF BURNS IN THE UNIVERSITY TEACHING HOSPITAL 1992-1998



	1992	1993	1994	1995	1996	1997	1998
Children	490	481	502	499	563	491	443
Adults	102	121	130	115	135	139	131

Figure 17. Review of Surgical Audits 1992-1998 show burns to be commoner in children.

CHILDREN-ADULT RATIOS

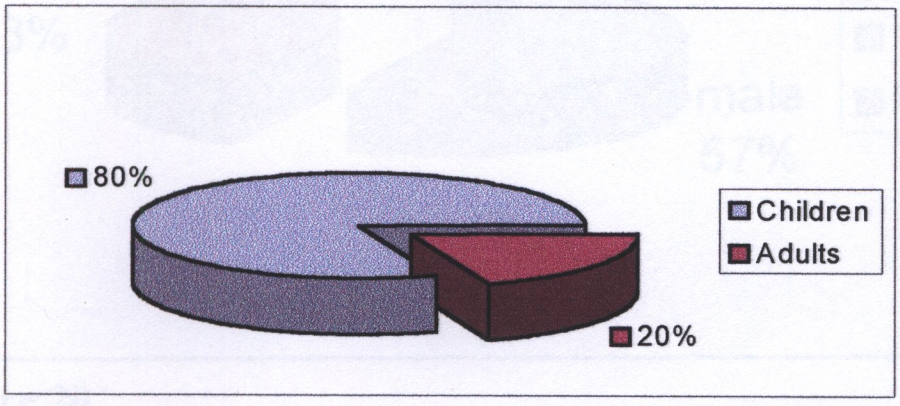


Figure 18. Eighty percent of patients were children (0-16years)

AGE DISTRIBUTION IN CHILDREN WITH BURNS

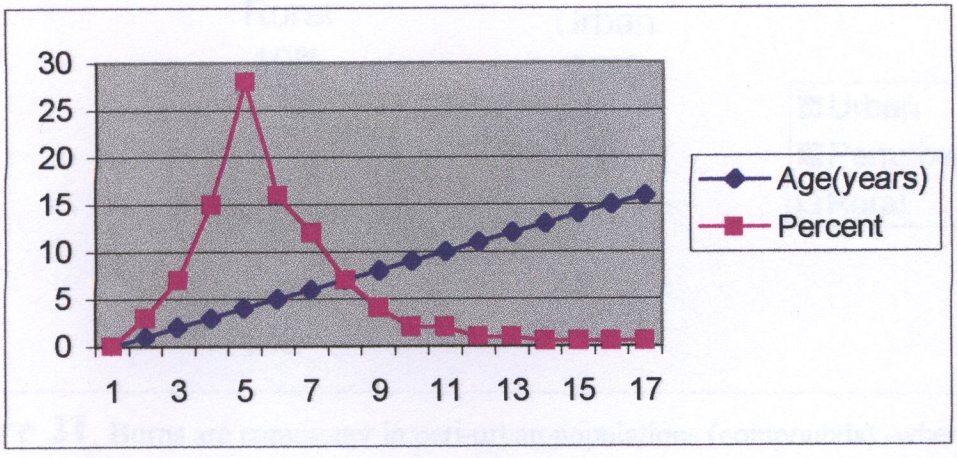


Figure 19.

SEX DISTRIBUTION OF CHILDREN WITH BURNS

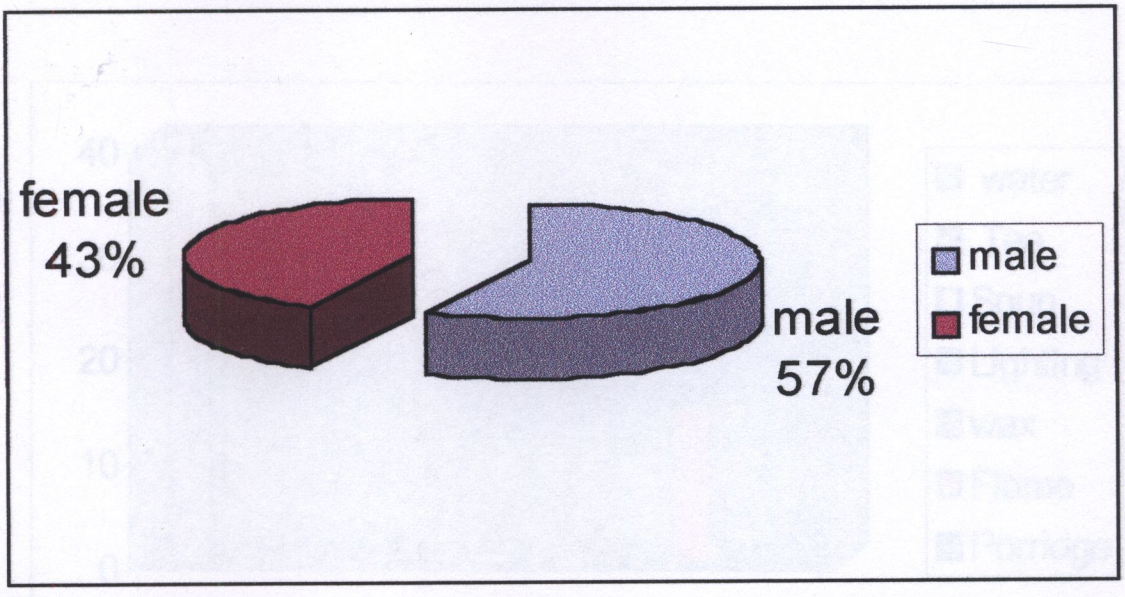


Figure 20.

RESIDENTIAL AREA (SOCIO-ECONOMIC BACKGROUND)

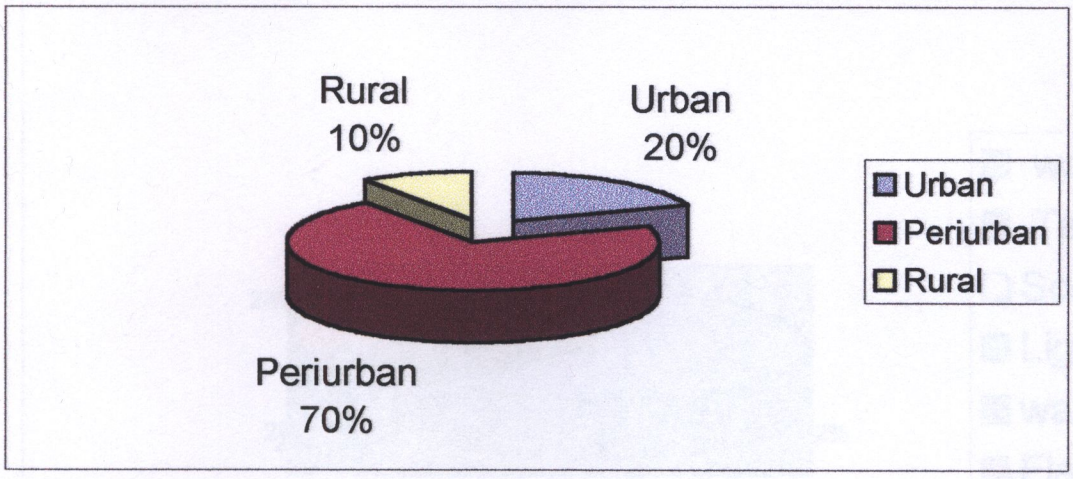


Figure 21. Burns are commoner in peri-urban populations (compounds) -where poor housing is located.

CAUSATIVE AGENTS OF BURNS
(n=62)

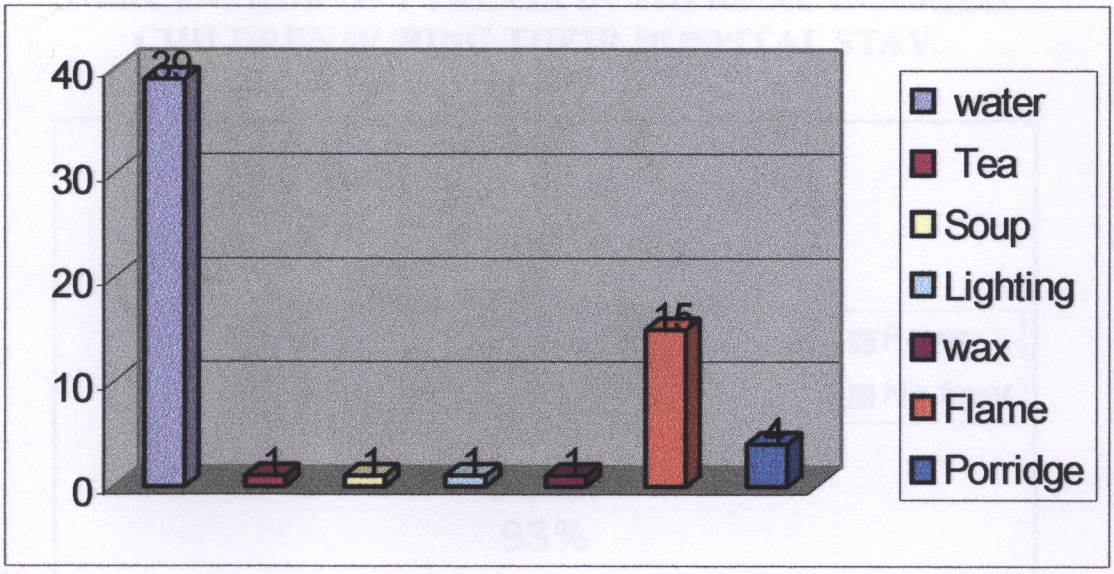


Figure 22. Hot water is the most common causative agent, with burns occurring while cooking meals.

