DISCUSSION

George L. Blackburn and Robert R. Wolfe, once in 1981, wrote thus: -

"The spontaneous changes in carbohydrate, lipid, protein and energy metabolism after injury are a normal occurrence and represent one of Nature's most elaborate and concerted efforts towards survival. To regard the response of the body to injury as "pathological" or as a "functional wasting" is to overlook its elegance and to fail to understand the mechanisms. Rather, these mechanisms should serve as a framework for designing fluid, electrolyte and nutritional support. Only when the severity of illness results in organ failure or systemic sepsis, does this metabolic response collapses. Proper use of nutritional support can considerably prevent these adverse effects of organ failure and sepsis."

Almost at the same time (in 1981, to be precise) Celine Traynor and G.M. Hall commented: -

"The neuroendocrine response to trauma appears to have evolved to assist survival in a more primitive environment by providing appropriate substrates to maintain vital functions. However in modern anaesthetic and surgical practice, where severe physiological disturbances are prevented or rapidly treated with prompt administration of suitable substrates, any benefits of this response are no longer apparent."
These are only few from the galaxy consisting, among others, celebrities like S.P. Allison (1969), L.H. Cooperman (1970), R.S.J. Clarke (1970), T. Oyama & T. Takazawa (1970), R.G. Merin (1971), N. Yoshimura (1971), A. Makelainen (1974), G.R. Gode (1977), K. Pandey (1977, 82) and N. Bose (1981) — who have differed on some particular topic at one time or other. One is left really amused and aghast to see these professional stalwarts expressing such diabolically different opinions on same subject.

There is an ancient Chinese proverb that whenever there exists some doubt, it is always better to confirm the things by doing a lot of legwork and a bit of brainwork.

So, with this objective being the motive force; this observer, in all his humbleness, undertook the present study.

The cellular metabolic response to illness, injury and infection is dependent upon the available fuel sources and their utilization (Blackburn et al, 1973; Clowes et al, 1974). The metabolic events occurring immediately after injury (upto 48 hours) are dominated by local and systemic effects of hormones, particularly catecholamines (Clowes, 1976; Wilmore et al, 1976). Catecholamines promote calorogenesis, glycogenolysis and lipolysis. Simultaneously insulin activity is suppressed. Insulin plays a key role in regulating energy metabolism by increasing the rate of glucose utilization and controlling the rate of FFA release from adipose tissue. It lowers cAMP level in adipose tissue and has a direct antagonist action on lipase activity (Sutherland et al, 1968). Concomitant release of growth hormone, glucagon and glucocorticoids also inhibit activity of insulin.
The overall objective of these changes is to maintain the body cell mass as constant as possible and also maintenance of proper ATP : ADP ratios and NAD : NADH oxidation : reduction states (Blackburn, 1977).

The anaesthetic hyperglycemia and hyperlipemia are mainly results of excessive hepatic glycogenolysis and adipose tissue lipolysis brought about by sympathoadrenal stimulation. The extent of this response will, therefore, vary with the sympathomimetic activity of the anaesthetic agent used. Hence the present work aims to observe the effects of inhalational agents on carbohydrate and lipid metabolism by studying changes in blood sugar and FFA.

Coming to the present series of study, the 90 patients studied by us, were divided into 3 groups (I, II & III) of 30 each according to the anaesthetic agent given (table - 1). An equal number of patients in each group eliminated the possible numerical superiority of one group over the other.

Furthermore in each group itself, the ratio of male : female patients was kept approximately 3 : 2 (table - 1). This obviated the need to take into consideration, the sex-dependent difference (if any), in response to anaesthesia and/or surgery.

Likewise no obese or emaciated person was included in the present study (table - 2; fig - 13), as the nutritional status is known to significantly affect the blood glucose and FFA level (Owen et al, 1967; Newsholme, 1977; Hansen and Parsons, 1978; Stanley, 1981).

The present study showed nearly similar weights for males
(50.54 - 52.29 kg.) and for females (42.33 - 45.64 kg.) in the three
groups. This obviated the influence of nutritional status on metabolism
(table - 2; fig - 13).

