The key factor in the development of modern anaesthesia and surgery is the safe outcome. The anaesthetic drugs, complicated surgical procedures and the patients' condition due to co-existing medical diseases increase the risk. During the past few decades there has been tremendous reduction in morbidity and mortality, due to increase in knowledge and understanding of pathophysiology and optimization of the disease processes, use of newer safe drugs, continuous monitoring and management of the perioperative events and excellent care in the postoperative units. The most important development in recent years is, understanding the series of physiological changes (stress response) due to anaesthesia and surgery. These changes in cardiovascular, metabolic, fluid and electrolytes etc directly affect the condition of patients and increases the risk. The efforts have been made in collaboration between the surgeons and the anaesthesiologists taking advantage of the knowledge of the precipitating factors and various effects of these physiological changes and applying the modulatory therapeutic methods in time. This allows even major procedures to be performed in patients with severe complicating diseases which were contraindicated in past and reducing the peri and post-operative mortality and morbidity.

**Stress response**

The body reacts to external stimuli, ranging from minor to massive insult both locally and generally. The general response is in the form of wide spread endocrinal, metabolic and biochemical reactions throughout the body. The magnitude of response is highly dependent on the severity, intensity and duration of stimulus. For triggering such reflex response and presenting a complex interplay of substances between the hypothalamic pituitary axis, the classical neuro-endocrinal hormone system and autonomic nervous system is brought to action and is called “stress response” or “alarm reaction”. The local response is of great importance for healing and defense against infection. This involves mediators, vascular endothelial cell products and even the intracellular products of single cells.

The stress response leads to secretion of many anabolic and catabolic hormones resulting in hypermetabolism, with the acceleration of most of the biochemical reactions. The response play as compensatory mechanism and provides maximum chances of survival because of the increased cardio-vascular functions, fluid preservation and supply of the increased demands for energy generating substrates. If the stress response is prolonged, the continuous hypermetabolic state may result in exhaustion of essential components of the body e.g. glucose, fat, protein, minerals, causing loss of weight, fatigue, decreased resistance, delayed ambulation and increased morbidity and mortality.

The net effect of stress response “The Neuro-endocrinal outflow”

- **Cardiovascular changes**: Rise in cardiac output, heart rate, blood pressure, increased myocardial contractility, increase oxygen demand.
- **Blood volume distribution**: Peripheral and splanchnic vasoconstriction coronary and cerebral vasodilatation.
- **Respiratory Changes**: Increased respiratory rate.
- **Fluid and electrolyte changes**: Sodium and water retention.
- **Coagulation**: Hypercoagubility and fibrinolysis.
- **Immunosuppression**: Wound Infections.
- **Metabolic Changes**: Substrate mobilization - hyperglycemia.
- **Urinary changes**: Reduced urinary output.

The stress changes are well tolerated by normal healthy patients (ASA grade I). The changes return to normal in due course of time. In patients with hypertension, coronary artery disease, myocardial infarction, valvular heart disease, aortic aneurysm, cerebral aneurysm or intracranial hypertension, diabetes mellitus, liver diseases, renal insufficiency, geriatric age group, (ASA grade III, IV, and V), these changes are life threatening.
This review will highlight the causes, development in the understanding of the release mechanism involved in the stress response to injury, effects on various systems and the methods that can modulate these responses for better outcome.

The primary stimuli of neuro-endocrine reflexes

Hypotension

The reduction in the effective circulating volume due to any reason (trauma, haemorrhage, burns, MI, CCF, tamponade, sepsis, neurogenic collapse etc.) is sensed by the pressure sensitive baroreceptors in aorta, carotid and renal arteries, proportional to the magnitude of the volume loss, directly through central autonomic pathway to activate release of pituitary hormones such as ACTH, vasopressin, growth hormone, beta endorphin and indirectly through the sympathetic nervous system to activate the release of catecholamine, glucagon, inhibiting the insulin release and resulting in retention of sodium and water and rise in heart rate, blood pressure and blood sugar.

Decrease in renal blood flow due to splanchnic vasoconstriction is sensed by the high pressure stretch receptors at juxtaglomerular complexes of kidney resulting in renin and angiotensin secretion which results in rise of blood pressure and reduction in urinary output. Uneven blood flow for longer time may lead to renal dysfunction.