CAUSATIVE AGENTS OF BURNS

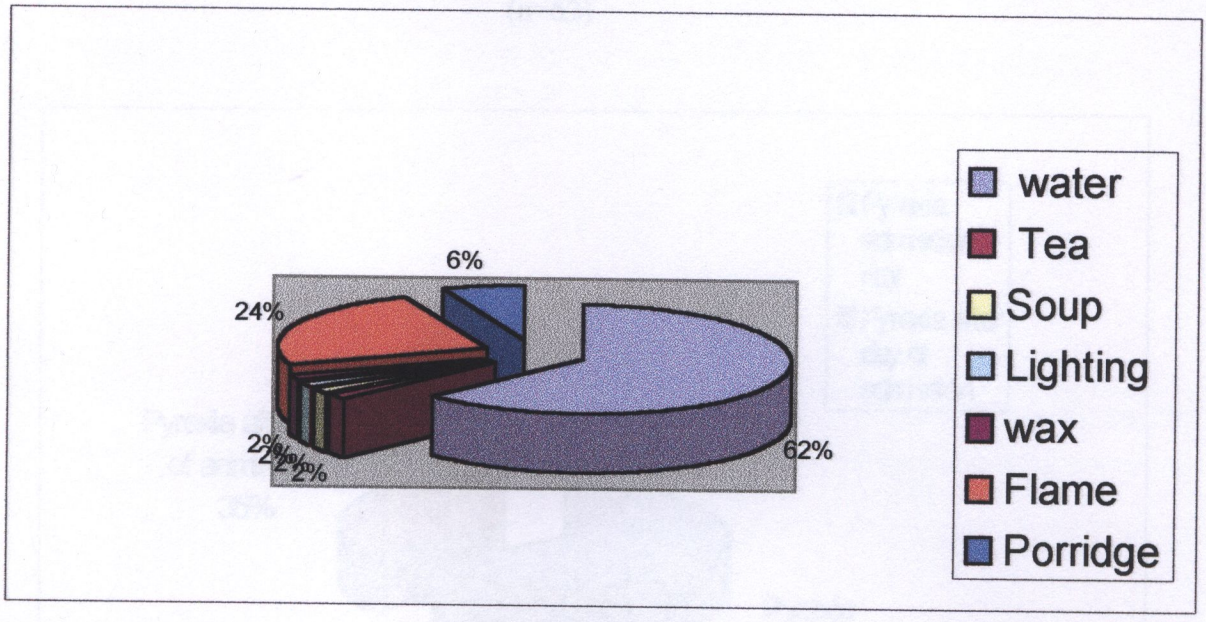


Figure 23. Hot water, flame and hot porridge are common agents which are associated with preparing of meals.

PERCENTAGE OF PYREXIA IN THERMAL INJURIED CHILDREN DURING THEIR HOSPITAL STAY.

(n=120)

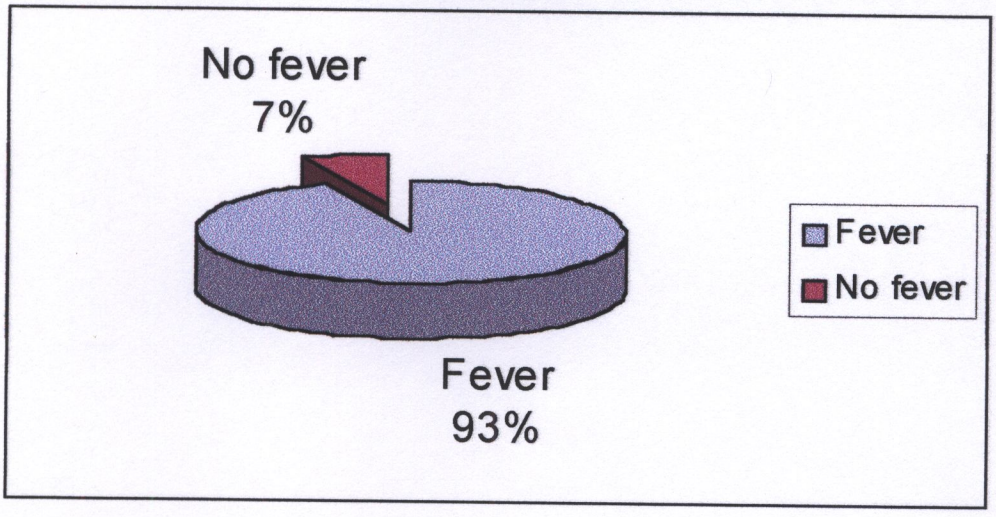


Figure 24.

PYREXIA ON DAY OF ADMISSION
(n=62)

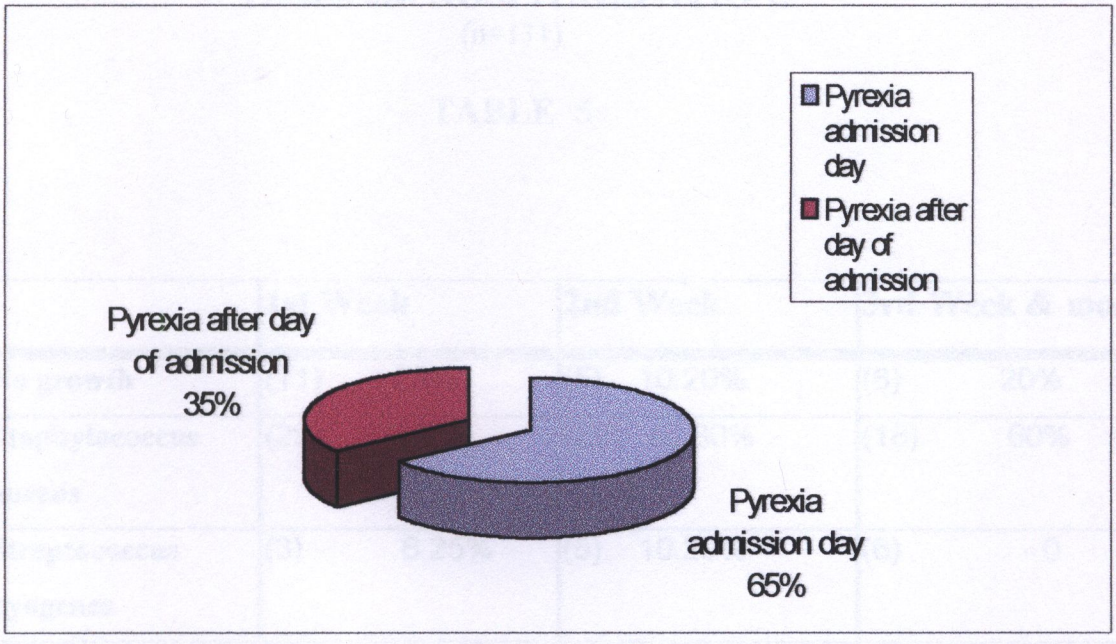


Figure 25. Sixty five percent of children had pyrexia within 24hours of admission. Most children were brought to the hospital on the day of injury.

BACTERIAL GROWTH FROM WOUND SWABS AT DIFFERENT TIMES OF HOSPITALIZATION.

(n=131)

TABLE 5

	1st Week	2nd Week	3rd Week & more
No growth	(11) 25%	(5) 10.20%	(6) 20%
Staphylococcus aureus	(29) 68.75%	(20) 40.80%	(18) 60%
Streptococcus pyogenes	(3) 6.25%	(5) 10.20%	(6) 0
Psedomonas aeruginosa	(3) 6.25%	(12) 24.49%	(6) 20%
Proteus mirabilis	(0) 0	(4) 8.16%	(0) 0
Escherichia coli	(0) 0	(3) 6.12%	(0) 0

Table 5.

WOUND SWABS ON ADMISSION
(n=18)

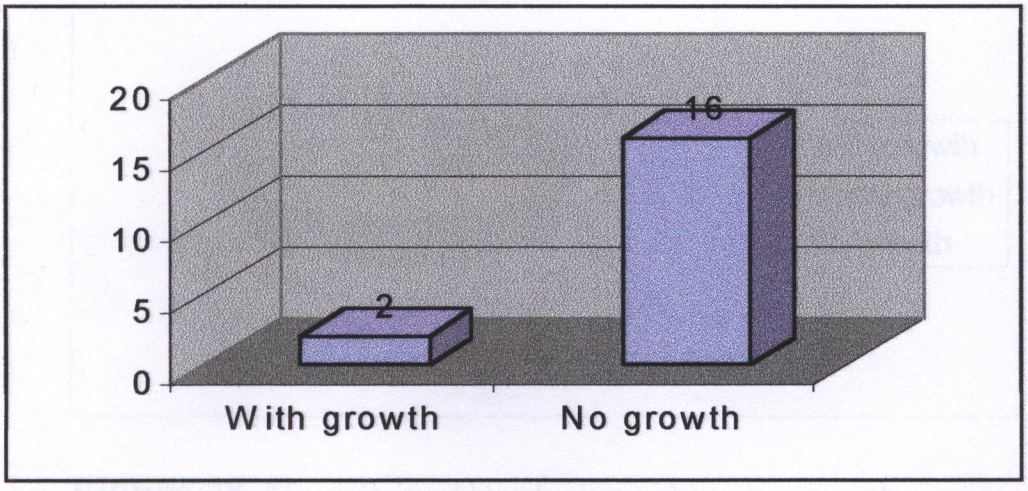


Figure 26.

