DISCUSSION
Suaxamethonium sensitivity is not a disaster but it can be quite inconvenient. If patients' cholinesterase status is known preoperatively, adequate precautions can be taken before hand.

It has been pointed out that atypical cholinesterase is the main cause of prolonged apnoea (editorial, Lancet, 1973). For the genetically normal cholinesterase Evans et al. (1952), Argent et al. (1955) and Vickers (1963) have shown that a substantial quantitative reduction of enzyme must occur before any significant prolongation of the apnoea takes place. Bourne et al. (1952), in their study of 546 cases noted the presence of lower serum cholinesterase levels in persons having delayed recovery after suxamethonium:

\[
\begin{align*}
\text{Delayed recovery} & \quad 38.3 \pm 6.8 \text{ units/ml.} \\
\text{Normal recovery} & \quad 88.5 \pm 6.9 \text{ units/ml.}
\end{align*}
\]

Mean \pm Standard Error (units of Callaway et al.)

Vickers (1963) stated that a less than 25 % enzyme activity was required to produce a significant prolongation of the apnoea; a level of less than 50 % has been stated as necessary by Whittaker (1980). Lievre (1980) is of the opinion that a low cholinesterase level is not an infallible indicator of complications due to prolonged apnoea.

In contrast, Kalow and Gunn (1957) had found the logarithmic relationship between dose and response to be linear
with normal distribution of the logarithms of the dose required to produce a standard effect and the logarithms of the duration of apnoea after standard doses. In agreement to this King and McQueen, in a guest discussion in an article by McLaren and Moffit (1976), state that as a generalisation, the lower the cholinesterase activity and the dibucaine number and fluoride number of a patient, the more prolonged is the response to succinylcholine. They have also explained the reason behind the failure of consistency of this relationship as being technically incorrect estimations.

Keeping these factors in mind, one of the aims of the present study was to try an establish, if possible, a relationship between serum cholinesterase levels and the duration of post-suxamethonium apnoea in the local population. On calculating the correlation coefficient between these two factors in patients of the normal genotype, it has been found that, \( r_1 = -0.4766392 \), obtained for them indicated that a limited degree of negative correlation exist between cholinesterase and the duration of apnoea in this study. Thus, as a generalisation, when cholinesterase value dropped, the duration of apnoea increased and vice-versa (Fig. 8).

A similar correlation was studied between dibucaine numbers and fluoride numbers with the duration of apnoea. For dibucaine number vs. duration, \( r_2 = -0.7152 \) was obtained. This suggested a stronger negative correlation with duration than that of cholinesterase activity (Fig. 10).
Fluoride number was also found to be negatively correlated to duration of action of suxamethonium (Fig. 11), implying an increase of apnoea in response to a fall in fluoride number \( r_j = -0.6358 \).

Thus although a generalised relationship between quantitative reductions of cholinesterase activity and the duration of action of suxamethonium in normal individuals has been demonstrated, it is of importance to note that of the four cases in the study who had an apnoea of over 10 minutes (Fig. 13), 3 (75\%) were of abnormal genotypes (two \( E^u_1 E^a_1 \) and one \( E^a_1 E^u_1 \)). The single normal homozygote \( E^u_1 E^u_1 \) having an apnoea over 10 minutes had an enzyme level of 30.0 units by the Steinitz et al. method – thus showing a 61.46\% reduction of its level as compared with the control group.

Thus although prolongation of apnoea is found to be generally associated with low cholinesterase levels, of the 4 cases having pronounced prolongation 3 had abnormal genotypes and the 4th a normal genotype had greater than 50\% quantitative reduction of enzyme. This is in accordance with Evans et al (1952), Argent et al. (1955), Vickers (1963) and Whittaker (1980).

The second aim of this study was to investigate the possible presence of any regional bias regarding cholinesterase levels and the incidence of atypical, fluoride resistant and silent genes, with a view of establishing an existing relationship
if any, with religious status.

Studies have indicated a probable absence of \( E_1^a \) gene in Japanese, Eskimos, South American Indians and a rare presence in Negroes, Australian aborigines, Filipinos and oriental populations other than Japanese (Lubin et al., 1971), and the absence of \( E_1^a \) gene in Zimbabwe - Rhodesia Africans (Whittaker et al. 1976).