As previous trauma, injury or infection result in significant
alterations in the hormonal and metabolic status of the patients
Stanley, 1981), care was exercised to include only those patients in
the present study who qualified for ASA physical status I or II
(i.e. who were in good health and were likely to have a minimal
pre-existing metabolic derangement) as shown in table - 3, fig - 14.

As a further precaution, almost an equal number of patients
belonging either to ASA I or ASA II were included in all the 3 groups
(i.e. 20/10, 19/11 and 19/11) and the ratio between cases of ASA I
and those of ASA II was approximately 2 : 1 in all the groups (table -3;
fig - 14). This meant that previous trauma or injury will not unduly
affect any particular group.

Various workers have attempted different modus operandi in
an attempt to study the effect of surgery on blood sugar and FFA.
Either they included patients undergoing variable surgery i.e. body
surface ——, thoracic ——, limb —— or intraabdominal surgery
(Cooperman, 1970; Clarke, 1970; Clarke et al, 1970; Dev et al, 1977;
Singh et al, 1977; Bose and Biswas, 1981) or they fixed this variable
i.e. they chose only some particular type of surgery during their study
(Sharma, Basu & Pandey, 1977; Gupta, Jain & Pandey, 1982).

In our series, to eliminate the significant difference between
the extent of metabolic response seen during different types of surgery,
the distribution of different operations was kept nearly uniform
(table - 4) but unforeseen technical problems beyond reasonable control of this observer, sometimes made the task rather difficult.

It is a well-known entity that the extent of metabolic and hormonal response is directly proportionate to the severity of injury or operative trauma (Annamunthodo, 1968; Singhal et al, 1979; 1982; Stanley, 1981). The severity of trauma depends, among other factors, on the duration of operation. Oyama et al (1971) found that an exposure of less than 60 minutes is also associated with metabolic and hormonal changes.

Thus in order to avoid and obviate any fallacious results, the mean operative duration (from skin to skin) was kept nearly identical (i.e. 58.50 - 64.30 minutes) for all the three groups (table - 5; fig - 15). This made possible a comparison to be carried out between the various groups for the comparable samples obtained during operative procedure itself (tables - 7, 10, 12 & 15; figs - 17, 18, 20 & 21). It further made possible a comparison between the changes caused by anaesthesia alone and changes caused by surgery with anaesthesia, because with drawal of samples was up to 45 minutes during both procedures (tables - 10 & 15; figs - 18 & 21).

During anaesthesia and surgery, there are several other factors operating beside the anaesthetic agent, which lead to sympathoadrenal stimulation. Among these are hypoxia (Johnstone, 1949), hypercarbia, hypotension (Wright, 1970) and handling of viscera (Dixit, 1972). In addition to these, pre-operative anxiety and emotional stress in patients awaiting surgery have been held responsible for rise in blood sugar and FFA levels (Allison, Tomlin and Chamberlain, 1969).
Merin et al, 1971; Gupta, Jain & Pandey, 1982). Excitement of induction and vasopressors given during the operation also play some role. All these factors may contribute to the stimulation of sympatoadrenal system resulting in the release of catecholamines and mobilization of glycogen from liver and FFA from adipose tissue.

Sedative premedicants, therefore, suppress this response which is mediated through the hypothalamus (Sharma, Basu & Pandey, 1977; Gupta, Jain & Pandey, 1982).

In order to achieve these objectives, every patient was carefully told about the anaesthetic and the operative procedure, properly assured and given lorazepam 2 - 4 mg. orally in the night preceding the operation.

Our primary aim was to obtain the basal values of blood glucose and FFA (when the patient was comparatively stabilized and free from anxiety or fear). These basal values were required to serve as the control, with which the subsequent samples were to be compared statistically (tables - 8 & 13).

