THE TIME COURSE OF RESPONSE TO CORTICOSTEROIDS IN BRONCHIAL ASTHMA.

ROGER ELLUL-MICALLEF. M.D.

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ABSTRACT OF THESIS

Name of Candidate Dr. ROGER ELLUL-MICALLEF, M.D.

Address

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Title of Thesis The time course of response to corticosteroids in bronchial asthma.

Clinical observation suggests that there is a time-lag between administration of corticosteroids to asthmatic patients and the appearance of improvement. This study was designed to follow changes during the period forty-eight hours before to thirty-six hours after the administration of a single oral dose of 40 mg of Prednisolone to chronic asthmatic patients. The investigation was divided into two stages. Besides the effect of prednisolone, the effect of a single intravenous dose of 200 mg hydrocortisone was also studied in the second stage. A number of pulmonary function tests was used to monitor the effects of the drugs given.

A statistically significant improvement in F.E.V. ($P < 0.025$) could be detected one hour after prednisolone administration, a statistically significant increase in P.E.F.R. ($P < 0.001$) occurred two hours after the drug had been given. In the group as a whole, the maximum change in various tests occurred nine hours after prednisolone had been given. The change in P.E.F.R. and $F.E.V._1$ was still statistically significant ($P < 0.05$; $P < 0.05$) thirty-three hours after administration of prednisolone but had fallen to non-significant levels by thirty-six hours. However specific conductance when last measured, thirty-six hours after treatment, was still significantly increased in the second group of patients

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studied ($P < 0.05$).

In contrast, the mean change in P.E.F.R. was significantly increased, one hour after the intravenous injection of hydrocortisone, the peak effect being attained in five hours. The mean change in P.E.F.R. was no longer statistically significant twelve hours after the injection.

Pulmonary gas exchange was studied before and nine hours after the dose of prednisolone, in the second stage of the study. Arterial PO_2 rose in all patients and the alveolar-arterial PO_2 difference decreased. Dead space:tidal volume ratio showed little change.

The changes in pulmonary function found in the chronic asthmatic patients investigated during this study appear to follow the time course of other biological effects of corticosteroids, such as those on carbohydrate metabolism and circulating eosinophils.

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SUMMARY:

Clinical observation suggests that there is a time-lag between the administration of corticosteroids to patients suffering from bronchial asthma and the appearance of improvement in their condition. Although various time intervals have been suggested, no systematic physiological studies have previously been carried out.

This study was designed to follow the course of events during the period forty-eight hours before to thirty-six hours after the administration of a single oral dose of 40 mg of prednisolone to patients with chronic asthma. The investigation was divided in to two stages. Besides the effect of prednisolone, the effect of a single intravenous dose of 200 mg hydrocortisone was also in tstudied in the second stage. Great care was taken in selecting patients to ensure that they were in a stable state. Patients were given placebo tablets on two days prior to the administration of prednisolone and on the following day. Eleven patients were studied during the first stage of the investigation and twelve patients during the second stage. Various pulmonary function tests including dynamic and static lung volumes, body plethysmographic measurements and flow-volume curves were used to monitor the effect of prednisolone. The tests were performed at fixed times during the day. Peak expiratory flow rate was measured hourly for twelve hours after the administration of hydrocortisone.

A statistically significant improvement in $F.E.V._1$ ($P < 0.025$) could be detected one hour after prednisolone administration, a

statistically significant increase in P.E.F.R. (P 0.001) occured two hours after the drug had been given. In the group as a whole, the peak effect in $F.E.V._1$, F.V.C., P.E.F.R. and SGaw occurred nine hours after prednisolone had been given. Flow-volume curves measured at the mouth and static lung volumes showed parallel changes. The change in P.E.F.R. and $F.E.V._1$ was still statistically significant (P 0.05; P 0.05) thirty-three hours after administration of prednisolone but had fallen to non-significant levels by thirty-six hours. However, specific conductance when last measured, thirty-six hours after treatment, was still significantly increased in the second group of patients studied (P 0.05).

In contrast, the mean change in P.E.F.R. was significantly increased at the time of its first measurement, one hour after the intravenous injection of hydrocortisone, the peak effect being attained in five hours. The mean change in P.E.F.R. was no longer statistically significant at the time of the last measurement, twelve hours after the injection.

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The changes in pulmonary function found in the chronic asthmatic patients investigated during this study appear to follow the time course of other biological effects of corticosteroids, such as those on carbohydrate metabolism and circulating eosinophils.

CONTENTS.