Oxygen, carbon dioxide and hydrogen ions

The changes in the concentration of oxygen, carbon-dioxide and hydrogen ions in the blood initiate cardiovascular, pulmonary and neuroendocrine responses through the activation of the peripheral chemoreceptors, aortic and carotid bodies. Decrease in arterial blood flow or oxygen tension, decreases the chemoreceptor oxygen extraction, decreasing venous PO2. The 9th and 10th cranial nerves carry these sensation to the hypothalamus resulting in to cardiac sympathetic outflow causing rise in heart rate, cardiac contractility and hyperventilation. Further hypovolemia may potentiate the hormonal reflex response to hypoxia.

Anxiety and emotions

Fear, anxiety, emotions, tension significantly reduces pain tolerance. The stimuli pass to the limbic system especially in the region of amygdala hippocampus and lower brainstem nuclei then transmitting the signals to the posterior hypothalamus. Stimulation of which controls the release of various hormones from pituitary. Pituitary secretes AVP, ACTH, cortisol, aldosterone and catecholamine through the stimulation of the ANS causing rise in heart rate, blood pressure.

Temperature

The change in the core temperature is sensed by the pre-optic area of hypothalamus induces the secretion of the stress hormones. The stress hormones increases the heat production but temperature alterations in certain clinical situations can be seen. The conditions like hypovolemia with inadequate hepatic blood flow, starvation, sepsis with peripheral vasomotor control burn with loss of thermal insulation and induced hypothermia during cardio-pulmonary bypass or neurosurgery, profound hypothermia for total circulatory arrest are known to induce neuroendocrine responses.

Anaesthesia

Certain drugs or procedures, light planes of anaesthesia and during the period of maximum stimulation (skin incision, tissue handling, stretching of mesentery or gut) show exaggerated responses.

a. Anaesthetic drugs

The use of cyclopropane, ether causes release of catecholamine.

b. Laryngoscopy and intubation

The mechanical stimulation of upper respiratory tract viz nose, epipharynx, laryngopharynx, the afferents are carried by glasso-pharangeal nerve and from tracheobronchial tree via the vagus nerve (Burstein, Lo, pinto and Newman 1950) which enhances the activities of the cervical sympathetic afferent fibres resulting in transient rise in heart rate and blood pressure.

c. Light anaesthesia

The use of poly-pharmacy, such as sedatives, anxiolytics, narcotics, muscle relaxants of different onset, peak action and duration may result in fluctuation of the depth of anaesthesia is assessed by PSRT scores (pressure, sweating, rate, tear). Inadequate drug titration may result in light or deep anaesthesia. During light planes of anaesthesia feeling of pain, inadequate sleep, amnesia or muscle relaxation results in stress response.

d. Pain

The superficial layer of the skin is densely supplied with the pain nerve endings. Woolf, Michael J cousins stated that the surgical procedures are not possible without producing damage to the nerve tissue which then become sensitized by the release of the inflammatory mediators., resulting in severe pain (cry of the injured nerves). Such pain is characterised by both “peripheral and central sensitization.”
Peripheral sensitisation - The damaged tissues evoke the typical local inflammatory response. The release of the traditional inflammatory mediators like cytokine, leukotrienes, nerve growth factor, histamine, serotonin, kallihekiri, proteoglycans etc. increase the sensitivity of nociceptors.

Central sensitization - The high intensity pain sensation is carried through the finely myelinated nociceptive fibres. A delta and smaller c fibres cutaneous nerve fibres pass through the lamina, where the change in the excitability of neurons in the spinal cord is triggered by the afferent impulses.

The exaggerated pain sensation affects the ascending reticular, limbic system, thalamus and hypothalamus which regulates the autonomic, neuroendocrine response by stimulating the hypothalamic-pituitary-adrenal–sympathetic axis resulting in release of all catabolic and anabolic hormones, before reaching the cortex. The pain sensation causing sympathetic stimulation even in deeper planes of anaesthesia during skin incision (e.g. rise in heart rate and blood pressure during sternotomy).

Surgery :- The surgery is a created injury for the treatment. The stress response depends on the extent of injury. The procedures of short duration, diagnostic procedures, body surface, eye, ear surgeries, the abdominal endoscopic surgeries requiring small incisions, minimum tissue handling evoke only a slight response. The major procedures (thorax, abdomen, hip, head neck etc) elicit more pronounced response in which the flow phase may last up to several days or weeks. This results in excessive weight loss, also delays the recovery, and ambulation resulting in increased morbidity and mortality.