WOUND SWABS WITH GROWTH AND NO GROWTH IN PERCENTAGE
(n=18)

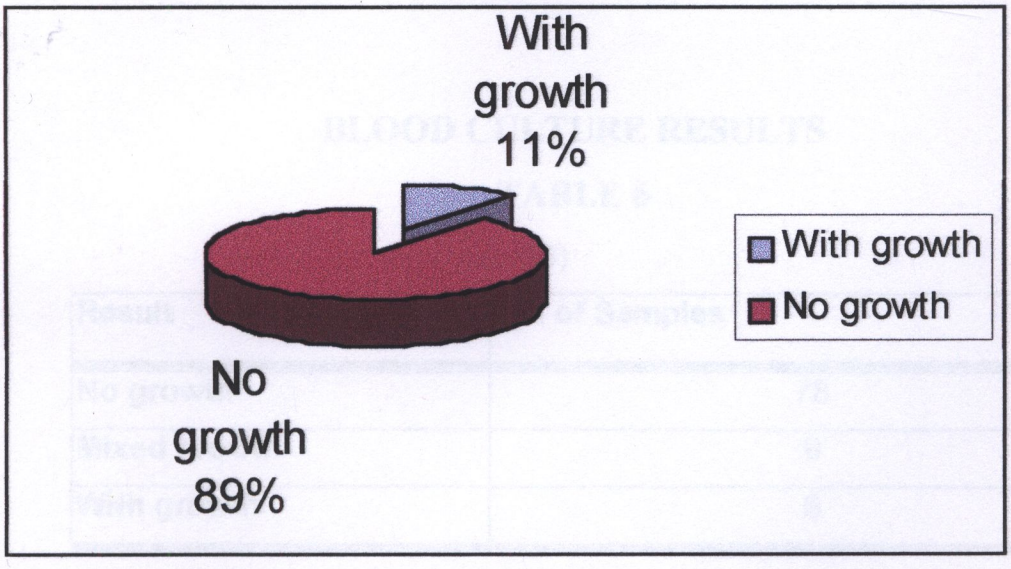


Figure 27.

BLOOD CULTURE IN PYREXIC PATIENTS WITH BURNS

(n=93)

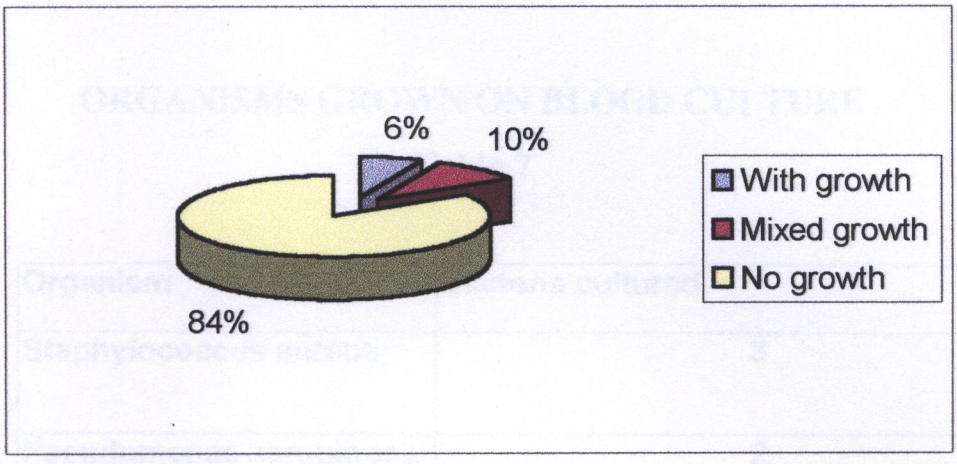


Figure 28. The majority of blood cultures showed no growth.

BLOOD CULTURE RESULTS

TABLE 6

(n=93)

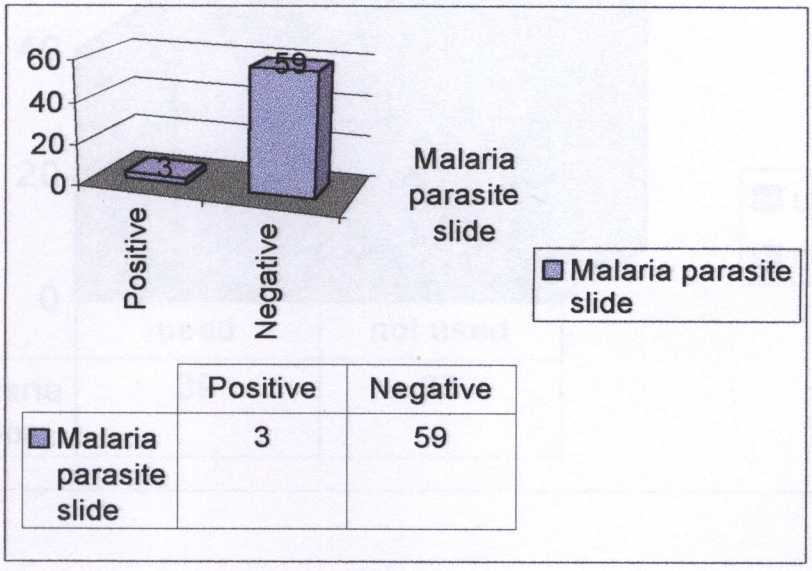
Result	No. of Samples
No growth	78
Mixed growth	9
With growth	6

ORGANISMS GROWN ON BLOOD CULTURE

Table 7

Organism	Bacteria cultured
Staphylococcus aureus	3
Pseudomonas aeruginosa	2
Salmonella	1

INCIDENCE OF MALARIA PARASITAEMIA IN BURNT CHILDREN WITH PYREXIA.



	Positive	Negative
Malaria parasite slide	3	59

Figure 29.

FREQUENCY OF MALARIA PARASITAEMIA

(n=62)

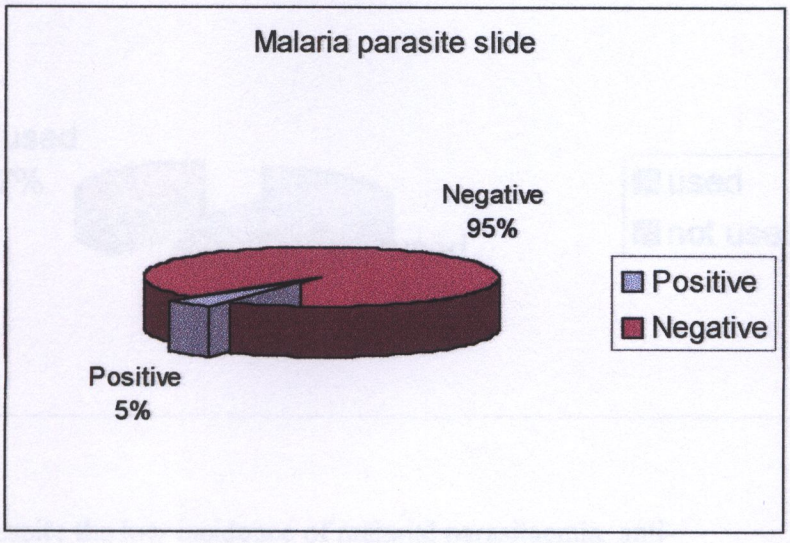


Figure 30.

ANTI-MALARIA MEDICATION USAGE

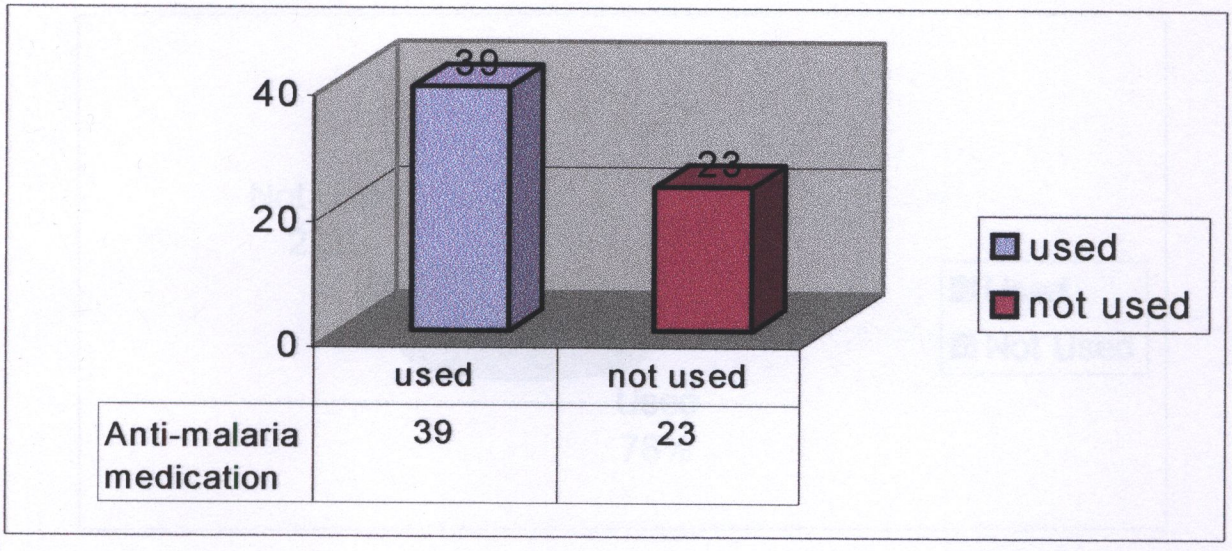


Figure 31.

