REVIEW OF LITERATURE
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Suxamethonium enjoys an enviable position among the drugs used in modern anaesthesia practice. It is used to produce muscle relaxation of short duration during anaesthesia.

Suxamethonium is the dicholine ester of succinic acid. It is a synthetic bis-quaternary ammonium compound with a melting point of 150°C. A white crystalline substance, it is unstable if warmed or in an alkaline solution.

\[
\begin{align*}
\text{CH}_3 & \quad + \\
\text{CH}_2 - & \quad \text{N-CH}_2 - \text{CH}_2 - \text{OOC-CH}_2 - \text{CH}_2 - \text{COO-CH}_2 - \text{CH}_2 - \text{N} - \text{CH}_3 \\
\text{CH}_3 & \quad + \\
\text{cl}^{-} & \quad \text{cl}^{-}
\end{align*}
\]

Suxamethonium chloride.

History:

The pharmacological properties of suxamethonium were first described by Reid Hunt and Taveau (1906). Its rapid hydrolysis by cholinesterase in the horse serum was demonstrated by Glick (1941).

The neuromuscular blocking properties of this drug were however first described by both Bovet et al. (1949) and Phillips (1949) separately. Demonstration of the breakdown of suxamethonium by cholinesterases and the inhibition of this hydrolysis by eserine was done by Bovet-Nitti (1949).
Animal experiments conducted by Castillo and de Beer (1950) confirmed these findings.

The first clinical use of suxamethonium was by Thesleff at the Karolinska Institute in Stockholm (1951), by Bucke et al. (1951) and Mayrhofer and Hassfurther (1951) in Austria.

**Normal Neuromuscular Transmission:**

Function of the neuromuscular junction is much better understood than its structure. The neuromuscular junction includes both the pre- and post-synaptic areas. The latter is also known as motor end-plate.

The myelinated motor nerve fibre divides into numerous non-myelinated terminal branches in the proximity of the muscle-fibres. Thereafter, these branches run parallel to the muscle fibre they supply, while lying embedded in a shallow "gutter" or depression in the muscle surface (Fig. 1).

At the myoneural junction the nerve-fibre is covered by a membrane-complex known as the Schwann, axoplasmic or perineural membrane - this separates the end-plate from the extracellular fluid. As shown in Fig. 2, these layers make regular folds, towards the muscle fibre lying close to and indenting the basement membrane of the latter. This region has a high concentration of cholinesterase. The folds described are called the junctional folds or secondary clefts.

Much of the basic information about the microanatomy
Fig. 1 – DIAGRAM OF NEUROMUSCULAR JUNCTION.

(a) Shows a small portion of the terminal axon branch N lying in a gutter formed by the surface of the muscle fibre M. The semicircular post-junctional folds are illustrated.

(c) Same in tangential section.

(b) Same in longitudinal section.
Fig. 2 - DIAGRAMMATIC REPRESENTATION OF THE NEUROMUSCULAR JUNCTION.
of the neuromuscular junction has been provided by the studies of Couteaux (1955 and 1958), Robertson (1956) and Waser (1970). It was suggested by Waser (1970) that these folds contain the sodium "pores", which allow the ionic flux, responsible for depolarization.

The narrow neck of each pore is guarded by two molecules of acetyl cholinesterase, each with two curare receptor sites. The acetyl choline receptors are scattered around the mouth of the pore. Depolarisation occurs when sufficient acetyl choline molecules combine with their receptors and cause a deformation of the surface, this pulls open the mouth of the pore, thus permitting sodium ions to pass inside the cell and result in depolarisation.

Non-depolarising drugs like curare act by combining with the active centres of the acetyl cholinesterase molecules - thus obstructing the neck of the pore.

The nature of the acetyl choline receptor is disputed. Mucopolysaccharides (Waser, 1970), phosphate (Nastuk, 1967) or a polypeptide or protein (Gill, 1965) have been suggested.

Dale et al. (1936) propounded the chemical theory of neuromuscular transmission according the which acetyl choline bridges the gap of 1 μm, between the motor nerve ending and the end-plate. This choline ester is synthesized and stored in the motor nerve ending in the form of vesicles containing quanta or packets of the substance. The vesicles have been
demonstrated in the region of nerve-ending by electron microscopy. On the arrival of an impulse the acetyl choline is released. (Feldman, S., in Wylie and Churchill-Davidson, A practice of Anaesthesia).

When sufficient molecules of the transmitter substance reach the end-plate, a threshold depolarisation results. This causes a wave of depolarisation or propagated action potential along the entire length of the muscle fibre with resulting mechanical contraction in its wake. The acetyl choline molecules excite the end-plate in the fraction of a millisecond before they are destroyed by cholinesterase within $1/500^{th}$ of a second (Feldman, S., in Wylie and Churchill-Davidson, A practice of Anaesthesia).

**Neuromuscular block caused by suxamethonium:**

A depolarising block is produced by suxamethonium. This is similar to the block caused by acetyl choline except for the greater extent and duration of the depolarisation. It was originally believed that this type of block was due to a lowering of the trans-membrane potential to a level which prevented initiation of the propagated action potential. Evidence towards this concept was advanced by Jenerick and Gerard (1953) and del Castillo and Katz (1956).

Katz and Thesleff (1957) discovered that loss of sensitivity of the membrane far exceeded the time for which it remained depolarised. This phase was termed by them as
the 'desensitisation phase' of depolarising neuromuscular block. Feldman and Tyrrell (1970) postulated that the determining factor as to whether a neuromuscular blocking drug acted as a depolarising or non-depolarising agent was whether or not it became bound to the receptor. A depolarising block is preceded by muscle fasciculations.

It has been demonstrated that prolonged administration of a depolarising drug (Jenden et al., 1951; Brennan, 1956) or its use in excessive doses produces a change in the nature of the neuromuscular block from a depolarising type to one with non-depolarising characteristics. Zaimis (1953) noted this in chicks and coined the term "dual block" for this phenomenon.

Zaimis et al. (1952) and Zaimis (1953) demonstrated the different responses to decamethonium in different species - a depolarising block was produced in some while others developed a block resembling a non-depolarising one. Churchill-Davidson and Richardson (1952) found electromyographically that an identical change in decamethonium activity occurred in patients of myasthenia gravis. Churchill-Davidson and Wise (1964) discovered that a similar block occurred in premature infants when depolarising drugs were administered to them. Churchill-Davidson et al. (1960) saw that this type of block could be produced on giving excessive doses of suxamethonium. It was found by Foldes et al. (1956), Argent et al.
(1955) and Brennan (1956) that this type of block could be reversed by neostigmine or edrophonium.