Wound

The tissue injury during surgical incision and tissue handling, activates inflammation and host defence system. The magnitude of the wound has direct relationship with the manifestations of the host response. The quantity of the mediators and spill over of these mediators affects the neuroendocrine reflexes.

Various substances like exotoxin, heat labile proteins produced by gram positive bacteria, the endotoxins the lipopolysacharide moiety of gram negative bacteria cell walls, cause the release of the mediator substances, such as interleukin I (IL-I) and tumor necrosis factor (TNF) from various cells stimulate the neuro-immune axis release of the hormones such as ACTH.

The stress response is divided in to two phases

Acute ebb or shock phase :- This is very transient and characterized by a hypodynamis state, a reduction in metabolic rate and depression of most of the physiologic processes.

Flow phase :- This hyperdynamic phase may last for few days to weeks depending on the magnitude of the surgical insult or occurrence of the complication. The flow phase corresponds to the period of compensation, with increase in metabolic rate, enzyme modulation directed to glucose production and consequent restitution of blood volume and stimulation of the immune system. If the compensatory system prevails, energy expenditure diminishes and metabolism shifts to anabolic pathways.

The stress hormones

The reflex neuroendocrine response to the injury is considered as autocrines, endocrines and paracrines.

1. Autocrines (Autonomic response) – Catecholamines, insulin and glucagon.

Catecholamines

The plasma catecholamines increase immediately after injury and achieve peak concentration in 24 to 48 hours depending on the severity. This exerts metabolic, hemodynamic and hormone modulating actions. Epinephrine causes hepatic glycogenolysis, gluconeogenesis, lypolysis increased insulin resistance, preventing glucose uptake by cells. The direct cardio-respiratory effect increases heart rate, myocardial contractility, blood pressure and respiratory rate.

Glucagon

The glucagon release is modulated by plasma glucose, amino acid concentration, ANS and CNS activities. Glucagon along with catecholamine and cortisol promotes and prolongs the liver glycogenesis. It does not exert its effect during acute hyperglycemia.

Insulin

The plasma concentration of insulin during stress has been noted to be biphasic, characterized by the suppression of insulin secretion followed by a normal secretion, which has been termed as the phase of physiologic insulin resistance.

2. Endocrines - Hormones under hypothalamic – pituitary control like cortisol, thyroxine, AVP, growth Hormone.

Cortisol

The central key is the excitation of the hypothalamus during stress resulting in the secretion of ACTH which in turn initiates sudden increase in cortisol level (fig–1). The metabolic effects of cortisol are directed to overcome the stressful state. There is a direct feedback mechanism for cortisol to both hypothalamus and pituitary gland to decrease
the concentration of cortisol in plasma but the potent stress stimuli always initiates either periodic exacerbations of cortisol secretion at multiple times during the day or prolonged cortisol secretion during chronic stress.

Cortisol has widespread effects on the metabolism and utilization of glucose, amino acid and fatty acids in hepatic and extra-hepatic tissues. The cortisol causes rapid mobilization of amino acids and fat from their cellular stores, making them immediately available both for energy and synthesis of other compounds including glucose needed by different tissues.14,16,18

**Effect of cortisol on glucose metabolism**

The cortisol and other glucocorticoids have the ability to stimulate gluconeogenesis by liver as much as 6 to 10 folds during stress.2,3 One of its effect is increase in glycogen storage in the liver cells which is the primary source of glucose production. The glucose production during flow phase is mediated through glucagon and insulin using amino acids, lactates, pyruvates and glycerol etc. Cortisol mobilizes amino acids from the extra-hepatic tissues and converts it in to glucose. It also decreases and delays the rate of glucose utilization in spite of increased insulin secretion, blood glucose concentration increases up to 50% of the normal. Fletcher et al. 1965. 7 to 30 mg% rise in BSL in non diabetic patients. In diabetic patients (fig.-2) Excess of glucose provides a ready source of energy to obligate tissues such as CNS, wound and red cells, since these cells do not require insulin for glucose transport and utilization.19

**Protein metabolism**

Cortisol mobilizes amino acids from the extrahepatic cells thereby diminishing the tissue stores. Increase in catabolism and decreased protein synthesis results in thinning and weakness of muscles. In contrast, liver increases the formation of essential plasma proteins and glucose.6,12

**Fat metabolism**

Cortisol helps in mobilization of fatty acids from the adipose tissues and also increases oxidation of fatty acids in the cells, changing the metabolic system of the cells in times of starvation or stress from utilization of glucose for energy. Ketogenesis depends on the severity of injury but is suppressed by the high insulin level.