A high incidence of the silent allele in the Alaskan Eskimos and some Caucasian South Africans was noticed and to this list were later added the Vsyas of Andhra Pradesh (Rao, 1979). The discovery of the presence of such ethnic groups in other places prompted an investigation into the genotype characteristics of Bundelkhand Region.

The incidence of \( E_1^s \) gene observed in the study was zero. This however may be a fallacious conclusion since though it is to recognise the \( E_1^s \) homozygote due to little or no enzymic activity, the detection of the \( E_1^s \) heterozygote through simple laboratory estimations is not so simple (Whittaker, 1980). Thus it is quite possible that some heterozygotes for the usual and silent genes may have been missed in this study.

The maximum number of cases in the present project were usual homozygotes \( (E_1^u E_1^u) \). These were 91.40 % in number. The heterozygotes \( E_1^u E_1^a \) were 5.38 % and \( E_1^u E_1^f \) were 2.15 %. There was one (1.08 %) atypical homozygote in the study (Fig. 12). An attempt to compare these incidences with these reported by
workers such as Viby - Mogensen et al. (1978) is not correct since the latter report was a patient showing prolonged suxamethonium apnoea while the patients induced here are from a study population which was not limited to ones showing suxamethonium sensitivity only.

Out of the 8 genetically abnormal patients, 7 (87.5%) were Hindus and 1 (12.5%) was a Muslim. The preponderance of Hindus among patients of abnormal genotypes can be explained by the 10.63 : 1 Hindu preponderance present in the whole study population. These 8 cases were not related to each other and belonged to different areas of Bundelkhand.

**Individual Cases presenting with prolonged apnoea**

**Case No. 3**:  
This was a sturdy 60 kg. male aged 35 years. He underwent surgical toilet and debridement of a wound caused by an accidental injury. On examination he was found to be a healthy person. There was no personal or family history of any operation or illness.

After a 75 mg. intravenous dose of suxamethonium he was intubated. Apnoea persisted for a period of 35 minutes during which time he was well ventilated with oxygen and nitrous oxide. Thereafter, small flickering movements appeared in the reservoir bag.

A preoperative blood sample yielded the following data after estimation. Serum cholinesterase activity of 50.5 Steinitz units/ml.; D.N. = 49; F.N. = 44. Suggested genotype: $E_u^1E_1^a$.  

On further enquiries and verification it was learnt that he had received an i.m. injection of 100 mg. Pethidine along with 25 mg. promethazine 2 hours ago in the emergency department. Central respiratory depression as a contributory factor to apnoea is a possibility with this case.

Case No. 24:

A well built 61 kg. Muslim male aged 35 years who underwent a gastrojejunostomy. His blood sugar, urea, Hb., T.L.C., D.L.C. and urine investigations were all within normal limits.

He displayed a 40 minutes suxamethonium apnoea after 75 mg. i.v. suxamethonium.

Serum cholinesterase value of 27.2 units/ml. were seen. D.N. 18 and F.N. 30 establish that this case was an atypical homozygote.

An earlier exploratory laparotomy under G.A. 7 years ago was uneventful. It could not be determined whether suxamethonium was used or not. There was no family history of any operations.

Case No. 66:

A 22 years Hindu female who underwent resuturing of a burst abdomen 13 days after a Caesarean section. She was 56 kg. in weight, had a moderate degree of anaemia and was of poor general condition. Her serum cholinesterase level (30.0 units/ml.) was the lowest seen in any of the normal homozygotes studies which she was ( D.N. 75; F.N. 68 ).
After a 60 mg. i.v. dose of suxamethonium, apnoea lasted 15 minutes. No other factor known to cause prolongation of apnoea such as hyperventilation was present. During her Caesarean section 13 days before she was administered suxamethonium (75 mg. i.v.). She had an apnoea of 11.5 minutes. No cholinesterase estimations were done then.

It is suggested that prolonged apnoea in this case was a result of a nearly 62% reduction in enzyme levels due to the preexisting anaemia, shock and the post-partum period.