It is considered better to refer the block as occurring in two stages - Phase I, which is potentiated by anti-cholinesterase drugs and by tetanic stimulation and Phase II, which shows characteristics of a non-depolarising block. In the latter phase a significant, though at times short-lived, reversal occurs on administration of an anti-cholinesterase. Tetanic stimulation produces some degree of post-tetanic facilitation and tachyphylaxis is seen to further doses of the depolarising drug.

Feldman and Tyrrell (1970) were of the opinion that the molecules of the depolarising drug became bound to the receptors in an increasing proportion, thus producing a significant degree of receptor occupancy; this resulted in the development of a non-depolarising component to the neuromuscular block. Galindo (1971) proposed a pre-synaptic site of action of the depolarising drug to be responsible. Despite these explanations it must be stated here that the cause of the Phase II block is still not known.

**Duration of action of suxamethonium:**

A single injection of suxamethonium (50-75 mg.) produces, on an average, respiratory paralysis for 2-4 minutes (Evans et al., 1952). These workers also demonstrated the close correlation of the duration of action of suxamethonium with the serum cholinesterase levels in the individual. If a
period of apnoea exceeds 10 minutes in the absence of any other factor which might cause the prolongation of action, it should be considered an abnormal response. (Feldman, S., in Wylie and Churchill-Davidson, A practice of Anaesthesia).

Evans et al. (1953) established that by prior raising of the cholinesterase level artificially, it was possible to shorten the apnoea produced by subsequent doses of suxamethonium.

The enzyme preparation cholas, which was a concentrated human globulin containing cholinesterase, was effective only when it was given before or simultaneously with suxamethonium (Goedde et al., 1967). Clinical experiments to terminate a prolonged apnoea by intravenous infusion of concentrated cholinesterase were not successful.

The highly purified concentrated preparation of cholinesterase (Doenicke et al., 1968; Goedde and Atland, 1971) was successful in terminating a prolonged apnoea within 8 minutes after its intravenous injection. Doenicke et al., (1968) showed that with a relatively small dose of 30 mg. of this cholinesterase preparation, a shortening of the duration of apnoea following 50-200 mg. suxamethonium was obtained. After 50 mg. suxamethonium the apnoea could be entirely neutralised.

Suxamethonium dissociates rapidly from the end-plate receptors and diffuses back into the plasma where it is hydrolysed by the commercial cholinesterase infused. The upset equilibrium causes more dissociation of suxamethonium and
repetition of this process ultimately results in termination of the apnoea (Stovner and Stadsklev, 1976).

Doenicke et al. (1968) have shown serum cholinesterase inhibition due to suxamethonium itself. Their in vivo experiments demonstrated that this enzyme inhibition was directly related with the duration of apnoea. The emergence of the patient from suxamethonium apnoea occurred as soon as no further enzyme inhibition was measurable.

Detoxication and Excretion of suxamethonium:

Suxamethonium is well known for its short duration of action. The short duration is due to its rapid hydrolysis by the enzyme serum cholinesterase. This process occurs in two stages:

1st Stage:

\[
\begin{align*}
\text{Succinyldicholine} & \quad \text{(Rapid)} \\
\text{(Suxamethonium)} & \quad \text{Serum cholinesterase} \\
& \quad \text{Succinylmono-} + \text{choline} \\
& \quad \text{choline}
\end{align*}
\]

The hydrolysis commences within seconds of the entry of suxamethonium into plasma. It is so rapid and effective that less than 5% of the injected dose reaches the muscles in the periphery and less than 2% appears in the urine (Foldes and Norton, 1954). As has already been mentioned, as soon as the suxamethonium-induced depression of serum cholinesterase ends, spontaneous respiration returns (Doenicke et al., 1968).

2nd Stage:

\[
\begin{align*}
\text{Succinylmonocholine} & \quad \text{(Slow)} \\
& \quad \text{Specific liver enzymes} + \text{serum cholinesterase} \\
& \quad \text{Succinic acid} + \text{choline}
\end{align*}
\]
A specific enzyme for the hydrolysis of succinyl monocholine is present (Greenway and Quastel, 1955), though a minor role is undertaken by serum cholinesterase also. Succinylmonocholine has 1/20th to 1/80th the activity of suxamethonium. Foldes et al. (1954) demonstrated that 5-7 mg./kg. of succinylmonocholine produced good relaxation in the anaesthetised patient for 8-12 minutes. These findings were confirmed by Brennan (1956).

In the absence of serum cholinesterase, alkaline hydrolysis of suxamethonium can occur. Kalow (1959) found that less than 5 percent per hour of suxamethonium is thus destroyed. Normally this process plays a very minor role and less than 50% of the injected drug is broken down in 10 hours.

The other processes which may play an important role in the absence of enzymatic hydrolysis are redistribution and excretion. Uptake of suxamethonium at various receptor sites reduces the drug concentration in the plasma (redistribution). The normally low levels of the drug excreted in urine may increase to much higher amounts in the absence of enzymatic hydrolysis (Wylie and Churchill-Davidson, A practice of Anaesthesia, 1978).

**CHOLINESTERASE**

Cholinesterases are the enzymes which hydrolyse the choline esters into the corresponding acid and free choline.

It was observed in 1914 by Sir Henry Dale that acetyl choline had a potent and short-lived action. He
suggested that an esterase destroys this compound in the human body.

Stedman, Stedman and Esson (1932) called this enzyme 'cholinesterase' and showed that it was of a specific nature.

Several biochemical differences in the cholinesterases of the R.B.C. and the serum of man were noticed by Alles and Hawes (1940). These two forms of the enzyme were named true cholinesterase and pseudocholinesterase by Mendel and Rudney (1943).

**True Cholinesterase** - This enzyme, also known as the "specific" or "aceto" or "e-type" cholinesterase is present in the red blood cells, neuromuscular junction and the brain. The Enzyme Commission has termed this enzyme acetylcholine acetylhydrolase with a code number E.C.3.1.1.7. Its main function lies in hydrolysing acetyl choline rapidly. True cholinesterase also hydrolyses certain other choline esters such as beta-methyl-acetylecholine. It does not hydrolyse suxamethonium.