ANTI-MALARIA MEDICATION USAGE (IN PERCENTAGES)

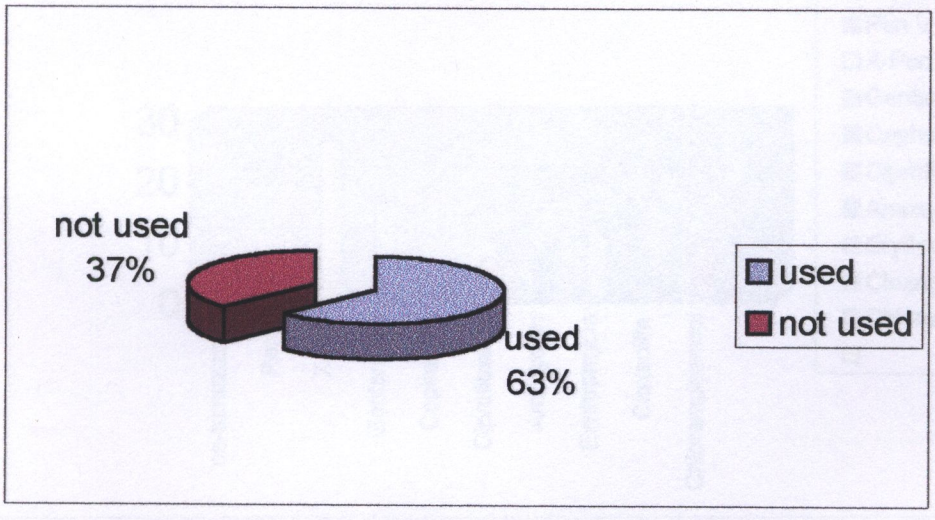


Figure 32. Despite the low incidence of malarial parasitaemia, anti-malarial drugs were commonly administered.

ANTIBIOTIC USAGE IN PYREXIAL PATIENTS
(n=62)

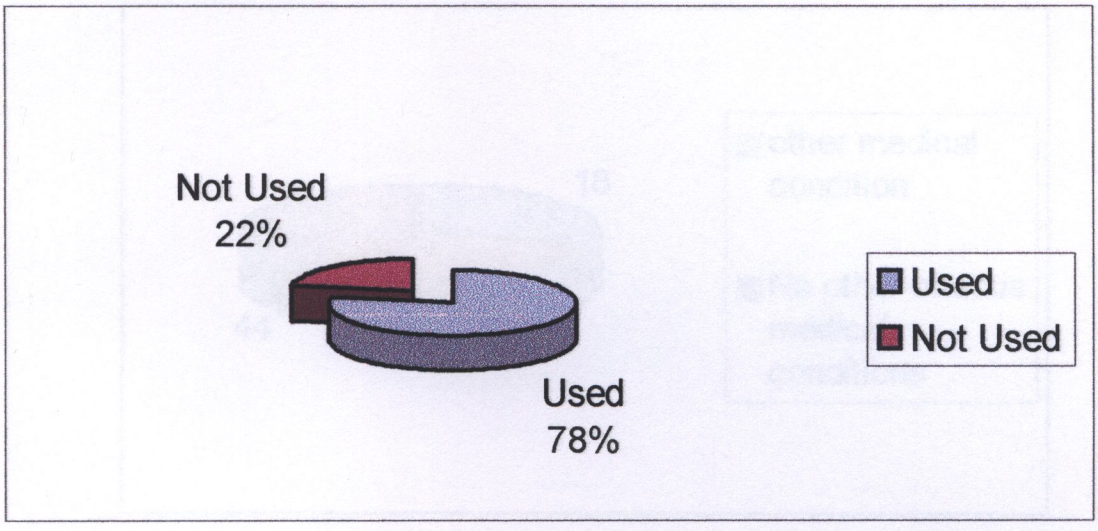


Figure 33.

TYPES OF ANTIBIOTICS USED

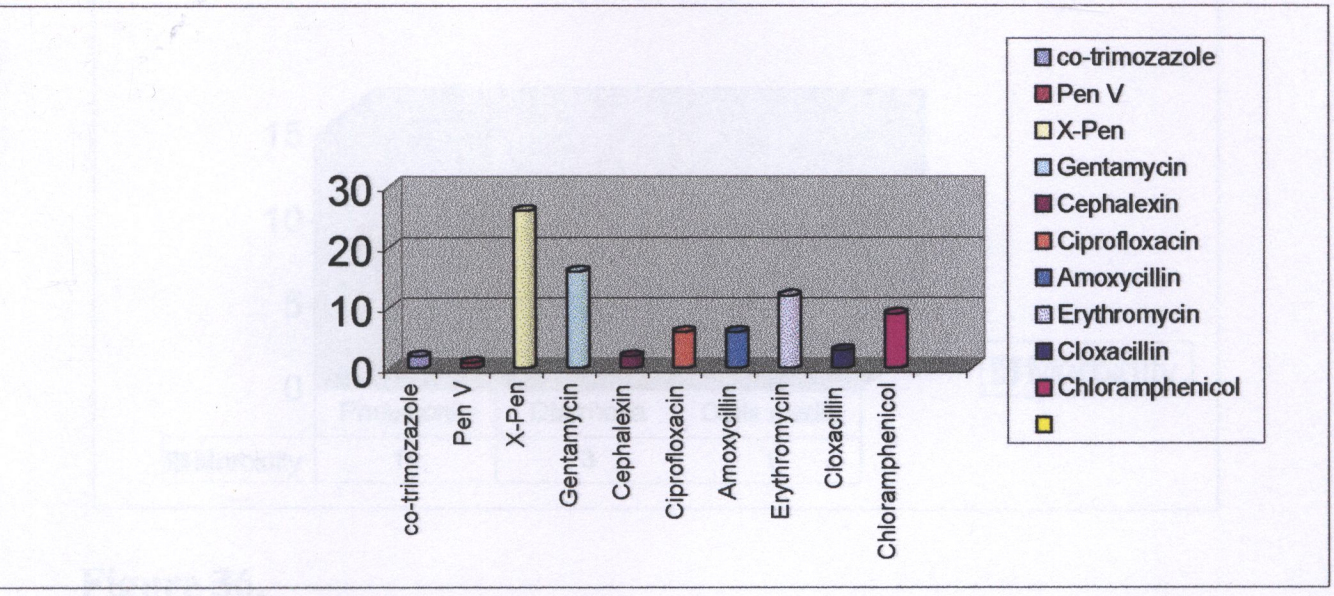


Figure 34. Most commonly used antibiotics were X-pen, Gentamicin, Erythromycin and Chloramphenicol.

MORBIDITY IN CHILDREN WITH PYREXIA IN BURNS

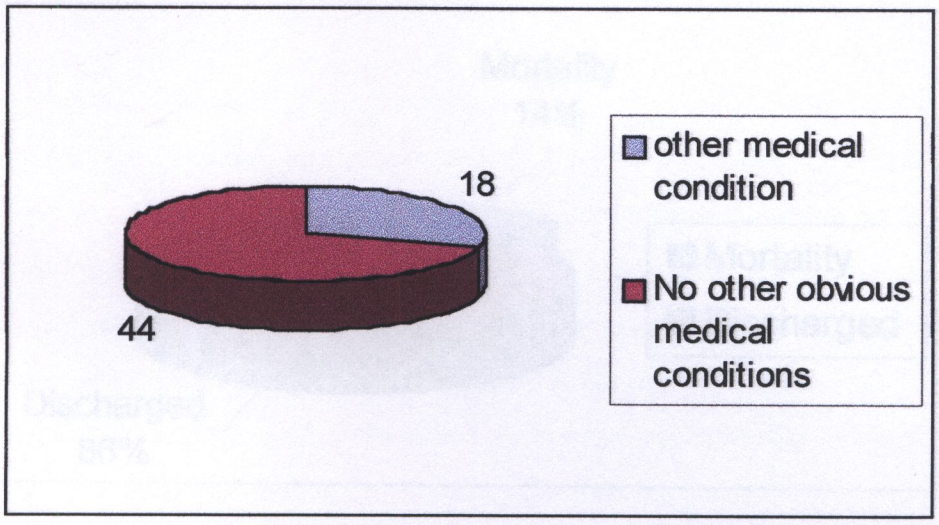


Figure 35.

CAUSE OF MORBIDITY IN BURNED CHILDREN WITH PYREXIA

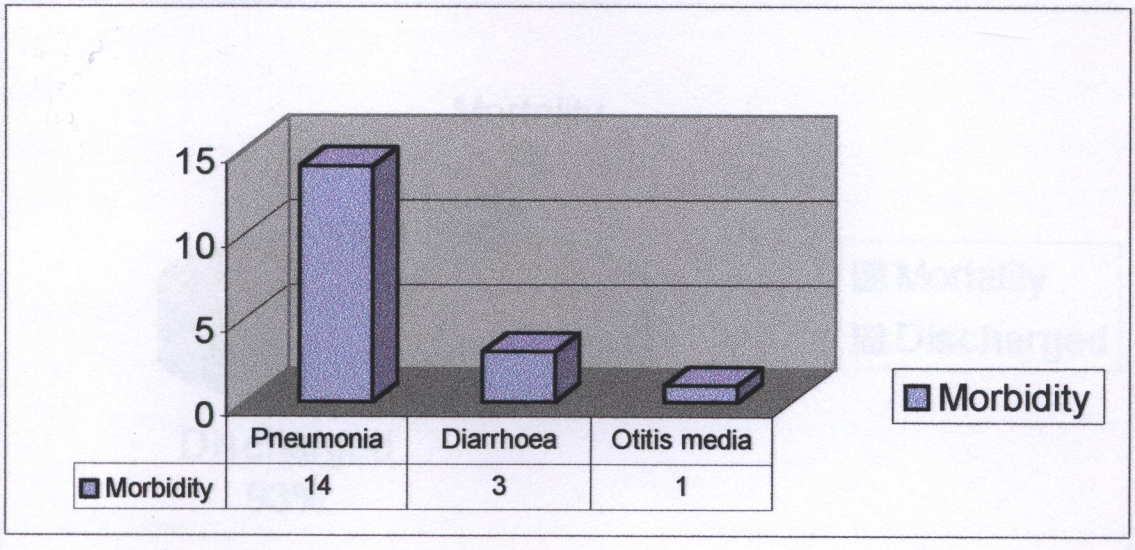


Figure 36.