(i)	Introduction	p.1
(ii)	The aetiology and pathogenesis of bronchial asthma.	p.6
(iii)	The pathology of bronchial asthma, including the role of smooth muscle in normal airways and in asthma.	p.24
(iv)	The status of the hypothalamic-pituitary adrenal axis in asthma.	p.34
(v)	Altered pulmonary function in asthma.	p.38
(vi)	Lung scans in asthma.	p.60
(vii)	Plan of study	p.63
(viii)	Methodology: Development of tests, physiological basis and procedure:	
	(a) Introduction	p.64
	(b) Measuring airway resistance	p.68
	(c) Measuring static lung volumes	p.87
	(d) Measuring dynamic lung volumes	p.97
	(e) Assessment of pulmonary gas exchange	p.119
(ix)	Results	p.137
(x)	Discussion	p.146
(xi)	Bibliography	p.171

INTRODUCTION.

The word asthma is derived from the Greek, which means "panting". The first clinical description is attributed to Aretaeus (ca. 300) who, emphasizing the breathlessness of asthmatic patients wrote, "they eagerly go into the open air, since no house sufficeth for their respiration". Van Helmont (1662) has provided us with a vivid description of a monk who had attacks "as oft as any place is Swept, or the Wind doth otherwise stir up the Dust"; the same monk also had attacks when "he eateth Fishes fried with Oyl". This is probably the first reference to allergy being involved in the aetiology of asthma. He is also thought to be the first to suggest that asthma is due to a "drawing together of the smallest terminal bronchi" (Speiss, 1840). Perhaps the most detailed description of asthma is that of Thomas Willis (1684) who identified two forms, "pneumonic" and "convulsive". He associated "pneumonic asthma" with "obstruction of the bronchi by thick humors, swelling of their walls and obstruction from without". He believed "convulsive" asthma to be due to "compression of the Bronchia, from the more Cramps of the moving fibres". In 1698, Sir John Floyer, himself an asthmatic, published his classical book on asthma. He adopted Willis's classification of two forms of asthma which he called "periodic" (convulsive) and "continued" (pneumonic) and assigned as a cause for the paroxysms "a contracture of the muscular fibres of the bronchi".

Longet, in 1842, first demonstrated that stimulation of the distal end of a cut vagus nerve induced contraction of the bronchi.

He gave momentum to the theories of "nervous asthma", first hinted at by Cullen (1784) and which were elaborated by Hyde Salter (1868) who believed that the lesion of spasmodic asthma resided in the vagus. Salter's book is notable in its account of the clinical aspects of the disease; he described eosinophils in the sputum before they came to be called as such by Ehrlich (1879).

For a long time asthma was considered to be a disease of moderate morbidity and negligible mortality. Indeed, Oliver Wendell Holmes is quoted in Osler's book as calling asthma "the slight ailment that promotes longevity" and Trousseau called it "le brevet de longue vie". Until Huber and Koessler's paper in 1922, it had been claimed that death did not occur in the asthmatic paroxysm. Although the dangers of asthma are now fully appreciated, it is disturbing to come across statements in the literature such as "Bronchial asthma alone rarely causes death. When it does prove fatal it is due either to the concurrent bronchitis and bronchiolitis or to heart failure (cor pulmonale)", (Spencer, 1968).

Between 1959 and 1966 a steady rise in mortality from asthma was observed in England and Wales, the increase being more pronounced at ages 5 - 34 years. Speizer et al (1968, a) showed that the rise was real and not due to a change in diagnostic methods or registration of cause of death. A similar but less marked increase in deaths from asthma, largely confined to the 5 - 34 age group has also been reported in Scotland (Pendreigh, 1968). Speizer et al,

(1968, b) subsequently examined the possible reasons and concluded that the increase in mortality was most likely due to changes in treatment. Sympathomimetic aerosols and corticosteroids were the only drugs to have been used by a large proportion of the patients who died. The use of corticosteroids, which had been introduced in 1951, did not seem to be related to the cause of death and sympathomimetic aerosols, introduced in 1961, were incriminated. Following the publicity given to the possible dangers of excessive inhalation, there was a drop in sales which has been paralleled by a downward trend in the reported number of deaths due to asthma (Inman and Adelstein, 1969; Fraser et al 1971).

Several mechanisms whereby sympathomimetic aerosols might be responsible for the increase in asthma death rate have been suggested. The induction of fatal cardiac arrythmias by sympathomimetic drugs, especially in the hypoxic state, is one of the explanations given (Lockett, 1965; Greenberg and Pines, 1967; and Collins et al, 1969). Fluorocarbons, used as propellent agents in the aerosols, have also been blamed for producing arrythmias (Bass, 1970). More recently, Conolly and his co-workers (1971) have claimed that prolonged administration of these bronchodilators might result in resistance being developed not only to the sympathomimetic drugs themselves but also to endogenous sympathetic stimulation. They suggest that this could have led to the deterioration, and finally to death, in asthmatic patients using sympathomimetic aerosols.