**Serum cholinesterase** - This enzyme is also known as "pseudocholinesterase" or "butyryl cholinesterase" or "non-specific cholinesterase" or "S-type cholinesterase". It has been found in the plasma, in most other tissues of the body like liver, kidney, intestine, pancreas etc. - but not in human erythrocytes. Its role shall be discussed later.
Nomenclature:

The modern name given to serum cholinesterase by the Enzyme Commission is acylcholine acylhydrolase (A.C.A.H.) with a code number E.C.3.1.1.8. (Dixon and Webb, 1974). The individual digits of this code-number express detailed information about the enzyme:

- 3 - stands for hydrolase (the general division).
- 1 - states the nature of bond hydrolysed -CHOH.
- 1 - means NADP (type of energy bond involved).
- 8 - denotes serial number of serum cholinesterase.

This classification also appears as such in the Enzyme Nomenclature Recommendations (1978).

The Second International meeting on Genetics in 1963 suggested some points regarding the terminology of cholinesterase. These were -

- E - denotes the gene for serum cholinesterase.

Subscript 1 stands for the first locus.

- $E^u_1$ - signifies gene responsible for formation of usual cholinesterase.

- $E^a_1$ - indicates the gene responsible for the formation of the atypical enzyme A.

- $E^s_1$ - implies the gene responsible for the absence of the enzyme (or as Whittaker, 1980 states - it denotes the gene responsible for an enzyme incapable of hydrolysing the cholinester bond).
E^f_1 - denotes the gene responsible for the fluoride-resistant enzyme.

Assuming there are four allelic genes, there are ten genotypes - E^u_1 E^u_1, E^a_1 E^a_1, E^s_1 E^s_1, E^f_1 E^f_1, E^u_1 E^a_1,
E^u_1 E^s_1, E^u_1 E^f_1, E^a_1 E^f_1, E^a_1 E^s_1, E^f_1 E^s_1.

**Site of Production:**

Serum cholinesterase, like albumin, is synthesized in the liver. Experiments on rats by Brauer and Root (1946) and by Ellis et al. (1947) demonstrated lowered serum cholinesterase following liver damage by carbon tetrachloride. This suggested that the enzyme was produced in the liver.

Experiment with carbon tetrachloride induced hepatic damage in dogs by Steensholt and Venndt (1945) had earlier showed a drop in serum albumin and rise of serum cholinesterase. Identical findings of an initial rise of the enzyme by Brauer and Root (1946) were attributed to outpouring of serum cholinesterase from liver during hepatic damage followed by a fall due to deficient production. These facts were brought out as early as 1946 in a compact from in the Transactions of the Fifth Conference on Liver Injury. Later work by Wescoe et al. (1947), Kaufman (1954) and Richterich (1961) proved beyond doubt that serum cholinesterase was produced in the liver. Histochemical evidence provided by Gurtner et al. (1963), further established that serum cholinesterase was produced only by functioning liver cells.
Physiological Role:

The physiological role of serum cholinesterase is still obscure. Lehmann and Silk (1953) suggest that it "protects" the "true" enzyme against many choline esters formed during metabolism which would otherwise inhibit the latter, by splitting them. Clitherow et al. (1963) agree with this theory. They propose that the main physiological function of serum cholinesterase may be to hydrolyze the butyryl-choline preferentially, so as to prevent its powerful nicotinic action, when it is produced during fatty acid degeneration. Thus Clitherow et al. (1963) suggest that serum cholinesterase is involved in lipid metabolism.

Others suggest that serum cholinesterase plays an essential role in transmission of slow nerve conduction processes (Bergmann and Wurzel, 1954), or that it functions in the removal of non-neurogenic acetyl choline, associated with spontaneous rhythmicity, and, at least in some animals, it is associated with the destruction of nervously-released acetyl choline also (Jamieson, 1963) which in supraoptimal concentration may inhibit the acetyl cholinesterase. Funnell and Oliver (1965) proposed that serum cholinesterase plays a regulatory role, in conjunction with choline acetylase in choline homeostasis in plasma.

In spite of intermittent proposals regarding role of the enzyme it must be clarified here that no unequivocal
role has yet been assigned to serum cholinesterase.

**Pharmacological Role:**

Evidence of the pharmacological role of serum cholinesterase in hydrolysing suxamethonium was obtained when Bovet-Nitti demonstrated this in 1949.

Serum cholinesterase can also hydrolyse a large number of other choline esters like benzoyl choline, phenylacetyl choline, Atrolacetyl choline, (Augustinsson, 1948) and some non-choline esters such as Tributyrin.

The local anaesthetic esters procaine and amethocaine owe their hydrolysis to serum cholinesterase. The hydrolysis of neostigmine also involves the enzyme intimately (Nowell Scott and Wilson, 1962).

**Half Life:**

The half life of cholinesterase has been estimated by measuring the fall of enzymic activity following the transfusion of plasma or injection of purified cholinesterase into an anenzymic patient and the various results of different workers are shown in the following concise table (Whittaker, 1980).

Cont'd. ...........
### Estimated half life of plasma cholinesterase.

<table>
<thead>
<tr>
<th>Half life</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 days</td>
<td>DFP</td>
</tr>
<tr>
<td>10 days</td>
<td>Plasma transfusion of an enzymic patient.</td>
</tr>
<tr>
<td>3 - 4 days</td>
<td>Plasma transfusion of an enzymic patient.</td>
</tr>
<tr>
<td>12 days</td>
<td>Purified ChE therapy of an enzymic patient.</td>
</tr>
<tr>
<td>8 - 9 days</td>
<td>Purified ChE therapy of an enzymic patient.</td>
</tr>
<tr>
<td>8 days</td>
<td>Purified ChE therapy of an enzymic patient.</td>
</tr>
<tr>
<td>44.7 h.</td>
<td>Purified ChE therapy of an enzymic patient.</td>
</tr>
</tbody>
</table>

'ChE' stands for plasma cholinesterase.

Whittaker (1980) regards the short half life reported in the last work (by Schuh, 1977) as very surprising due to the remarkable stability of the enzyme. Whittaker (1980) is of the opinion that a half-life in the range of 8 - 12 days seems probable.

**Stability:**

No appreciable variations in the cholinesterase activity of a given individual measured at irregular intervals over a period of 5 years were found by Wetstone and LaMotta (1965) in a study of 82 healthy adults. Lanks and Sklar (1976) found no significant change in enzyme activity in random specimens of whole blood stored at 4°C for 30 days but this procedure is not recommended due to frequently occurring haemolysis. Levels in plasma anticoagulated with heparin or EDTA declined only slightly. Therefore massive transfusions do not contraindicate suxamethonium administration. In separated plasma or serum, the enzyme remained stable for several weeks when stored at 0 - 5°C.
Witter, 1963). Epstein (1980) found that plasma frozen for 7 weeks at 70°C showed no decrease of enzyme activity. In the same study it is also reported that in bank blood stored at 4°C, of the total drop of enzyme activity 88% occurred during the first 2 days of storage.