MORTALITY IN CHILDREN WITH PYREXIA
(n=62)

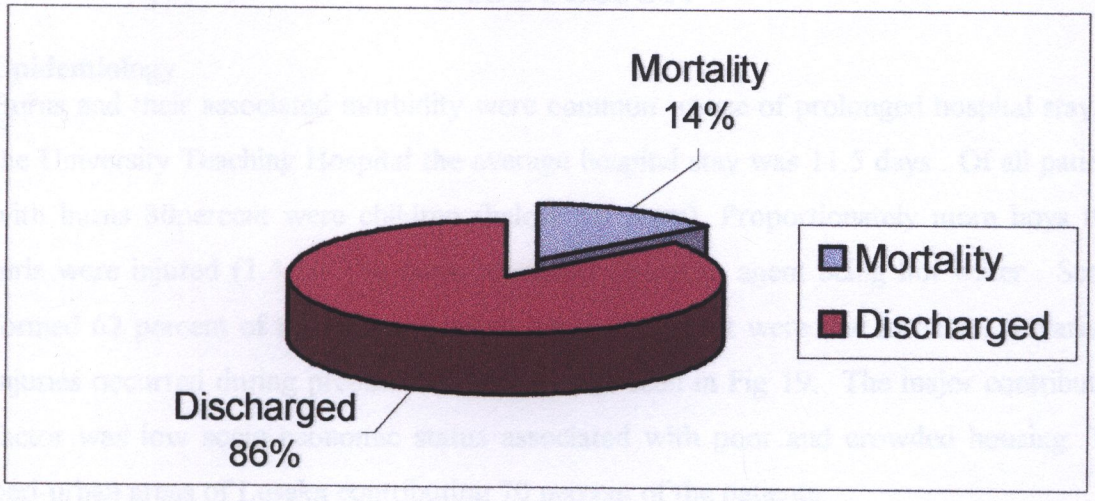


Figure 37.

MORTALITY IN CHILDREN WITHOUT PYREXIA
(n= 24)

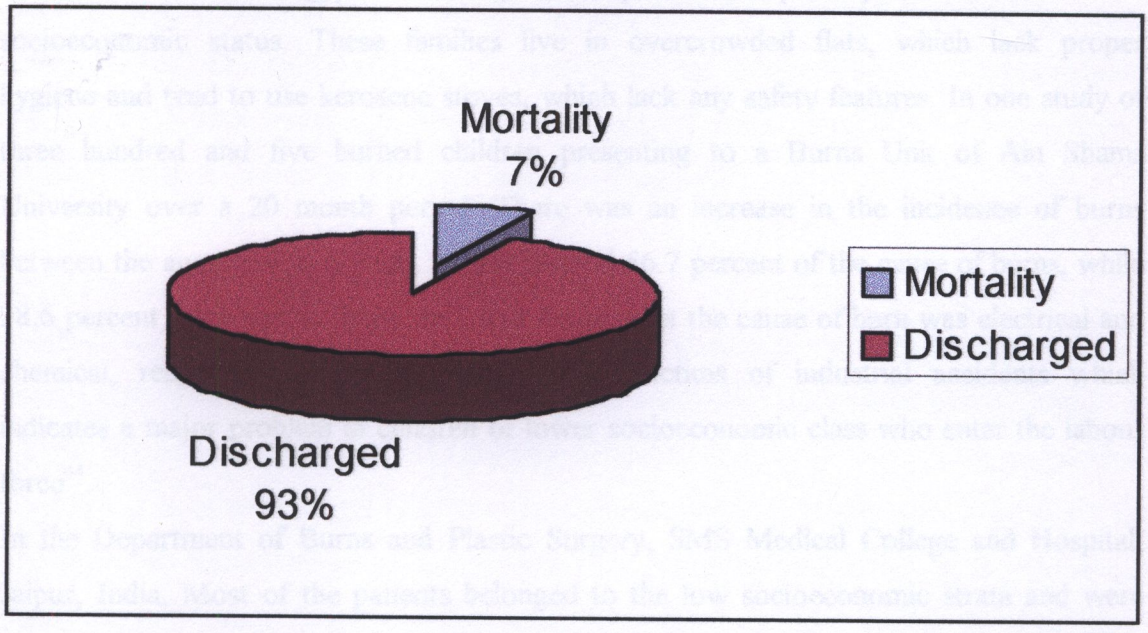


Figure 38.

DISCUSSION

Epidemiology

Burns and their associated morbidity were common cause of prolonged hospital stay. In the University Teaching Hospital the average hospital stay was 11.5 days . Of all patients with burns 80percent were children (below 16 years). Proportionately more boys than girls were injured (1.4:1). The most common causative agent being hot water . Scalds formed 62 percent of the cause of burns, while 24percent were due to flame. Invariably injuries occurred during preparation of meals, as seen in Fig 19. The major contributing factor was low socio-economic status associated with poor and crowded housing. The peri-urban areas of Lusaka contributing 70 percent of the patients.

Since most of the patients are from deprived background, this could contribute to the increased morbidity and possibly an immunocompromised status due to malnutrition.

The findings in this study are similar to other reports from other countries in the developing world[44,45].

Childhood burns in Egypt are a significant problem, especially in families of low socioeconomic status. These families live in overcrowded flats, which lack proper hygiene and tend to use kerosene stoves, which lack any safety features. In one study of three hundred and five burned children presenting to a Burns Unit of Ain Shams University over a 20 month period. There was an increase in the incidence of burns between the ages of 4 to 6 years. Scalds formed 56.7 percent of the cause of burns, while 38.6 percent were due to flame. In 3 and 1.6 percent the cause of burn was electrical and chemical, respectively. Twenty patients were victims of industrial accidents which indicates a major problem in children of lower socioeconomic class who enter the labour force[44].

In the Department of Burns and Plastic Surgery, SMS Medical College and Hospital, Jaipur, India. Most of the patients belonged to the low socioeconomic strata and were members of medium or large size families. The commonest cause of burns was scalds in children under 5 years of age and flames in the older child. The overall mortality was 19.7 per cent [45].

Pyrexia on 1st day.

In this study 65 percent of children admitted with burns had pyrexia on the first day. Throughout their hospital stay 93 percent of the children with burns did at some time have pyrexia (see Fig 24). The high number of negative pus swabs cultured early in hospitalization suggests that infection was not the cause of fever. Other studies have shown that fever is not a predictor of infection in burned children[46]. Although children with burns often develop fevers. In a study by **Parish R A et al** it was observed that the highest mean temperature in burned children occurred at 38 to 96 hours after the burn injury; the peak temperatures appeared at the same time, regardless of whether the child had an infection. So they concluded that fever has no predictive value for the presence of infection and that physical examination is a reliable source of information about wound infection, sepsis, or other childhood infections, and should be the primary tool used in making the diagnosis of infection in burned children [46].

Recent studies have shown that the cause of early(1-3days) fever in the burned child is endotoxaemia that is caused by release of cytokines. One such study was conducted at the Trauma Center, Postgraduate Medical College, 304 Hospital of People's Liberation Army, Beijing. Plasma endotoxin was determined by modified synthetic chromogenic limulus amaebocyte lysate assay in burned patients. Cytokine studies were not included in our study, thus their role in pyrexia was not determined.

Endotoxaemia

In this study investigations could not be done on endotoxins, but various other workers have studied their role in the aetiology of pyrexia in the early period of a burned child.

In the Department of Surgery, University of California, San Diego, serial circulating endotoxin measurements (quantitative chromogenic limulus assay) were performed in sera from 19 burned patients to determine the profile of circulating serial circulating endotoxin after burn and the effect of early wound excision on serial circulating endotoxin levels. Results indicated an early endotoxaemia with the peak serial circulating endotoxin levels 7 to 12 hours and 4 days after the burn. More importantly, the level of circulating serial circulating endotoxin diminished following early excision; late wound

excision was associated with a transient increase of serial circulating endotoxin level. Early excision, therefore, may play a critical role in limiting endotoxaemia after burn injury[47,48,49].

From the foregoing it can be concluded that early burn excision and closure prevent the accentuated response to endotoxin that is seen when the burn wound is left intact, even if it is uninfected[48]. Endotoxin promotes bacterial translocation of the gut flora[49] . It is possible that such translocation leads to systemic sepsis and multiple organ failure as a terminal event in the severely burnt child.

Wound swabs.

Eighty nine percent of pus swabs taken on the day of admission from number pyrexial patients showed no growth. Of the 11 percent that had growths, only staphylococcus was grown.

A study on wound sepsis in , Lagos revealed that 96.7 per cent of burn wounds were sterile on admission[32]. The Lusaka results are in accord with the Lagos findings, nevertheless there appears to be a higher culture positivity in the Lusaka study. This could be explained by the delay in presentation to the University Teaching Hospital as some of the patients were referred from rural areas. (See Fig 21).

Wound swabs taken at different periods of hospital stay (Table 5.) showed that in the first week the gram positives were more prominent and for the patients that stayed in hospital for longer periods of time the gram negative organisms gradually became more prominent. This partially agrees with other findings ; in the study done by **Atoyebi et al** in bacterial flora of burn wounds, demonstrated bacterial colonization reaching 80.6 percent within the first week after admission. Although the Gram-negative organisms, as a group, are predominant, staphylococcus aureus (38.2percent) was the most prevalent organism in the first week. However pseudomonas aeruginosa colonisation increased dramatically from the second week onwards as with our patients. Anaerobes were conspicuous by their absence. Similarly, beta-haemolytic strepococcus was not isolated

from any patient. Proteus mirabilis was unusally prominent, forming 19.4 percent of all isolates[37].

A survey in Aligarh, India showed that on the 1st to 3rd postburn day (PBD) most of the wound remained sterile and Streptococcus Haemolyticus was the first bacteria isolated on 1st PBD. Gram-positive and Gram-negative bacteria, especially pseudomonas, invaded the burn wound as early as 3rd PBD, it was more so with the patients of extensive burn. Among the Gram-positive bacteria Staphylococcus aureus was most notorious and invaded burn wound very early. Pseudomonas had maximum growth followed by Klebsiella and Escherichia Coli, multidrug resistance was more common with pseudomonas. Positive blood cultures for bacteria were seen during 2nd, 3rd and 4th postburn weeks. Pseudomonas was the commonest bacteria isolated. Biopsies were done and showed maximum incidence of bacterial infection followed by fungal infection. Biopsies of the burn wound played an important role in the accurate diagnosis and thus helped in starting early specific therapy to prevent death from sepsis[52].
Burn Biopsy was not performed in this study.