Various workers have used samples taken many hours before operation (Sharma, Basu & Pandey, 1977; Bose and Biswas, 1981) or after adequate sedation (Cooperman, 1970; Clarke, 1970; Dev et al, 1977; Singh et al, 1977) as the control. Some other workers (Paul and Bhattacharya, 1977) have also used sample values obtained from some normal person and compared them with those of the patients. This last method suffered from the obvious disadvantage that values of a normal person are hardly comparable with those of another person (i.e. patients).

The control values for blood sugar in the present series
were 76.90 ± 10.83; 76.80 ± 11.38 and 71.23 ± 10.49 mg/dl. for the ether, trilene and halothane groups respectively (table - 6; fig- 16). These values are in accordance with those obtained by Basu et al. (1977), Singh et al (1977), Sharma et al (1977), Singhal et al (1979) and Gupta et al (1982); but differ from those obtained by Clarke (1970), Clarke et al (1970) and Cooperman (1970).

The control values for plasma FFA in the present series were 0.616 ± 0.095, 0.600 ± 0.079 and 0.632 ± 0.098 mEq/litre for the ether, trilene and halothane groups respectively (table - 11; fig - 19). In other words, values were nearly identical for all groups.

These values are in accordance with those obtained by Cooperman (1970) and Bose et al (1981); but differ from those of Clarke et al (1970), Sharma, Basu and Pandey (1977), Singhal et al (1979) and Gupta et al (1982).

One possible explanation for the difference in these values may be that, some of the workers (Cooperman, 1970; Clarke, 1970 and Clarke et al, 1970) have studied white coloured population in western countries and thus some racial or geographical factor may be operative.

The other attractive possible reasons may be fluctuations in the emotional status of patient (anxiety and apprehension leading to increased sympathoadrenal activity), the time of obtaining samples, duration of starvation, type of premedication given or the difference in techniques employed for estimation of blood sugar or plasma FFA (Cooperman, 1970; Clarke, 1970; Dev et al, 1977; Sharma et al, 1977; Singhal et al, 1979; 1982; Gupta et al, 1982).

The procedure of intubation is known to be most stormy one during anaesthesia (Singhal et al, 1982) and is associated with
considerable metabolic and hormonal changes; catecholamine level suddenly rises markedly and the occurrence of cardiac dysrhythmia is most common.

In the present series, intubation caused significant \( P < 0.01 \) increase of 6.14 - 8.20 mg./dl. over control values in blood sugar in a very short period of 5 minutes. This increase was nearly uniform (8.07% - 10.66%) over the control irrespective of the anesthetic agent used (table - 8; fig - 18).


The corresponding values for plasma FFA during intubation recorded a significant increase \( P < 0.01 \), but for ether \( P < 0.001 \) of 0.062 - 0.104 mEq/litre in the same period of 5 minutes. This increase was to the tune of 33.66% - 50.00% over the control regardless of the anesthetic agent given (table - 13; fig - 21).

These findings are in complete unison with those recorded by Clarke et al (1970), Sharma et al (1977), Bose and Biswas (1981) and Gupta et al (1982); but differ from those of Cooperman (1970) and Singhal et al (1979).

Possible explanation for these differences may be due to different premedications (quininebarbitone by Cooperman, 1970) and different methods of estimation (Duncombe's method, 1963 used by Singhal et al, 1979 and Trout's modification of Dale's method, 1960 used by Cooperman, 1970) as compared to oral lormazepam over night and Millian Novakh's technique, 1956 in the present series.

Griffiths (1953) and Annam Mathoda (1958) attributed the
hyerglycemia caused by ether anaesthesia to direct action of the anaesthetic on liver leading to glycogenolysis. Increased sympathoadrenal activity results in significant rise in the level of plasma adrenaline and noradrenaline both (Elliot et al, 1968; Black et al, 1969; Singhal et al, 1982).

Also ether is one of the strongest stimulants of adrenocortical activity (Vandam & Moore, 1960) in an exposure of less than 60 minutes (Oyama et al, 1971) leading to a resistance against insulin. It also interferes with the cellular metabolic processes (Cohen et al, 1972).