Johnston (1965) reports an approximately 30% decrease of cholinesterase activity resulting from a single freezing and thawing of plasma. Whittaker (1980) however is of the opinion that plasma or serum may be stored at -20°C for several years without an appreciable loss of activity provided repeated freezing and thawing are not present. She further states that outdated plasma from National Blood Banks can be an useful source of large scale cholinesterase studies.

Interesting to note here is the observation of Pribilla (1957) that cholinesterase activity in plasma separated from autopsy blood upto 72 hours after death did not differ appreciably from the activity of samples from live subjects.

**Physical and Chemical Properties:**

A highly purified concentrated preparation of the serum cholinesterase is now available (Doenicke et al., 1968 and Goedde and Atland, 1971).

Serum cholinesterase is a glycoprotein with a molecular weight of about 300,000 (Surgener and Ellis, 1954)
This large molecule is composed of four polypeptide chains, each of molecular weight of about 80,000.

Serum cholinesterase migrates between alpha-2 and beta globulins in conventional paper electrophoresis. Svensmark (1961) has shown the presence of sialic acid, a mannose derivative. This is split off on incubation of serum with sialidase, leaving the same chemical activity as before but a gamma globulin like electrophoretic mobility. Svensmark (1961) suggests the attachment of several sialic acid molecules to each enzyme molecule at the non-active sites.

Starch-gel electrophoresis has resulted in the suggestion that serum cholinesterase may be heterogenous (Dubbs, Vivonia and Hilburn, 1960).

Wilson (1954) suggests that each cholinesterase molecule has two active sites which combine with one substrate molecule. The first of these - the esteratic site is presumed to be responsible for substrate hydrolysis by combining with it at the ester linkage. The second or anionic site is thought to be the negatively charged region of the enzyme surface which combines with the positively charged nitrogen atom in the choline radical of the substrate.

Unlike acetyl cholinesterase the serum cholinesterase has not been crystallised.
Methods of Estimation:

A variety of techniques have been employed by workers to estimate the values of serum cholinesterase. On the basis of these a list of the methods employed has been drawn up:

(1) The acid liberated can be titrated as it forms by a standard solution of an alkali (Kaufman, 1954).

(2) The acid liberated can be allowed to react with bicarbonate and the amount of CO₂ produced measured manometrically (McArdle, 1940).

(3) The rate of change of pH with time may be measured (Johnson and Whitehead, 1965).


(5) Measurement of acetyl choline ester remaining by using the hydroxamic acid reaction (de la Huerga's modification of Hestrin's method, 1952).

(6) Measurement of the amount of phenol liberated from a phenyl benzoate substrate (Smith, et al., 1959).

(7) Histochemical assay by the thiol analysis of acetyl thiocholine (Koelle and Friedenwald, 1949).
The Steinitz et al. modification (1963) of Rappaport et al. method, which has been used in this study has the advantage that large number of sera can be easily tested resulting in a screen test. Exact dibucaine and fluoride numbers can be obtained.

Different ways of reporting the velocity of enzyme reactions tend to cause confusion. The amount of substrate transformed has arbitrarily been expressed in terms of milligrams, moles, equivalent and gas volumes or the reaction has been related to such changes in the reaction media as pH, absorbance, viscosity or turbidity. The manner in which time has been expressed has ranged from seconds to hours, while the reaction conditions have varied with respect to substrate, temperature, pH, buffer (type and molarity), ionic strength, co-factor concentrations and sample size (Bowers and McComb, 1970). The confusion arising from the use of arbitrary units composed of a multiplicity of variables has been vividly demonstrated for serum cholinesterase by Wetstone and La Motta (1965).

Results obtained by the different methods are not, in general, directly comparable because of the many differences of test-conditions described above. It is, therefore, necessary to compare results on a relative basis (Michel, 1961).

An 'Acholest' test strip method for detection of patients with low plasma cholinesterase is available, though
it is now considered that this method is inadequate (Dietz, 1972).

Normal Levels:

Normal values of serum cholinesterase by different methods are:-

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Method</th>
<th>Values (units/ml. of serum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>McArdle (1940)</td>
<td>60 - 120</td>
</tr>
<tr>
<td>2.</td>
<td>de La Huerga, et al. (1952)</td>
<td>150 - 305</td>
</tr>
<tr>
<td>3.</td>
<td>Biggs et al. (1958)</td>
<td>90 - 150</td>
</tr>
<tr>
<td>4.</td>
<td>Lehmann (1962)</td>
<td>60 - 120</td>
</tr>
<tr>
<td>5.</td>
<td>Steinitz et al. (1963)</td>
<td>60 - 100</td>
</tr>
<tr>
<td>6.</td>
<td>Johnson and Whitehead (1965)</td>
<td>207 - 403</td>
</tr>
</tbody>
</table>

Figures quoted here are for normal healthy adults.

A McArdle unit is defined as the amount of enzyme which will produce 1 microlitre of carbon dioxide by hydrolysis of acetyl choline in a bicarbonate buffer. The units of different workers' methods are different and the name of the worker whose method has been employed is usually given along with the values of cholinesterase mentioned.

Cholinesterase activity in healthy individuals:

Conflicting results regarding the influence of age and sex on the enzyme activity of normal healthy adults have been reported. No influence of age or sex was observed by Hall and Lucas (1937). Similar conclusions were drawn by
Callaway et al. (1951) in a series of 247 adults and by Vorhaus and Kark (1953). On the contrary, other workers such as Kalow and Gunn (1959), Wetstone and La Motta (1965) and Propert and Brackenridge (1976) are of the opinion that adult males have a higher cholinesterase activity than females.

At birth the enzyme activity is low (Lehmann et al., 1957) — it compared with about 50% of the non-pregnant adult level (Zsigmond and Downs, 1971). The latter stated that this remains so until 6 months of age. In contrast, earlier workers like McCance et al. (1949) mentioned a dramatic rise to a greater — than — adult level in the first 3 weeks followed by maintenance till 3 years of age.

In the 3 to 6 years of age group Dabew (1970) found a mean cholinesterase activity of about 30% above the adult level — this started decreasing during the fifth year to reach the adult level at puberty.

In adult level Kalow and Gunn (1959) reported a negative correlation of enzymic activity with age, while in direct contradiction to this a positive correlation was reported by Propert and Brackenridge (1976).

No correlation between the serum cholinesterase levels and physical activity, diet, heart rate and blood pressure was noticed by Hall and Lucas (1937). During muscular exercise, Croft and Richter (1943) observed the rise of serum cholinesterase; Stoner and Wilson (1943) could not corroborate
this. No relation of enzyme level to weight, height or surface-area could be demonstrated by Vorhaus and Kark (1953).