TRH-TSH-T3/T4

During injury the peripheral conversion of T4 to T3 is impaired. The plasma concentration of free and total T3 are decreased after injury.3,8

**Growth hormone**

The secretion of growth hormone is governed by hypothalamic factors, autonomic stimulation and non-hormonal signals. The primary metabolic action of GH during stress is to promote protein synthesis and enhance lipid break down, and glucose stores.13

**Arginine vasopressin**

Secretion of AVH is increased after major trauma, hemorrhage, sepsis, pain. Immediate AVH release, following acute reduction of circulating volume, is a complex event acting through afferents including baro, chemoreceptors and left atrial receptors. The preservation of water and sodium reduction in the urine volume occurs as a compensatory phenomenon.

**Aldesterone**

ACTH and angiotensin increases and stimulates aldosterone concentration following injury. The primary aldosterone secretion is related to sodium and water resorption from the distal convoluted tubules.
Renin-Angiotensin

Renin release is under the control of juxtaglomerular neurogenic receptors and the macula densa. Decreased circulating volume, ACTH, AVP, glucagon, prostaglandins, potassium, magnesium and calcium influence the renin secretion. Angiotensin II acts directly on cardiovascular system, fluid electrolyte balance, hormonal modulation and metabolism. It is a potent vaso-constrictor, also stimulates heart rate, myocardial contractility and increases vascular permeability.

3. Paracrines - The activated local tissue, vascular endothelial cell system and single cell initiates response during hemorrhage sepsis inflammation and other form of injury. It releases the cell derived mediator likes cytokine, leukotrienes, prostaglandins, histamine, serotonin, TNF, interleukin I, II, VI, plasminogen activator, eicosanoids, kallikreins-kinins and other mediators. These mediators are also released as a consequence of cell injury or death which have direct effect on the ANS and CNS on the classical hormone system releasing cortisol, EP and NE and other stress hormones in small quantity. Some mediators affect the vascular, metabolic, coagulation, angiotensin and immunological system. The preventive measures for the release of such mediators may play an important role in reducing the stress hormones.5,14

Cytokines and other mediators

The mediators may be the result of cellular injury or death due to hypoxia, sepsis, inflammation. They exert paracrine, autocrine and endocrine effects even in very low concentration.

a. Interleukins :- IL-1,IL-2, IL-6- The release of interleukins is during inflammatory, infectious and immunologic process.2,3,6 They act on CNS inducing fever by stimulating local release of prostaglandins in the anterior hypothalamus, inducing anorexia but increasing the basal metabolic rate and oxygen consumption. They promote the synthesis of hepatic acute proteins and breakdown of muscle protein to amino acids, necessary for the immune stimulation, defence and energy production. They also have central hormonal modulating effects causing release of ACTH, CRF and marginal increase in catecholamines.2,16

b. Tumour necrosis factor :- During injury the TNF stimulates the release of prostaglandin E2, neutrophil aggregation, thromboxane synthesis (potent vasoconstrictor and promotes platelet aggregation), cytotoxicity, eicosanoids, platelet activating factor. They also cause decrease in lipoprotein lipase activity in adipose cells and reduces the transmembrane potential in skeletal muscle.

c. Eicosanoids – The eicosanoids are derived from the arachidonic acid of the cell membrane phospholipids of all neucleated cells. The stimuli for the increased synthesis of eicosanoids are hypoxia, ischemia, tissue injury, NE, AVP, angiotensin II serotonin.