Case No. 93:

A 25 years old 46 kg. Hindu lady in poor general condition and with severe anaemia. She received 50 mg. i.v. suxamethonium during a hysterotomy and ligation. Apnoea lasted for 25 minutes. Her serum cholinesterase activity was 36.2 units/ml.; D.N. was 59 and F.N. 42.

One of the greatest difficulty in any study of the enzyme serum cholinesterase is the virtual inability to compare the results those obtained by with any other method due to different reaction conditions (Bowers and McComb, 1970; Wetstone and La Motta, 1965; Michel, 1961). It is therefore necessary to compare results on a relative basis (Michel, 1961).

It was demonstrated by Milhorat, 1938 that low enzyme levels were present in cases of malnutrition and anaemia. These findings were supported by the work of Faber, (1943) and Vorhaus and Kark (1953) for malnutrition cases and by Scudamore et al.
(1951) and Sawitsky (1949) for chronic anaemias. In the present study too, low levels of enzyme activity have been obtained for the anaemia and malnutrition cases. Barclay (1973) obtained a high incidence (83%) of low serum cholinesterase levels in study of 302 cases of malnutrition. In the present study, the mean enzyme level for the anaemia and malnutrition cases is the lowest for any of the disease groups studies.

It is worth noting here that the presence of sub-clinical liver dysfunction or occult biliary disease is widely acknowledged (Isselbacher, 1980). A variety of conditions such as anaemias long standing malnutrition, congestive cardiac failure and infective hepatitis may result in a symptomatic liver dysfunction and may thus reflect on the serum cholinesterase levels in spite of the absence of any overt hepatic or biliary disorder.

A mean cholinesterase level of 57.77 units/ml. was obtained in cases of pregnancy in the present study. This reduction of the enzyme level from the normal healthy non-pregnant adult was of the order of 25.78%. This is closely comparable to the values of the reductions of enzyme activity observed during pregnancy which are 18% (Robertson, 1966); 21% (Hazel, 1955); 25% (Levine and Hoyt, 1949); 28% (Schnider, 1965) and 30% (Redderson, 1973). It is in contrast to the findings of Mall and Lucas (1937) and Meade and Rosalski (1963) both of whom found no change in enzyme activity during
pregnancy and early puerperium.

In early post-partum cases a reduction of 32 % in the normal enzyme levels on the third day of puerperium was noted by Hazel and Monier (1971). A figure of 33 % reduction was observed by Whittaker (1980) in Blitt et al's' (1977) study on the third post-partum day.

All the cases in the post-partum group underwent serum cholinesterase estimations on the third day of puerperium. A value showing 34.80 % reduction from the non-pregnant adult activity was noticed. This compared closely with the trends observed by Hazel and Monier (1971) and Blitt et al. (1977).

A higher incidence of prolonged apnoea in heterozygotes was seen for the pregnancy group (50 %) as compared with the non-pregnant healthy adult (0 %) this can be explained by Whittakers' (1980) opinion that a higher incidence of prolonged apnoea in heterozygotes is seen in pregnant individuals as compared to healthy non-pregnant adults. This is due to the low enzyme characteristics of heterozygotes.

When seen in the control group, where no other factor was present to affect the serum cholinesterase levels none of the 2 heterozygotes (one of E1^u E1^a type) showed an apnoea above 10 minutes. Kalow and Gunn (1957) had also observed that a heterozygote for a typical serum cholinesterase does not have greatly prolonged responses to succinylcholine.
In the dehydration group was encountered the longest mean duration of apnoea (9.22 minutes). Contributing towards this was a 35 minutes apnoea in a case heterozygous for the usual and atypical cholinesterase. Never the less, mean cholinesterase level of this group a patients was lower by a highly significant degree from the control group.

Mean cholinesterase levels of the pregnancy, post-partum, malignancy, liver and biliary disease, anaemia and malnutrition groups were all reduced by highly significant degrees from the mean level of control cases. This is in agreement with findings of most workers.