**Quantitative deficiency of Serum Cholinesterase:**

It has already been pointed out that the deficiency of serum cholinesterase may be of a quantitative or a qualitative nature. In either of these conditions, the patients' ability to metabolise suxamethonium is impaired.

Among the first workers to study the variations of serum cholinesterase activity in different physiological and pathological conditions were Hall and Lucas (1937). Others who followed them were legion. The type of disorders causing a reduction in serum cholinesterase activity cover a broad spectrum.

That serum cholinesterase is produced in the liver has already been discussed. Antopol et al. (1938) first observed an invariable depression of the enzyme activity when hepatic parenchyma was diseased. Their finding was supported by Wescoe et al. (1947), Kunkel and Ward (1947) and Kaufman (1954). Vorhaus and Kark (1953) stated that on the whole, depression of the enzyme activity is more marked in patients ill with chronic liver disease such as cirrhosis, than in patients suffering from acute conditions. McArdle's (1940) finding were in agreement with the above general contention. A normal activity was noted in obstructive jaundice by McArdle (1940), Molander et al. (1954), Moore et al. (1957)
and many others. McArdle (1940) recorded depression of the enzyme activity in patients with tumours metastatic in the liver.

The relationship between serum albumin and cholinesterase levels was first observed by Faber (1943). Wetstone et al. (1960) reported a significant correlation (38 %) between the enzyme activity and serum albumin. Kunkel and Ward (1947) established that the only condition in which hypoalbuminaemia and a normal or high serum cholinesterase coexisted was the nephrotic syndrome.

Depression of the enzyme activity due to albumin transfusion was noticed by Vorhaus et al. (1950); an autoregulative mechanism for the control of these two was suggested to be responsible.

**Value of serum cholinesterase estimation as a liver function test:**

Although isolated serum cholinesterase estimations were proposed as an index of liver function by many workers (Vorhaus and Kark, 1953; Kaufman, 1954; Molander et al., 1954), this was not advocated by Whittaker (1980). The argument for the latter opinion is that due to the wide range of normal results obtained and the difficulty in comparing the results with those of various other investigators because of numerous differences in technique, isolated cholinesterase estimations are not advisable or of value as an index of liver function.
Further complicating the issue are a host of factors affecting serum cholinesterase activity; it may not be practically possible to eliminate all of these in subjects undergoing cholinesterase estimations for the purpose of assessing liver function. Serial estimations of the enzyme in the same patient, however, are of greater value in assessing the prognosis of disease and the recovery (Vorhaus and Kark, 1953; Kaufman, 1954; Hunt and Lehmann, 1960). Serial assays of the enzyme have been used by Hunt and Lehmann (1960) in determining the prognosis of venous shunt operations of the portal system.

Leyine and Hoyt (1949), Molander et al. (1954), Wetstone et al. (1960), Kaniaris et al. (1979) and Ghooi et al. (1980) found reduced serum cholinesterase activity in cases of malignancy. The reduction of activity was more in instances where the tumour had spread to other sites – specially to the liver (Ghooi et al., 1980). The carcinomas were associated with maximum reduction of the enzyme activity (Wetstone et al., 1960). The site of the primary growth had a bearing on the fall of the enzyme levels. Maximum reduction was seen when the primary sites were lung, gastrointestinal tract and genitourinary tract – carcinoma of the lung being associated with most markedly reduced enzyme levels (Kaniaris et al., 1979). The cause of this malignancy – associated reduction of enzyme activity was not primarily the hepatic parenchymal involvement due to either tumour cell invasion or prolonged extrahepatic
biliary obstruction. Carcinomatous tissue per se was responsible (Wetstone et al., 1960); this was presumed to be responsible for production of a serum cholinesterase inhibitor (Kaniaris et al., 1979).

Depressed serum cholinesterase levels were also reported in cases with malnutrition by Milhorat (1938), Faber (1943) and Vorhaus and Kark (1953). Their findings were supported by the work of Waterlow (1950) and Barclay (1973). A high incidence (83%) of low enzyme levels was discovered in a study of 302 malnutrition cases by Barclay (1973). Almas and Prathapkumar (1969) showed decreased levels in cases of kwashiorkor with vitamin A deficiency. Khalil (1980) reported lowered levels in 3 patients of Crohn's disease.

It was demonstrated by Milhorat (1938), Sawitsky (1949) and Scudamore et al. (1951) that low levels of serum cholinesterase existed in various forms of chronic anaemias and blood dyscrasias. Abnormal levels have, however, never been found in patients ill with sickle cell anaemia (Sawitsky, 1949) or hypoplastic anaemias or polycythemia (Vorhaus and Kark, 1953). Scudamore et al. (1951) found that the serum cholinesterase level increased slowly, parallel to the improvement in haematological and clinical status of the patient.

Levine and Hoyt (1949) could not demonstrate any decrease in the level of serum cholinesterase in patients with
pulmonary tuberculosis. This was in contrast to the earlier results of Jones and Stadie (1939) who had found low levels in far advanced tuberculosis and carcinoma. Mc Ardle (1940) found decreased activity in uraemia. Reduced levels were reported in uraemia and shock (Editorial, British Medical Journal, 1951).

Surgical shock was found to share a place among the factors causing a depression of the enzyme activity (Doenicke and Holle, 1962). This depression has been attributed to the surgical intervention itself rather than the anaesthetic agents since patients undergoing only ophthalmic, rather than general surgery showed no change in the enzyme activity.

It was observed by Hall and Lucas (1937) that low serum cholinesterase values were frequently found to be associated with acute infections. The converse was not always true. Antopol et al. (1937) and Vorhaus and Kark (1953) substantiated these findings. Hodges and Harkness (1954) noticed that low enzyme levels were most characteristic ally associated with "ill", debilitated patients in a condition which was easier, perhaps, to recognise than to define. Hyperpyrexia has also been found to be associated with low cholinesterase levels (Antopol et al., 1937).

Therapeutic radiation has been reported to be associated with low enzyme levels by Hodges and Harkness
(1954). Low levels have been seen to occur after dialysis with the Kolff twin-coil kidney (Holmes et al., 1958) and in patients on haemodialysis (Thomas and Holmes, 1970).

In the latter instance, the workers have suggested the patient's renal failure rather than the dialysis to be the responsible factor. Low values were seen in patients who underwent plasmapheresis by Wood and Hall (1978) and Evans et al. (1980). A single 4 liter plasma exchange can reduce cholinesterase by 64% and repeated daily plasma exchanges can virtually remove cholinesterase altogether.