They are the prostaglandins, from kidney, platelets, blood vessels, thromboxanes from platelets and macrophages, leukotrienes from WBC, synovial tissues, lung parenchyma. They have wide spread effects on systemic, pulmonary, regional vasoregulation, effect on central and peripheral neurotransmission. They are powerful vasodilators and vasoconsictors and proaggregatory substances.6,20

d. Serotonin – It is found in the enterochromaffin cells of intestines and platelets during tissue injury. It stimulates vaso-consstriction, bronch-spasm, platelet aggregation, increases heart rate and myocardial contractility.

e. Histamine - Elevated concentration of histamine has been observed during hypotension, trauma, thermal injury, endotoxemia. It causes severe vasodilation resulting in hypotension, peripheral pooling, increased capillary permeability and ultimately cardiac failure.2,6

f. Kallikreins-Kinins – The kinins are potent vasodilators, causes tissue oedema, evoke pain, increases hepatic prostaglandins, inhibit gluconeogenesis, reduction in renal blood flow, increase in renin formation during injury.

g. Heat shock proteins – A group of intracellular proteins named after the heat stimulation induced by hypoxia, ether anaesthesia, trauma and haemorrhage. This protects the cells from the deleterious effects of stress. The experimental work has shown that the HSP action is in parallel with the hypothalamic – pituitary- axis activation, adrenal cortex and specific vascular cells providing evidences for stress induced interaction of the neuro-endocrinial system and the molecular response to stress.4,5

Immune response

Infectious complications continue to be one of the causes of post-operative morbidity. The body protects itself against foreign organisms or substances. The mechanism of Immunosupression in the post-operative period is not fully understood. The known mediators of immune depression are neuro-endocrine response as well as intravenous opioids and inhalational agents which have shown an increase in the susceptibility to infection through a significant decrease in the cytotoxic activity of the natural killer cells. Yeager and Tuman et al found a significant reduction in post-operative infections in patients receiving epidural anaesthesia and analgesia due the cytoprotective and anti-inflammatory effects of local anaesthetics.20
Modifying factors of the stress response

The stress response to surgery, anaesthesia and other injuries has been considered as the a homeostatic defence mechanism, important for the body for adaptation and developing resistance to the noxious insults. But such exaggerated physiological changes in patients with co-existing diseases is always life threatening. This can be prevented by appropriate fluids, electrolytes and glucose to reduces nitrogen loss. Timely therapeutic intervention can reduce the myocardial strain. Absolute post – operative pain relief reduces the catecholamine release and pulmonary complications. The feeling of well being, less weight loss, early recovery and ambulation reduces the morbidity.7

The pre- anaesthetic screening plays an important role in identifying, quantifying and optimization of the disease processes. The recognition of the factors which initiate the stress response can be considered for modification in the pre-operative period.

1. General anaesthesia

General anaesthesia may limit the perception of sensations due to injury, but does not abolish the response completely as hypothalamus reacts to the noxious stimuli even in the deeper planes of anaesthesia (e.g. rise in HR and blood pressure, during sternotomy). All the intravenous agents and volatile anaesthetics in normal doses have minor influence on the endocrine and metabolic functions.2,3,6.

2. Regional blockade

The neural blockade by regional anaesthesia with local anaesthetics have direct influence on endocrinal and metabolic response.11,12,14 The basic mechanism of neural blockade on stress response to surgery is the total prevention of the nociceptive signals from the surgical area from reaching the central nervous system. The inhibitory effect of neural blocked on endocrine and metabolic response to surgery is involved through both afferent and the efferent pathway but differ among the individual endocrine glands.16,19 The afferent pathway is involved in the release of pituitary hormones whereas adrenocortical hormones release is complex. The cortisol release is through the efferent neural to pituitary and neural efferent pathway to adrenal cortex by ACTH.15

The efferent pathway is also involved in the release of cortisol, rennin angiotensin and epinephrine. Extensive neural blockade T_2 to S_3, during lower abdominal surgeries, prevents cortisol response. The hyperglycemic response to surgery appears due to the release of stress hormones through the afferent and effenter neural pathway.13,14 The insulin response to hyperglycemia and plasma glucogen response to peripheral glucose are inhibited only by higher thoracic T_4 to T_6 dermatome block. The T_9 to T_10 block for lower abdominal surgeries has no influence on insulin secretion.15,19,21

3. Alleviation of anxiety

Anxiety initiates catecholamine release harming the cardio-respiratory impulses due the exaggeration of the oxygen consumption and hemodynamic responses. The pre-operative use of various anxiolytic drugs, cardiac drugs eg-beta-blockers, other anti-hypertensive and anti anginal can prevent the morbidity.