All these processes result in marked hyperglycemia (Brewster et al, 1952; Cullingford, 1956; Oyama et al, 1971) and acting via cAMP-dependent lipase-system (Sutherland et al, 1968), to increased lipolysis and marked rise in plasma FFA level (Henneman et al, 1961; Oyama et al, 1971; Singhal et al, 1979).

Trichloroethylene, on the other hand, raises the plasma levels of the catecholamines (Dixit, 1972; Lakshmi et al, 1973; Dev et al, 1977; Singh et al, 1977) and thereby enhances mobilization of tissue glycogen and triglycerides leading to hyperglycemia (Krantz and Carr, 1965; Dixit, 1972). Olson and Spencer (1968) observed that this agent also interferes with cellular metabolic processes and this may further contribute to the already raised levels of blood sugar and plasma FFA.

Halothane, not to be outdone and outsmarted, strives hard to produce a small rise in plasma catecholamines (Black et al, 1962; Elliot et al, 1968; Singhal et al, 1982). It also inhibits the glycolytic enzymes (Schweizer et al, 1959) and cellular uptake of
glucose (Green, 1965; Ngai, 1972), depresses FFA uptake by the myocardium (Merin et al., 1969) and suppresses activity of insulin (Aynsley-Green et al., 1973). Makelainen (1974) observed an increase in catecholamines level leading to increased mobilization of hepatic glycogen and adipose tissue triglycerides with resultant elevation in blood sugar (Allison et al., 1969; Merin et al., 1971; Oyama et al., 1971; Lakshmi et al., 1973; Makelainen, 1974 and Gupta et al., 1982) and in plasma FFA (Cooperman, 1970; Merin et al., 1971; Makelainen, 1974; Gupta et al., 1982).

Thus we can see that there are some common factors with all the three inhalational agents used, which lead to increased level of blood sugar and plasma FFA. These are:

1. Only partial (and not complete) suppression of afferent stimuli like pain etc., going to cerebral cortex and hypothalamo-mesencephalic complex even during deep anaesthesia.

2. Stimulation of beta-adrenergic receptors leading to variable but definite increase in the levels of plasma catecholamines in an attempt to offset the depressant effects of anaesthetic agent (Black et al., 1969).

(N.B. - The body metabolic mechanisms are so sensitive that even a very small increase in plasma catecholamine levels results in a far greater mobilization of glycogen and triglycerides according to Rube Goldberg sequence).

3. Abolition of powerful antidiabetogenic and antilipolytic effects of insulin (the activity of which is suppressed to a variable extent).
4. Un-restrained activity of glucagon and cortisol etc.

5. Interference with the cellular metabolic processes
(glycolysis, oxidative phosphorylation, electron transfer etc.).

In our study, anaesthesia with ether (in absence of surgery) showed a pattern of constant rise at various time intervals and the quanta of increases were highly significant \( (P < 0.001) \) for both blood sugar and plasma FFA (tables - 7, 8, 12 & 13; figs - 17 & 20).

Halothane and trilene also followed the same pattern, though on a much smaller scale. But they did show a similar trend of constant rise at subsequent time intervals and these raised values were highly significant \( (P < 0.001) \) for both blood sugar and plasma FFA (tables - 7, 8, 12 & 13; figs - 17 & 20).

Similar findings were noted by the various workers as mentioned earlier.

An interesting feature to emerge during the present study was that (because intubation causes nearly similar quanta of increase in blood sugar and plasma FFA in all types of general anaesthesia — inhalational, muscle relaxants or neuroleptanaesthesia etc.) if we deduct the change caused by intubation procedure from the total change caused by anaesthesia alone, then the change caused by anaesthesia (minus intubation) were far too less (7.20 - 12.60mg./dl. for blood sugar; 0.072 - 0.205 mEq/litre for plasma FFA) as compared to that caused by anaesthesia with surgery (23.10 - 28.73 mg./dl. for blood sugar; 0.447 - 0.516 mEq/litre for plasma FFA) for all the three agents (tables - 9, 10, 14 & 15; figs - 18 & 21).