Exposure or poisoning by a variety of organophosphorous compounds has been reported in man by Barnes and Davies (1951). Phosphorylation of the active enzyme site by the organophosphorous compound permits accumulation of the acetyl choline at the nerve ending and patients present symptoms typical of cholinergic poisoning in such cases.

Unlike the unanimous opinion regarding depressed cholinesterase levels in patients of liver and biliary diseases, the view regarding the enzyme levels during pregnancy and the post-partum period is divided. Although Hall and Lucas (1937) and Meade and Rosalski (1963) found no correlation between enzyme levels and pregnancy or early puerperium, the majority evidence favours the presence of a decreased cholinesterase activity during the above periods.

This reduction of serum cholinesterase activity has
been found to commence after the 10th week of pregnancy (Robertson, 1966). In agreement are Hazel and Monier (1971), Blitt et al. (1977) and Evans and Wroe (1980), who state that the fall of enzyme activity starts during the first trimester of pregnancy. This reduction of enzyme activity, which is maintained during the rest of pregnancy, has been reported by various workers, to be of the order of 25% (Levine and Hoyt, 1049), 21% (Pritchard, 1955), 28% (Shnider, 1965), 18% (Robertson, 1966), 21% (Hazel and Monier, 1971) and 30% (Redderson, 1973).

Post partum levels of the enzyme have been found to be depressed further. Hazel and Monier (1971) and Blitt et al. (1977) found a 33% and 32% reduction respectively of the enzyme level on the 3rd day post partum. The gradual return of the enzyme level to normal occurs between the tenth day to seventh week post partum (Wildsmith, 1972).

Pritchard (1955) attributed this fall of enzyme activity to haemodilution. Robertson (1966) later suggested that the incriminating factors might be haemodilution altered hepatic function, anti-cholinesterase effects of oestrogen and malnutrition present in these patients. The reduction of enzyme activity has been found to be less marked in patients with toxaemia by Pritchard (1955) and Robertson (1966).

A higher proportion of heterozygotes would be expected to show sensitivity to suxamethonium during pregnancy than when non-pregnant according to the lower cholinesterase
characteristics of the heterozygote.

Tetanus has been assigned a place among the conditions resulting in a reduction of serum cholinesterase (Porath et al. 1977). Earlier, Werle and Stuttgen (1942) had noted the cholinesterase depressing effect of tetanotoxin, which was found to be nearly equal to that of organophosphorous compounds. Hanna et al. (1979), however, noted an increased cholinesterase activity in 3 out of 6 tetanus patients and observed that this increase was related to the severity of the disease.

Moore et al. (1957) and Sharma and Seth (1978) discovered low levels of serum cholinesterase in myocardial infarction. It was suggested that a persistently falling enzyme level was seen in fatal cases. Reduction in enzyme levels was seen in 50 cases of acute head injury by Rao et al. (1978), who also stated the prognostic value of the estimation and found that - significantly low levels implied poor prognosis. Bush et al. (1962) found reduced values in severely burned patients and it has since been suggested that the concurrent hepatic lesion of burns is the main culprit here. Myxœdematous patients were seen to possess serum cholinesterase activity upto 30 % lower than normal (Thompson and Whittaker, 1965).

Rheumatoid arthritis (Milstor, 1970) and polyarteritis nodosa (Potts and Thornton, 1961) have been seen to be associated with low enzyme values. In polyarteritis nodosa the decrease has been blamed upon the more than frequently recognised liver
involvement. It has been stated that all muscle relaxants should be avoided or used with extreme caution in the presence of polymyositis, dermatomyositis, systemic lupus erythematosus and polyarteritis nodosa, unless prior investigations of hepatic function have been found to be normal.

Another cause of reduction of enzyme activity is the use of the anticancer drug AB - 132 (Wang and Ross, 1963) where a dose related effect was observed. Reduced levels are also seen due to the anticholinesterase drugs neostigmine, physostigmine, pyridostigmine, ecothioptate iodide, edrophonium, hexafluorenium (Kopman et al., 1978) and due Ketamine hydrochloride, fluothane, ethrane (Carraresco et al. 1978). Pancuronium (Stover et al., 1975).

Propanidid and trimethaphan have also been implicated in their association with drugs causing reduced serum cholinesterase levels. Oral contraceptives containing oestrogen cause a decreased cholinesterase activity (Robertson, 1967) and also a modification of cholinesterase isoenzymes (Bergmann and Warzel, 1954). These changes are reversible by withdrawal of the contraceptive.

**Quantitatively increased levels of serum cholinesterase:**

There were conditions in which quantitatively increased levels of serum cholinesterase were observed. Berry et al. (1954) observed higher than normal levels in 'fat' individuals in a study of 354 cases. A highly significant
positive correlation was found by them between surface fat and serum cholinesterase. Later Thompson and Trounce (1956) attributed the high cholinesterase levels seen sometime in diabetes to the associated obesity and not to the disease itself.

An increase of serum cholinesterase to about 20% above the normal level was seen in thyrotoxicosis patients by Thompson and Whittaker (1965). High values have also been observed in asthma and alcoholism by Vaccarezza and Peltz (1960), nephrosis by Kunkel and Ward (1947), essential hypertension by Vorhaus (1952) and in psoriasis, nodular goitre and hyperlipaemia. In certain mental disorders like anxiety or depressive states (Tod and Jones, 1937) and schizophrenia (Tod and Jones, 1937; Antebi and King, 1962; Propert, 1979) the serum cholinesterase levels have been found to be increased. Propert (1979) did not find the increased levels to be of significance.

Relationship between low serum cholinesterase levels and suxamethonium apnoea;

Various workers have put forward differing opinions regarding the presence or absence of any relationship between serum cholinesterase activity and the duration of action of suxamethonium.

Lehmann and Ryan (1956) reported 27 cases of prolonged apnoea. Out of these 6 patients had normal and the
remaining 21 low enzyme levels. Argent et al. (1955) found 1 patient with low enzyme level in a study of 7 cases of prolonged apnoea, Kalow (1959) found that approximately 10% of his cases of prolonged apnoea were due to very low enzyme activity.

Bourne et al. (1952) noted lower mean cholinesterase levels in patients who showed delayed recovery, in their study of 546 cases:

\[
\begin{align*}
\text{Delayed recovery} & \quad 38.3 \pm 6.6 \text{ units/ml.} \\
\text{Normal recovery} & \quad 88.5 \pm 6.9 \text{ units/ml.}
\end{align*}
\]

Mean ± Standard Error (units of Callaway et al.)