4. Pre-operative fluid balance

The appropriate pre-operative fluid therapy with sufficient amount of glucose, is essential to maintain fluid balance and calorie requirement to avoid undue catabolism.6,7

5. Peri-operative management

It is essential to prevent the hemodynamic changes during induction endotracheal intubation, skin incision and maintenance of the depth of anaesthesia are adequate to attenuate the stress response. The careful titration of inhalational anaesthetic drugs, short acting opioids, use of cardio-stable muscle relaxants are helpful. The continuous infusion anaesthetic drugs relaxants and opioids technique has proved to be excellent in preventing the fluctuation of the depth of anaesthesia.

The continuous monitoring of vital parameters HR, BP, ECG, CVP, SpO_2, PCO_, temperature, blood sugar, the timely interpretation of any changes and instant therapeutic intervention throughout the procedure, plays an important role in stabilizing the patient’s condition.

General anaesthesia combined with neural blockade- The G.A. plus epidural analgesia in hip replacement, thoracic surgery, abdominal surgeries certainly reduces circulatory, hyperglycemic responses due to inhibition of the cortisol and catecholamines.6,15,16,17.

The postoperative care including multi-component regimen.

Absolute pain relief during the peri and postoperative period is a “gold standard” for preventing the protein breakdown.5,7,16,22

a. The local wound infiltration - The use of local anesthetics during wound infiltration completely block the pain transmission, local inflammation and the pitutary response.

b. Preemptive analgesia-The pre-operative NSAIDs or continuous infusion of local anesthetic bupivacaine at low concentration, through the epidural catheter provides
excellent perioperative analgesia which can be continued postoperatively.21

c. NSAIDs - The NSAIDs has no direct effect on the classical stress response but the arachidonic cascade metabolites are involved in various steps of the response to injury. The use of NSAIDs and aspirin may help as an anti-prostaglandins, anti-serotonins, antihistaminics, anti-inflammtatory, anti-coagulant and immuno-suppressive effects may result in slight modification.6

d. Systemic opioids :- Epidural morphine does not abolish the stress response. High doses of fentanyl (50 mgkg−1) and etomidate selectively inhibit the hypothalamus thus preventing endocrinal and metabolic response.15,18,23

e. Stimulation of inhibitory descending pathway and alpha-2-agonist :- The stimulation of the descending inhibitory pathway from brain stem using electrical stimulation or administration of the final serotonin, clonidine and enkephalins reduces pain sensation.3,5,6

f. Peripheral blocks:- Retrobulbar block reduces the effect of stress response as compared to general anaesthesia.3,6

g. Prevention of deep vein thrombosis :- Vasodilatation due to sympathetic block during spinal or epidural blockade, use of aspirin and early ambulation reduces the hypercoagulation response in the postoperative period.11,18

h. Anabolic and catabolic hormone modulation – Beta blockers, growth hormone and insulin reduces protein breakdown and improves nitrogen balance.7,21

i. Substrate administration - The demand of certain substrates increases during starvation and injury. The administration of glucose and amino acids, though the fundamental characteristic of catabolism is not abolished but it reduces to a great extent during stress.23

Conclusion

The body reacts to noxious stimuli called stress response. These responses can be life threatening when the patient is suffering from medical problems like hypertension, MI, angina, diabetes etc. The responses are less pronounced during minor or endoscopic procedures. The complex thoracic, abdominal, vascular surgical procedure show wide spread reaction. These responses can be modified in the pre, peri and postoperative period. General anaesthesia does not abolishes the response completely. The local anaesthetics when used intrathecally or epidurally, abolishes the response to a great extent, particularly in lower abdominal operations. Preoperative use of appropriate anxiolytics, fluid, glucose, maintain hydration and nutrition reduces undue catabolism. The prevention of stress response during laryngoscopy, intubation and skin incision protects the myocardium. Stabilization of depth of anaesthesia and hemodynamics peri-operatively reduces the response. The postoperative analgesia with epidural local anaesthetics and fentanyl for 2 to 3 days reduces catecholamine release. The release of paracines is suppressed by aspirin and NSAIDs. The pain free postoperative reduces nitrogen loss, pulmonary complications and initiates early ambulation.

References


12. Bevan DR,: Modification of metabolic response to trauma under epidural analgesia. 1971; 26: 188


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**ISACON 2003**: 51st Annual National Conference of ISA : BHUBANESWAR  
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