Blood Cultures

Blood cultures were performed in 62 . As shown in Figs.28, 84 percent had no growth, 6percent showed a growth and 10percent had mixed growths- of which in half of them, a repeat showed no growths. It appears from this study that blood culture in most patients is of limited use in management.

A study by **Marvin JA et al** confirms that careful daily clinical evaluation and serial quantitative burn wound biopsy cultures provided the most effective means of establishing an early diagnosis of would sepsis. Serial blood cultures were of very limited value in the recognition of growths that were not recovered until 5-10 days following documentation of heavy bacterial colonization of the burn wound[51].

Bharadwaj R et al found that blood cultures were of only prognostic value. Full thickness biopsy culture and quantification of the number of bacteria in the burn wound

was felt to be the best method for rapid diagnosis and for assessing the progress of burn wound infection[52].

Krupp S et al found that as opposed to blood cultures biopsies are useful for monitoring wound infection. Not only does this method have a diagnostic value, but it also helps to evaluate the effectiveness of local and systemic wound treatment, to determine the appropriate time of skin autografting and finally to assess the chance of survival [53].

Antibiotic use

Seventy eight percent of all children with pyrexia in burns were put on antibiotics (Figs. 27 and 28). Antibiotic use was determined by availability and was often inadequate. Determination of sensitivity pattern was inconsistent because of the lack of antibiotic sensitivity discs.

Morbidity

Of the 62 patients in this study 29percent had other morbidities apart from the burns (Fig 36)

The most common were pneumonia and diarrhoea.

Malaria parasitaemia

In the burnt children with pyrexia only 5percent were positive for malaria parasitaemia notwithstanding this finding however, the anti-malaria drugs were used in 63percent of the patients. Literature search with medline revealed no studies on Malaria parasitaemia in burnt children with pyrexia. This findings therefore appears to be unique in the recent literature and merits further research by other workers.

Toxic Shock Syndrome

No investigations were done to prove the existence of staphylococcal toxaemia in this study, although during the survey in pyrexia in children with burns it was noticed not uncommonly that the degree of toxicity was out of proportion with the thermal injury.. Staphylococcus aureus was the most common organism cultured from wound swabs and

blood. For pus swabs Staphylococcus Aureus was isolated in 68.8 percent in the first week, 40.8 percent in the second week and 60 percent in the third week. In view of the fact that 25 percent of all *S. aureus* strains are toxigenic and that roughly 4-10 percent of normal people harbour toxigenic strains at any given time,[15] there could have been an undetermined significant occurrence of Toxic Shock Syndrome in the University Teaching Hospital burnt patients. Unfortunately this could not be confirmed in this study because of lack of the necessary research tools. Other studies and findings around the world have shown Toxic Shock Syndrome to be a matter of growing concern in children with burns, whereas in developing countries little attention has been given to this problem[43]. Early recognition of the prodromal features to facilitate early therapy will depend on the knowledge and training of paediatricians and casualty staff[42].

The features of toxic shock syndrome in burned children includes a 'prodromal' 24-48 h period with diarrhoea, vomiting, general malaise, pyrexia, tachycardia and tachypnoea. The white cell count and haemoglobin concentration fall prior to the 'shock' phase, which occurs 3-4 days postburn. Once 'shock' has occurred the mortality of the condition is approximately 50 per cent; in the absence of 'shock' it is much reduced[43].

CONCLUSIONS

1. Sixty five percent (n=40) of children were pyrexial on the first day of admission, whereas during their inpatient stay this figure rose to 93percent (n=58). Aetiology of pyrexia on the first day of admission could not be determined from this study. Nonetheless, the literature reviewed indicates toxaemia of burns as being the main factor.

2. Eighty four percent (n=78) of blood cultures were negative with only 6 samples showing a pure growth. The commonest organism cultured was Staphylococcus Aureus followed by Pseudomonas Aeruginosa during the second week. The mixed growth seen in 9 samples could have been the result of contamination, because the cultures which were subsequently repeated in nearly half the samples (n=5) showed no growth. A single blood culture therefore as performed in this study could not be relied upon to give a true picture of the causative organism. The relationship of bacteraemia to pyrexia could not be determined in this study.

3. There was no correlation between organisms cultured from wound swabs and the development of pyrexia. There was a high incidence of Staphylococcus Aureus colonisation on skin during the first week of admission. The relationship of the organism to the development of the Toxic Shock Syndrome was not determined in this study because appropriate laboratory investigations were not available. The literature however, indicates Toxic Shock Syndrome is a factor in mortality.

4. Malaria Parasitaemia was encountered in 5 percent (n=3) of patients, therefore it is not a significant contributory factor in the aetiology of pyrexia in burn patients in this study group. Antimalarial medication was used in 63 percent (n=39) of patients based on a presumed clinical diagnosis of malaria.

RECOMMENDATIONS

1.Feeding should be commenced on admission to lessen the burden of catabolism on the body.

2.Encourage more frequent cleaning and application of Silver Sulphardiazine cream or similar ointment to reduce wound sepsis. The Silver Sulphadiazine could be produced within the hospital to cut costs.

3. More attention is required in avoiding hospital acquired gram negative infections particularly in long stay patients.

4. In view of the excessive use of anti-malaria medication (mostly chloroquine) a more selective use of chloroquine is justified. This should be based on blood smear examination.

5.Biopsy culture should replace blood culturing because it is more useful for monitoring wound infection. Not only does this method have a diagnostic value, but it also helps to evaluate the effectiveness of local and systemic wound treatment, to determine the appropriate time for skin autografting and finally to assess the chance of survival. Such a recommendation however needs to have its feasibility determined in view of the invasive nature of the test and the need for labour intensive laboratory support.

6.Future laboratory-based studies on the role of Staphylococcus Aureus and the toxic shock syndrome are warranted.

7.Personnel managing children with burns should be conversant with the concept of Staphylococcal toxaemia and the toxic shock syndrome.

8.Antibiotic usage should be selective. Early antibiotic use should be directed against gram positive organisms. During subsequent weeks antibiotics with a broader spectrum of activity, in particular against gram negative and mixed organisms, is warranted.

REFERENCES

1. **Lerer LB.**
The epidemiology of fatal childhood burns (letter)
South African Medical Journal. 1994; 84(3): 169.

2. **Morrow SE, Smith DL. Cairns BA, Howell PD, Nakayama DK, Peterson HD.**
Etiology and outcome of pediatric burns.
Journal of Pediatric Surgery. 1996; 31(3): 329-33.

3. **Durtschi MB, Kohler TR, Finley A, Heimbach DM**
Burn injury in infants and young children.
Surgery Gynecology Obstetrics 1980;150(5):651-6

4. **Hansbrough JF, Hansbrough W**
Pediatric burns.
Pediatrics Review 1999;20(4):117-23;

5. **Cotran RS, Kumar V, Robbins SL**: Robbins Pathologic Basis of Disease. 5th edition. Philadelphia, W.B. Saunders, 1994: 399.

6. **Merck & Co.,inc.** The Merck Manual 16th Edition, New York, Rahway, 1992: 978-90

7. **Smith A, BarclayC,Quaba A, Sedowofia K, Stephen R, Thompson M, Watson A, McIntosh N.**
The bigger the burn, the greater the stress.
Burns 1997; 23(4): 291-4

8. **Charles V. Mann. R.C.G. Russel.** Bailey & Love, Short practice of surgery.22nd ed. London Chapman &Hall. 1995: 141

9. **Ikeda H, Kobayashi K**
Pathophysiologic changes in patients with severe burns: role of hormones and chemical mediators. [Article in Japanese]
Nippon Geka Gakkai Zasshi 1998;99(1):2-7

10. **Kawakami M, Okada Y**
Immunological alterations after extensive burn injury.[Article in Japanese]
Nippon Geka Gakkai Zasshi 1998;99(1):26-30

11. **Yao YM**
Endotoxemia in severely burned patients. [Article in Chinese]
Chung Hua Wai KO Tsa Chih 1993 ; 31(7): 435-8

12. **Peitzman AB, Udekwu AO, Ochoa J, Smith S**
Bacterial translocation in trauma patients.
Journal of Trauma 1991;31(8):1083-6; discussion 1086-7

13. **Sheng Z, Yao Y, Yu Y**
The relationship between gut-derived endotoxemia and tumor necrosis factor, neopterin: experimental and clinical studies.
Chinese Medical Journal(English) 1997 ;110(1):30-5

14. **Demling RH, Wenger H, Lalonde CC, Hechtman H, Wong C, West K**
Endotoxin-induced prostanoid production by the burn wound can cause distant lung dysfunction.
Surgery 1986;99(4):421-31

15. **Huang YS, Yang ZC, Yan BG, Yang JM, Chen FM, Crowther RS, Li A**
Pathogenesis of early cardiac myocyte damage after severe burns.
Journal of Trauma 1999; 46(3):428-32

16. **Jeffrey A. Gelfand, Charles A. Dinarello**
Harrison's Principles of Internal Medicine 11th edition
New York: McGraw-Hill, 1999:161-66

17. **Robert S. Munford ,**
Harrison's Principles of Internal Medicine 11th edition
New York: McGraw-Hill, *1999:*131-150

18. **Dinarello CA**
Cytokines as endogenous pyrogens.
Journal of Infectious Diseases 1999 ;179 Suppl 2:S294-304