Foldes et al. (1956) demonstrated that the decreased levels seen in association with liver disorders did not usually cause more than a three fold increase in the duration of apnoea.

Lievre (1980) in a study of 280 randomly selected surgical patients found that only 11 (3.9%) had levels below the normal range; of these only 1 developed prolonged apnoea. It was concluded therefore that a low cholinesterase level is not an infallible indicator of post-surgical complications.

Blitt et al. (1977) found no correlation between the enzyme activity and duration of paralysis when they administered a 40-80 mg. per body surface area dose of suxamethonium.

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.

Reduction of the enzymatic activity to less than 25% by Vickers (1963) and less than 50% by Whittaker (1980) has been felt necessary before any significant prolongation of the suxamethonium is observed.

As a generalisation, however, the lower the cholinesterase activity and the dibucaine and fluoride numbers, the more prolonged is the response to succinyl choline. The failure of consistency of this relationship is due to technically incorrect estimations. A valid assay of cholinesterase can only be carried out at 37°C - such an assay shows good correlation between cholinesterase activity and patient sensitivity (McLaren and Moffit, 1976).

Genetic variants of the enzyme:

Prolonged apnoea in response to the administration of suxamethonium was noticed by many earlier workers (Bourne, et al., 1952; Argent et al. 1955). Forbat (1953) first postulated the idea that the result of an inherited defect in the enzyme metabolism. Lehmann and Ryan (1956) suggested that the genetic defect was transmitted as an autosomal recessive trait. Over the period 1957 - 1960, Kalow and his associates worked to demonstrate a qualitative difference between the altered enzyme and the normal one. Kalow (1956) had earlier identified the former enzyme and termed it "atypical" esterase, since it
demonstrated a reduced affinity for and hydrolysis rate of choline ester substrates such as suxamethonium.

Kalow and Genest (1957) demonstrated that the atypical cholinesterase could be detected by its inhibition with varying concentrations of a suitable inhibitor such as the local analgesic drug dibucaine hydrochloride (Cinchocaine or Nupercaine). Kalow and Genest (1957) introduced the term dibucaine number (D.N.). This was defined as the percentage inhibition by a fixed concentration of dibucaine (10^{-5} M) of the rate of hydrolysis of benzoylcholine under standard conditions of temperature, pH, buffer and fixed concentration of 10^{-5} M dibucaine is routinely used to determine dibucaine numbers in different sera.

Dibucaine number in patients very sensitive to suxamethonium is approximately 20, while in normal patients is around 80. An intermediate group with a dibucaine number of about 60 is also found. The table below shows the dibucaine numbers of various types of sera:

<table>
<thead>
<tr>
<th>Genetic status</th>
<th>Dibucaine number</th>
<th>Population in group</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Normal homozygote</td>
<td>$E_1^u E_1^u$</td>
<td>70 - 85</td>
</tr>
<tr>
<td>B. Heterozygote</td>
<td>$E_1^u E_1^a$</td>
<td>50 - 65</td>
</tr>
<tr>
<td>C. Abnormal homozygote</td>
<td>$E_1^a E_1^a$</td>
<td>16 - 25</td>
</tr>
</tbody>
</table>


The biosynthesis of serum cholinesterase is controlled by two allelic genes, $E_1^u$ and $E_1^a$ (Kalow and Staron, 1957), and
these are a non-dominant autosomal in nature. Only one gene can exist at locus 1 on each of the chromosome of a pair. Each gene controls the production of its enzyme.

Separation of two types of enzymes from presumed heterozygotes by Lidell et al. (1962) confirmed that there were actually two physically different entities. Only one enzyme could be separated from homozygotes using paper electrophoresis or column chromatography using anion exchange material diethyl aminoethyl cellulose.

A knowledge of the dibucaine number can help in predicting the genetic configuration of the patient.

The advantage of dibucaine number determination is that a clear trimodal distribution indicating three distinct genotypes is present which is totally tacking in the Gaussian distribution of activity (Whittaker, 1980).

The dibucaine number of any person changes only after transfusion of blood from an individual with a different genotype (Whittaker, 1980).

It is regarded that the presence of atypical cholinesterase is the main and more serious cause of suxamethonium apnoea of prolonged duration (Editorial, Lancet, 1973).

Whittaker (1980) feels that, higher proportion of heterozygotes would be expected to show sensitivity to suxamethonium during pregnancy than when non-pregnant. This is due to the low cholinesterase characteristics of the heterozygotes $E_1E_1$.
It is significant to mention here that the ethnic group lacking the $E_1^a$ gene, like Zimbabwe - Rhodesia Africans are very susceptible to leprosy (Whittaker et al., 1976).

Lubin et al. (1971) found a heterozygote male preponderance among Caucasians of 1.85 : 1 in a preschool nutrition survey. They suggested the possibility of a sex modification and environmental influence on this polymorphic system. They were of the opinion that the atypical allele was presumably absent in Japanese, Eskimos and South American Indians and was rare in Negroes, Australian aboriginees, Filipinos and Oriental populations (other than Japanese).

Kalow and Gunn (1957) observed that heterozygotes to atypical plasma cholinesterase do not have greatly prolonged responses to succinyl choline. 

Silent gene:

The discovery of this and the events leading to it are interesting. In case of an atypical homozygote ($E_1^a E_1^a$) for simple Mendelian recessive inheritance, both parents must have at least one $E_1^a$ gene and moreover all the children of such an individual should have an $E_1^a$ gene. But in a family in Kalow and Staron's (1957) study, such inheritance patterns were not seen (Fig. 3). The presence of a silent - gene was then proposed. Whittaker (1980) suggests that this gene is not really 'silent' since it does not imply non-production of the gene, but the biosynthesis of cholinesterase lacking
Fig. 3 - PEDIGREE OF FAMILY WITH UNUSUAL INHERITANCE AS DETERMINED BY DIBUCaine NUMBERS.
the structure required to hydrolyse the choline-ester bond. Thus no enzymic activity is present.

Applying this concept to the individuals in Fig. 3 $I_2$ should be a heterozygote $E^u_1 E^s_1$ (D.N. = 80) while her children $II_2$ and $II_3$ become heterozygotes $E^a_1 E^s_1$ (D.N. = 20).

Later Lidell and his colleagues (1962) reported the presence of silent-gene with no enzymatic activity ($E^s_1 E^s_1$). Many such anenzymic individuals have since been described. In some ethnic groups like Alaskan Eskimos, some Caucasian South Africans there is a large incidence of the silent gene. Vysas of Andhra Pradesh have also been seen to have a high incidence of the silent allele (Rao, 1979).