Possible explanations for this may be that once the stormy period of intubation is over (and provided that hypoxia, hypercarbia
& too light or too deep a plane of anaesthesia are avoided) there are hardly any stimuli to result in an alarm reaction (as depicted in fig - 4) to result in excessive mobilization of glycogen or adipose triglycerides and consequently there are little changes during anaesthesia (beyond intubation).

The total changes caused by anaesthesia without surgery were; in ether series (20.80 mg./dl. for blood sugar; 0.309 mEq/litre for plasma FFA), in trilene series (13.40 mg./dl. for blood sugar; 0.177 mEq/litre for plasma FFA) and in halothane series (14.17 mg./dl. for blood sugar; 0.144 mEq/litre for plasma FFA) as shown in tables - 10 & 15 and figs - 18 & 21.

All these changes were highly significant (P < 0.001) for all the three agents, although the 't' values showed fluctuations (4.25 - 5.33 for blood sugar; 4.81 - 10.54 for plasma FFA) (tables - 10 and 15).

As is apparent from careful perusal of above data, the maximum changes were seen with ether anaesthesia in both blood sugar and plasma FFA while trilene and halothane caused more or less similar changes in both these parameters.

The possible explanation is that there are some common factors operating during any type of general anaesthesia (as mentioned earlier) and they cause a certain amount of mandatory increase. But besides these, the most important factors for producing metabolic changes are the degree of sympathomimetic activity of the agent used & the capacity of that agent to suppress the activity of insulin. Ether is the most potent inhalational agent causing sympathetic stimulation and some degree of insulin suppression (Singhal, et al, 1979; Singhal et al, 1982).
Trilene is associated with remarkable cardiovascular stability (Kohli, Punnoose, Srihari & Gode, 1977) and some vagal stimulation (Holmes et al, 1952; Prior et al, 1965), thus implying that sympathomimetic activity is not much with this agent.

Halothane on the other hand, associated with some degree of central autonomic paresis & ganglionic blockade, nevertheless does cause some sympathomimetic activity (Singhal et al, 1982).

Thus the nearly similar but smaller changes caused by trilene and halothane as compared to ether in the present study are easily accounted for.

Anaesthesia with surgery, on the other hand, is associated with marked degree of sympathomimetic activity (Clarke et al, 1970; Halter et al, 1977; Nistrup Madsen et al, 1976; 1978; Engquist et al, 1980; Clutter et al, 1980) and increased activity of catabolic hormone glucagon in presence of decreased activity of key anabolic hormone insulin (Stanley, 1981), handling of vital organs (Dixit, 1972) and only partial suppression of pain stimuli even in deep anaesthesia.

Thus, when all these factors combine together to tear apart the citadel of metabolic integrity, it is no wonder that the results are simply devastating.

Therefore it is hardly surprising to see that in our study, surgery with anaesthesia, accounted for much greater changes

(23.10 - 28.73 mg/dl for blood sugar; 0.447 - 0.516 mEq/litre for plasma FFA) which were nearly uniform for all the agents

('t' value = 5.93 - 6.72 for blood sugar and 7.89 - 10.36 for plasma FFA) and were highly significant (P < 0.001) in all the three groups (tables - 10 & 15; figs - 18 & 21).
These observations are in excellent harmony with those of Clarke (1970), Clarke et al (1970), Singh et al (1977), Sharma et al (1977), Singhal et al (1979), Bose and Biswas (1981) and Gupta, Jain & Pandey (1982). These findings are understandable and can be easily accounted for, on the strength of the foregoing texts.

If we arrange the three agents in a descending order according to their capacity to cause changes, then the sequence for blood sugar becomes :-

I. Ether  II. Halothane  III. Trichloroethylene;

while that for plasma FFA becomes :-

I. Ether  II. Trichloroethylene  III. Halothane.

As a fitting finale to the whole show, J.C. Stanley (1981) walked away with an Oscar award for his splendid epilogue :-

"Di-ethyl ether is unique among the inhalational agents in causing a liberation of glucogenic hormones other than catecholamines, as well as raising the blood sugar, in producing lactic acidosis and in failing to lower the elevated FFA level."