19. **Hori T**
Cytokines and fever.
Japanese Journal of Medicine 1991;30(6):609-11

20. **Stern RC**
Endogenous pyrogen as a cause of fever.
New England Journal of Medicine 1978 22;298(25):1425

21. **Luheshi G, Rothwell N**
Cytokines and fever.
International Archives of Allergy and Immunology 1996;109(4):301-7

22. **Luheshi GN**
Cytokines and fever. Mechanisms and sites of action.
Annals of the New York Academy of Science 1998 29;856:83-9

23. **Mukaida N**
Cytokine network involved in inflammatory reactions.[Article in Japanese]
Rinsho Byori 1997;45(6):513-8

24. **Amarasekera N**
Pyrexia of unknown origin (PUO).
Ceylon Medical Journal 1997;42(2):67-8

25. **Were FN**
Pyrexia of undetermined origin in children.
East African Medical Journal 1991;68(9):673-4

26. **Arnow PM, Flaherty JP**
Fever of unknown origin.
Lancet 1997; 23;350(9077):575-80

27. **Rachmilewitz D, Elkan M**
Fever of unknown origin. [Article in Hebrew]
Harefuah 1974 ;15;86(2):57-60

28. **Morgenstein KM**
Fever of unknown origin.
Journal of the American Medical Association 1978 ;19;239(20):2115

29. **Heumann D, Glauser MP, Calandra T**
Molecular basis of host-pathogen interaction in septic shock.
Biochemical and Biophysical Research Communications 1997 ;17;240(2):298-303

30. **Murphy K, Haudek SB, Thompson M, Giroir BP**
Molecular biology of septic shock.
New Horizon 1998; 6(2):181-93

31. **Esmon CT, Fukudome K, Mather T, Bode W, Regan LM, Stearns-Kurosawa DJ, Kurosawa S**
Inflammation, sepsis, and coagulation.
Haematologica 1999; 84(3):254-9

32. **Haeney MR**
The role of the complement cascade in sepsis.
Journal of Antimicrobes and Chemotherapy 1998; 41 Suppl A:41-6

33. **Gordon DL, Hostetter MK**
Complement and host defence against microorganisms.
Pathology 1986 Oct;18(4):365-75

34. **Symeonides S, Balk RA**
Nitric oxide in the pathogenesis of sepsis.
Infectious Diseases in North America 1999;13(2):449-63,

35. **Hattori Y, Akimoto K, Nakanishi N, Kasai K**
Glucocorticoid regulation of nitric oxide and tetrahydrobiopterin .
Current Opinion in Microbiology 1998 ;1(1):49-55

36. **Schumann RR**
Function of lipopolysaccharide (LPS)-binding protein (LBP) and CD14, the receptor for LPS/LBP complexes: a short review.
Research in Immunology 1992; 143(1):11-5

37. **Atoyebi OA. Sowemimo GO. Odugbemi T.**
Bacterial flora of burn wounds in Lagos, Nigeria:a prospective study.
Burns. 18(6)448-51.

38. **Still J M Jr. Belcher K. Law EJ.**
Management of candida septicemia in a regional burn unit.
Burns. 1995 21(8): 594-6,

39. **Wurtz R. Karajovic M. Dacumos E. Jovanovic B. Hanumadass M.**
Nosocomial infections in a burn intensive care unit.
Burns. 21(3): 1995 181-4,

40. **Reingold AL, Hargrett NT, et al.**
Toxic shock syndrome surveillance in the United States, 1980 to 1981.
Annals of Internal Medicine 1982; 96: 875-880.

41. **Bergdoll MS, Reiser RF, Crass BA, Robbins RN, Thompson NE**
Toxic shock syndrome--the role of the toxin.
Postgraduate Medical Journal 1985;61 Suppl 1:35-8

42. **Davis TC, Griffin NK**
The consequences of toxic shock syndrome in an 18-month-old boy with 20percent scalds.
Journal of Rehabilitation and Social Medicine 1996 ;89(2):115-6

43. **McAllister RM, Mercer NS, Morgan BD, Sanders R**
Early diagnosis of staphylococcal toxaemia in burned children.
Burns 1993 ;19(1):22-5

44. **El-Badawy A, Mabrouk AR**
Epidemiology of childhood burns in the burn unit of Ain Shams University in Cairo, Egypt.
Burns 1998; 24(8):728-32

45. **Gupta M, Gupta OK, Goil P**
Paediatric burns in Jaipur, India: an epidemiological study.
Burns 1992 ;18(1):63-7

46. **Parish RA, Novack AH, Heimbach DM, Engrav LR.**
Fever as a predictor of infection in burned children.
Journal of Trauma 1987 ;27(1):69-71

47. **Dobke MK, Simoni J, Ninnemann JL, Garrett J, Harnar TJ**
Endotoxemia after burn injury: effect of early excision on circulating endotoxin levels.
Journal of Burn Care and Rehabilitation 1989;10(2):107-11

48. **Demling RH, LaLonde C**
Early burn excision attenuates the postburn lung and systemic response to endotoxin.
Surgery 1990 Jul;108(1):28-35

49. **Demling RH, LaLonde C**
Early burn excision attenuates the postburn lung and systemic response to endotoxin.
Surgery 1990 ;108(1):28-35

50. **Marvin JA, Heck EL, Loebl EC, Curreri PW, Baxter CR**
Usefulness of blood cultures in confirming septic complications in burn patients: evaluation of a new culture method.
Journal Trauma 1975;15(8):657-62

51. **Bharadwaj R, Joshi BN, Phadke SA**
Assessment of burn wound sepsis by swab, full thickness biopsy culture and blood culture-- a comparative study.
Burns 1983;10(2):124-6

52. **Bariar LM, Vasenwala SM, Malik A, Ansari GH, Chowdhury TE**
A clinicopathological study of infections in burn patients and importance of biopsy.
Journal of the Indian Medical Association 1997;95(11):573-5

53. **Krupp S, Baechler M, Bille J**
Assessment of burn wound sepsis.
Journal of Hospital Infections 1985;6 Suppl A:133-7

APPENDIX 1

Proforma for Data collection

Questionnaire

Name: *File No:* *Study Serial No.*

Age:
Sex:

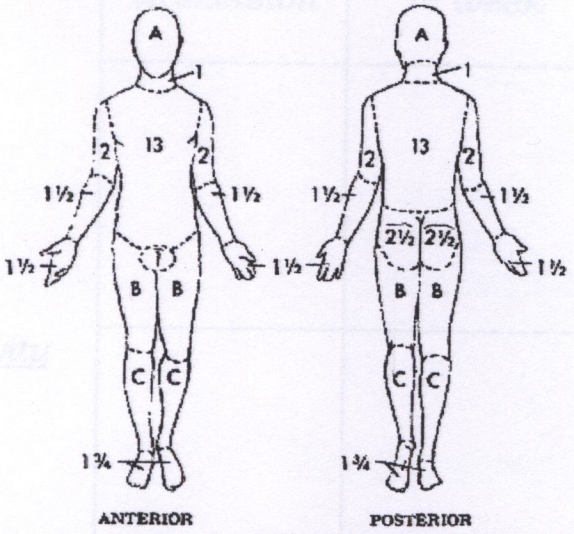
M	*F*

Occupation of parents (guards) Father / Mother : ...../.....

Residential area:.....

No. of children in the home:.....

Where accident took place::.....



Relative percentage of body surface areas (% BSA) affected by growth

	0 yr	*1 yr*	*5 yr*	*10 yr*	*15 yr*	*Adult*
A—½ of head	9½	8½	6½	5½	4½	3½
B—½ of 1 thigh	2¾	3¼	4	4¼	4½	4¾
C—½ of 1 lower leg	2½	2½	2¾	3	3¼	3½

Body Surface Area:

Agent:.....

Nature of burns:

Key

1st Dedree	
2nd Dedree	
3rd Degree	

TOTAL BSApercent.....:.....

Age of burns on admission(in days) ☐

When Pyrexia first noted: *On Admission* ☐

After No. of days post-admission ☐

Wound Culture and Sensitivity

Blood Culture

	Admission	*1st week*	*2nd week*	*3rd week*
Culture				
Sensitivity				

Wound swabs

	Admission	*1st week*	*2nd week*	*3rd week*
Culture				
Sensitivity				

Preexisting medical condition: Epilepsy
Malaria
Diabetes Mellitus
Fever
Others .....

Management:

Wound management

Open ☐
Closed ☐

Topical medication(application)

Yes ☐
No ☐

Type of application.:.....

Other Medication:

Antipyretics:	
Antimalarials	
Antibiotics	
Haematinics	
Others	

Daily axillary Temp

Consent Form

Research on causes of fever in children with burns.

Investigations:

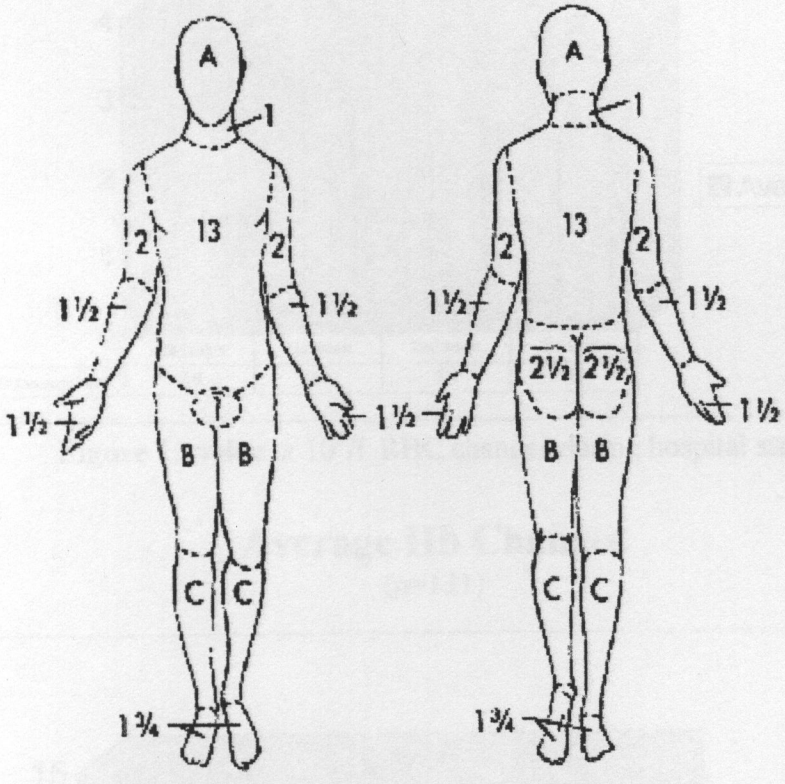
- Pus swabs
- Temperature follow-up
- Blood Culture
- Malaria Parasite Blood slide

I .....have been informed about the investigations being carried out on my child .