Two different types of silent gene have been recognised (Scott and Wright, 1976). One type of cholinesterase deficiency is definitely anenzymic with no activity; the other type has 2 - 8% of the normal mean cholinesterase activity. Scott and Wright (1976) point towards at least two or three genetic defects in the enzyme which may be present. The probability of other silent gene variants leaves this field open to further research (Whittaker, 1980).

While homozygotes for $E^s_1$ gene are recognised due to little or no enzyme activity, the detection of the $E^s_1$ heterozygote is very difficult without extensive family studies. The reason for this is that the inhibition reactions of homozygotes of other variants (like $E^a_1 E^s_1$) and the heterozygote of that variant and silent gene (like $E^a_1 E^s_1$) are similar.
Fluoride-resistant gene:

Another gene controlling the cholinesterase biosynthesis is the fluoride-resistant gene \( E_1^f \). It was discovered by Harris and Whittaker (1961) by using sodium fluoride to differentially inhibit it. The fluoride number (F.N.) is the percentage inhibition by a fixed concentration (5 x 10\(^{-5}\) M) of sodium fluoride of the rate of hydrolysis of benzoyl choline under standard conditions of temperature, pH, buffer and fixed concentration of substrate. The dependancy of fluoride-inhibition on temperature must be stressed here.

A high frequency of the \( E_1^f \) gene has been found in psychoses and Huntington's disease (Whittaker and Berry, 1977).

Other rare variants:

Other variants of cholinesterase at the \( E_1 \)-locus have been suggested. Whittaker (1960) reported the presence of a chloride-resistant gene.

Two other rare genes - \( E_1^j \) (Rubinstein et al., 1976) in one family and \( E_1^k \) (Ruvinstein et al., 1978) in two family have been found.

Another gene associated with a very high cholinesterase activity has been described by Nietlich (1966). It is known as the E. Cynthiana variant or the Nietlich variant. Its locus of functioning is not known. However, it has been suggested that mutation of normal or silent gene to an abnormal or rare one may occur at times (Evans and Magill, 1974).
An electrophoretic variant (C₅⁺) was discovered by Harris et al. (1963). It functions at the cholinesterase locus E₂ and is genetically determined due to an autosomal dominant gene. Persons having this variant have a high cholinesterase activity but Whittaker (1980) does not consider it to be of importance to the anaesthetist.

Identification of the cholinesterase variants:

A variety of inhibitors have been used. These include sodium chloride, urea, sodium bromide, succinyl-dicholine, RO2 - 0683 the dimethyl carbamate of (2-hydroxy-5-phenyl-benzyl) trimethylammonium bromide, formaldehyde, thyroxine and alkyl alcohols. These inhibitors have been used with either choline esters or non-choline esters as substrates (Whittaker, 1980).

Whittaker (1980) states that though such numerous and diverse systems can be daunting, as new techniques become available, the number of recognised cholinesterase variants will increase.

Screening programmes for cholinesterase variants:

Genetically important relatives of individuals of individuals known to be sensitive to suxamethonium should be investigated for cholinesterase variants (Whittaker, 1980). There is no significant morbidity or mortality directly attributable to succinyl choline apnoea which requires to be balanced against a limited success rate for generalised screening of all patients about to receive suxamethonium (McLaren and Moffit,
Lievre (1980) states that programmes concerning aberrations occurring in 1 - 10% frequency are feasible; those occurring in less than 1% frequency are not feasible. The frequency of homozygotes is less than 0.1% but heterozygotes occur in 3.8% frequency. This puts abnormal cholinesterase levels into the range of feasible genetic screening programmes.

The problem of increased sensitivity to suxamethonium is not purely genetic, but on the basis of those at comparable risk due to acquired abnormality seems justifiable (McLaren and Moffit, 1976; Lievre, 1980; Whittaker, 1980).

### Some causes of increased plasma cholinesterase activity

<table>
<thead>
<tr>
<th>Type</th>
<th>Condition</th>
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</thead>
<tbody>
<tr>
<td>Inherited</td>
<td>Electrophoretic variants C₅⁺</td>
</tr>
<tr>
<td></td>
<td>Nietlich or Cynthiana variant</td>
</tr>
<tr>
<td>Acquired</td>
<td>Obesity</td>
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<tr>
<td></td>
<td>Hyperlipaemia</td>
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<td>Nodular goiter</td>
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<td>Essential hypertension</td>
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<td>Nephrosis</td>
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<td>Asthma</td>
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<td>Anxiety states</td>
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<tr>
<td></td>
<td>Alcoholism</td>
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<td>Schizophrenia</td>
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(Whittaker, M., 1980).
Some causes of decreased plasma cholinesterase activity

<table>
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<th>Type</th>
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<td>Physiological variance</td>
<td>Last trimester of pregnancy</td>
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<td>New borns and infants</td>
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<tr>
<td>Acquired causes</td>
<td>Liver diseases (acute hepatitis and hepatic metastasis)</td>
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<td>Myocardial infarction</td>
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<td></td>
<td>Collagen diseases (progressive muscular dystrophy, congenital myotonia, dermatomyositis)</td>
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<td>Hyperpyrexia</td>
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<td>Tuberculosis</td>
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<td>Chronic debilitating diseases</td>
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<td>Organophosphorus insecticides</td>
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<td>Burned patients</td>
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Contd. ........
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<td>Rheumatic fever</td>
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<td>Typhus</td>
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<td>Kwashiorkor</td>
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<td>Epilepsy</td>
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(Whittaker, M., 1980).

Contd. ............
### Distribution, suxamethonium sensitivity and biochemical characteristics of the plasma cholinesterase variants in a British population

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Relative mean enzymic activity</th>
<th>Dibucaine number</th>
<th>Fluoride number</th>
<th>Frequency</th>
<th>Suxamethonium sensitivity</th>
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<tr>
<td>$E^{u}<em>{1}E^{u}</em>{1}$</td>
<td>100</td>
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<td>50</td>
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<td>77-83</td>
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<td>56-68</td>
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<td>$E^{f}<em>{1}E^{f}</em>{1}$</td>
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<td>67</td>
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<td>$E^{a}<em>{1}E^{s}</em>{1}$</td>
<td>22</td>
<td>21</td>
<td>8-28</td>
<td>19</td>
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<td>$E^{s}<em>{1}E^{s}</em>{1}$</td>
<td>Enzymic activity nil or too low to measure</td>
<td>1 in 100,000</td>
<td>All very sensitive</td>
<td></td>
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</table>

(Whittaker, M., 1980).