Reduced enzyme levels for liver diseases were observed by Jones and Stadie (1939); McArdle (1940); Foldes (1940); Lehmann et al. (1962) and Hunter (1966). Lehmann et al. (1962) found a level of 8 - 59 units/ml. (as compared to a normal level of 60 - 120 units/ml.). Hunter (1966) found a mean enzyme activity of 86 units in the cases with liver and biliary diseases while Foldes (1940) found a mean level of 59 ± 9.5 units/ml. and Jones and Stadie (1939) found a mean level of 41 units/ml. in advanced Tuberculosis and carcinoma. They attributed it to temporary injury to liver. This study shows a drop of enzyme activity in the liver disease group, but not to the extent found by Lehmann et al. (1962).

This was probably due to absence of cases with true parenchymal damage to the liver. The cases of this group in the present study were of chronic cholecystitis predominantly.
Malignancy cases presented a range of enzyme activity from 40.6 - 69.9 units/ml. There was a lowered activity in malignancy cases studied by Jones and Stadie (1939) and Mc Ardle (1940). No evidence of hepatic metastases was seen in any of the cases in this study. Hepatic metastases had been associated with a still greater drop of enzyme activity as observed by Kaniaris et al. (1979); Ghooi et al. (1980). Wetstone et al. (1960) had suggested the reason for the drop in enzyme activity to be due to the carcinomatous tissue itself which perhaps was thought to be responsible for production of a serum cholinesterase inhibitor (Kaniaris et al., 1979).

As regards the changes in mean cholinesterase activity with the age it was noticed in present study that slightly higher levels are present in children. A fall in activity of the enzyme occurred around puberty and was maintained till 50 years of age after which a subsequent rise to still higher levels was seen in the age groups (51 - 60) years and (61 - 70) years. The significance of this increase in later years was doubtful since the two groups comprised of 2 and 1 individuals only. Results of present study are comparable to the work of McCance et al. (1949) who noticed a dramatic rise of the cholinesterase levels in the early childhood. Dabew (1970) found a 30% increase in the activity of enzyme in 3 to 6 year old children followed by a gradual fall to the adult level by puberty. In the oldest two groups the rise of enzyme activity is in contrast to the
observations of Kalow and Gunn (1959) and in agreement to those of Propert and Brackenridge (1976). The values for children in this study (mean age of 11.12 years) was found to be 3.64% higher than the controls.

In cases of obesity, high serum enzyme level was noted by Bery et al. (1954) in study of 354 cases. Thompson and Trounce (1956) also held the obesity present in patients of diabetes to be the cause of reduction of cholinesterase activity in such cases. The present study shows the highest mean cholinesterase level present for any of the groups studied (106.95 units/ml.) have observed. It has also been noticed here that cases of thyroid disorder too had an increased mean cholinesterase level but difference from the controls was not significant. However, one patient (case No. 53) had higher enzyme levels and displayed signs of mild thyrotoxicosis. Although in some of the mental disorders like anxiety and depressive states and schizophrenia (Tod and Jones, 1937; Antebi and King, 1962 and Propert, 1979) higher levels of the esterase were found. The higher activity seen in the present study is not significantly different from the control group.

No influence of residential status or diet was seen on the enzyme levels in this study. The alcohol users had slightly higher levels. Alcoholism has been shown to be associated with higher levels of cholinesterase (Vaccarezza and Peltz, 1960).
A non-significant increase of cholinesterase in the adult males as compared with the non-pregnant adult females was seen to be present (Ralph and Gunn, 1955; Wetstone and La Motta, 1965 and Propert and Brackett, 1976). These reports are in conformity with the present study. However, the findings are in contrast to Hall and Lucas (1937); Callaway et al. (1951) and Vorhau and Kark (1953). The present study shows a clear trimodal distribution of the population when the cases were grouped according to diencephalic number. Three distinct genotypes were seen in separate groups (Fig. 14). Our findings regarding the trimodal distribution of the population are in agreement with Whittaker (1950).

An increased mean enzyme level was observed in the routine cases as compared to the emergency cases. However, it was insignificant. In various dietary groups studied, no significant variations of serum cholinesterase were noticed. This is in agreement with the findings of Kaufman (1954).
Fig. 14 - SHOWING CLEAR TRIMODAL DISTRIBUTION INTO THREE DISTINCT GENOTYPES WHEN CASES WERE GROUPED ACCORDING TO DIBUCAININE NUMBER.