Signed:.....

APPENDIX II

Lund and Browder chart



Relative percentage of body surface areas (% BSA) affected by growth

	0 yr	*1 yr*	*5 yr*	*10 yr*	*15 yr*	*Adult*
A—½ of head	9½	8½	6½	5½	4½	3½
B—½ of 1 thigh	2¾	3¼	4	4¼	4½	4¾
C—½ of 1 lower leg	2½	2½	2¾	3	3¼	3½

APPENDIX III

Data collected but not discussed on.

Average RBC Changes

(n=131)

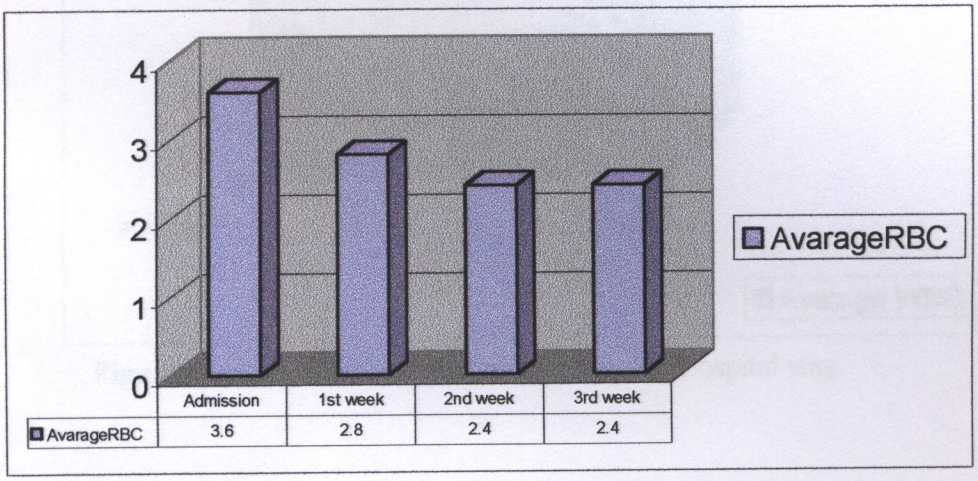


Figure 1. value x 10^9/l RBC changes during hospital stay

Average Hb Changes

(n=131)

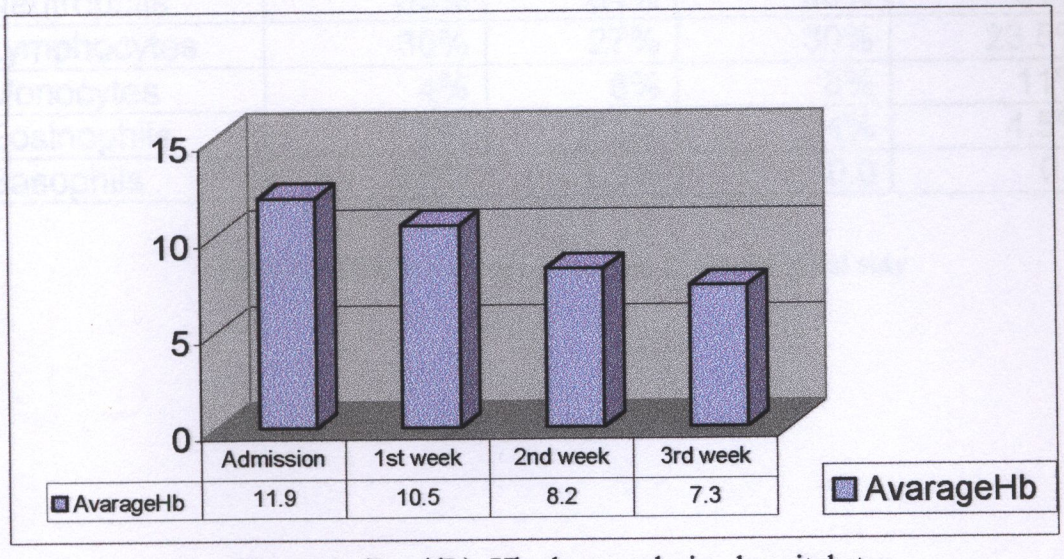


Figure 2. (In g/dL) Hb changes during hospital stay

Average WBC Changes
(n=131)

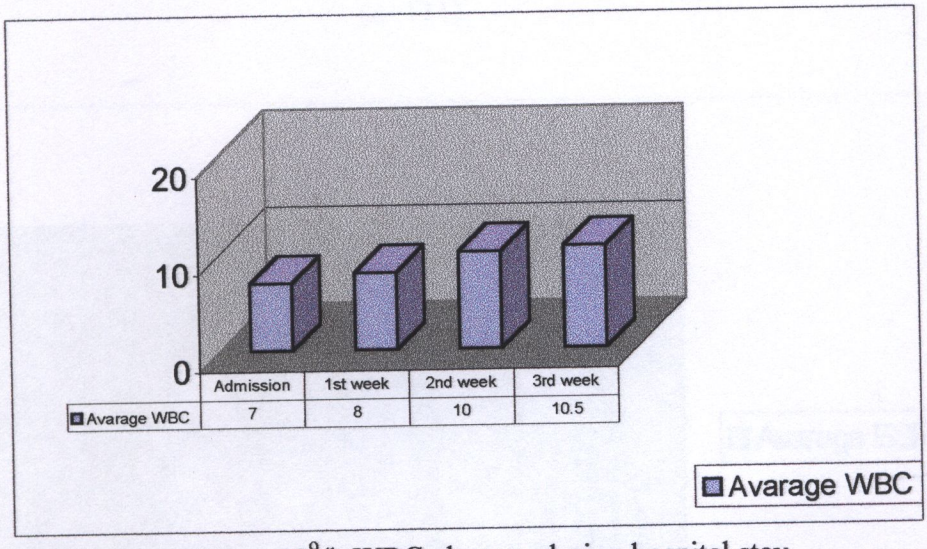


Figure3. value x 10^9/l WBC changes during hospital stay

Average Differential Count
(n=131)

	Admission	*1st week*	*2nd week*	*3rd week*
Neutrophils	63%	64%	53%	61%
Lymphocytes	30%	27%	30%	23.5%
Monocytes	4%	5%	8%	11%
Eosinophils	2%	2.5%	4%	4.5%
Basophils	1.0%	1.5%	0.0	0.0

Table1. Differential count changes during hospital stay

APPENDIX V

Average ESR Changes

(n=131)

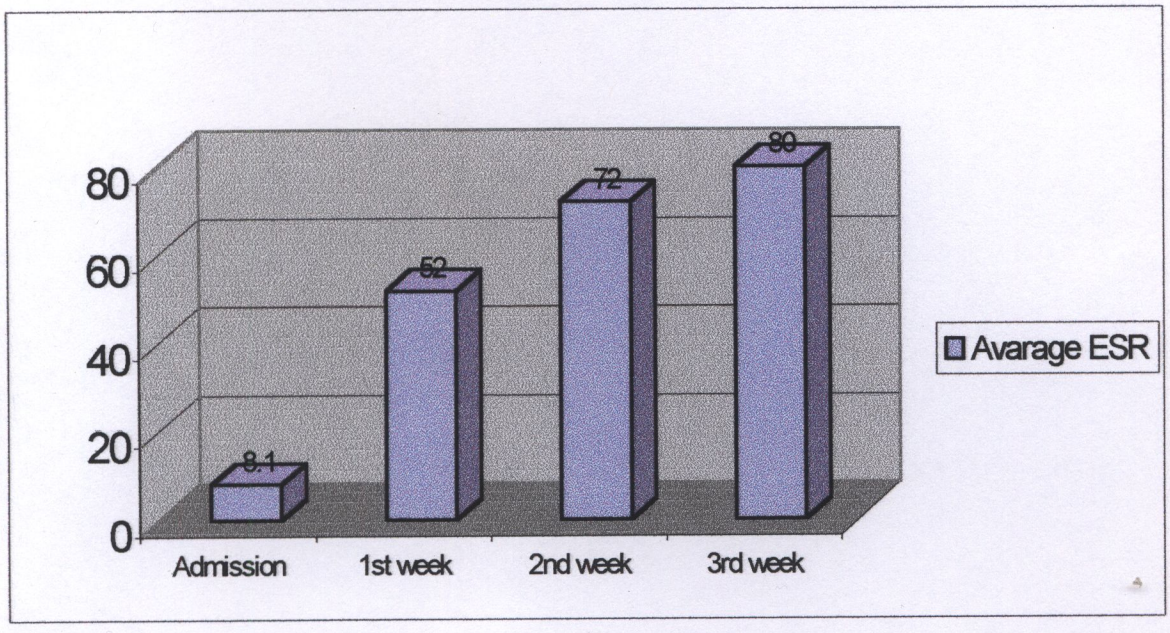


Figure 4. Average ESR(mm/hour) changes during hospital stay