Asthma, which may best be regarded as a complex functional state which can be triggered off by a wide variety of agents, still presents a great number of difficult problems and there are far more questions to be asked than answers to be given. Although there have been several attempts at defining the condition (Ciba Guest Symposium, 1959; American Thoracic Society 1962; Scadding, 1969), there is still no agreement between clinicians, respiratory physiologists, immunologists and pharmacologists on a final definition. (Working Group on the Definition of Asthma, 1971).

Naturally, this lack of agreement on a final definition, makes the selection of patients for a study of some of the aspects of asthma rather difficult. In contrast to the great amount of work carried out on the effect of sympathomimetic drugs in asthma there is scanty information available regarding the time course of action of corticosteroids in this condition and comparatively little data on how these drugs alter pulmonary function in asthma. A systematic study of the effects of corticosteroids in chronic bronchial asthma has therefore been carried out in an attempt to try to find out when and in what manner pulmonary function alters with this form of treatment.

For the purpose of this present work, chronic asthma is defined as a condition in which diffuse reversible airway obstruction is present continuously, with, and sometimes without, brief spontaneous remissions. It was considered impractical to carry out this study on acutely ill patients. The reasons for this were two-fold.

Acutely asthmatic patients frequently require other forms of therapy, such as intravenous aminophyllin, which would interfere with the investigation; it would have been unethical to withhold such drugs from these patients. Furthermore, patients with acute asthma, because of the very nature of their illness, would have found it extremely difficult if not impossible, to co-operate fully in carrying out repeatedly the number of tests employed in this study.

THE AETIOLOGY AND PATHOGENESIS OF BRONCHIAL ASTHMA.

The aetiology and precise pathogenesis of bronchial asthma are still uncertain although a great deal of evidence is now forthcoming about the various factors that are capable of triggering off an attack. The relative importance of genetic predisposition, environmental allergens, immunological mechanisms, infection and emotional factors, in determining the different patterns of the disease is far from clear. It appears likely that these various factors contribute to a different degree and in a different manner in various patients and act upon some final common path resulting in the clinical picture that is so well known.

(i) Hereditary factors.

As early as 1916 Cooke and Van der Veer stressed the hereditary nature of allergic diseases. However, as pointed out by Ratner and Silbermann (1953), although the clinical evidence of inheritance of atopic diseases is often very suggestive, the evidence is not as conclusive as it is sometimes made out to be.

Williams and Williams (1949) found that about 50% of patients gave a history of allergy in close relatives. Schwartz (1952) produced evidence suggesting that asthma is an inherited disease and pointed out that both vasomotor rhinitis and Besnier's prurigo were genetically related to asthma. His evidence for a hereditary factor in the aetiology of asthma has been claimed to be the

best available in the literature (Frankland 1968). A genetic relation between asthma, atopic dermatitis and atopic rhinitis has also been found by Schnyder (1960). Leigh and Marley (1967) found that about 40% of first degree relatives of patients with asthma developed the disease by the age of sixty-five years.

Rajka (1960) pointed out that what may be inherited is not the allergic manifestation but the allergic disposition. Although it has been suggested that atopy is determined by a single, autosomal, dominant gene with reduced penetrance (Schnyder, 1960), the exact genetic factor and the mode of inheritance are still far from certain.

(ii) Immunological aspects.

Bronchial asthma is often very broadly classified into two major sub-divisions, 'extrinsic' and 'intrinsic' asthma. In extrinsic asthma an external allergen can be demonstrated, the age of onset is usually early and a Type I (Gell and Coombs, 1968) immediate allergic reaction is generally the cause. The term intrinsic asthma was applied by Rackemann (1947) to describe a group of patients in whom no external allergen could be shown (prick tests being negative to a wide range of antigens) and whose symptoms began in adult life. Although the division is a convenient one, it must be realised that it is only provisional, as allergic factors may in due course be discovered (Crofton and Douglas, 1969).

The type of hypersensitivity most commonly encountered in extrinsic asthma is that due to a Type I immediate reaction. In Type I allergy the antibody responsible for mediating the release of pharmacological factors responsible for this kind of asthma was originally termed "reagin" (Coca and Grove, 1925). It is a heat labile, 'non-agglutinating', 'non-precipitating' and 'non-complement' dependent' antibody. Reagin has been shown to belong to a separate class of immunoglobulin (Ishizaka et al, 1966, Johansson, 1967) now termed IgE (WHO, 1968). IgE is present in very small quantities in normal individuals, but levels of over 700 ng/ml, representing a six-fold increase, were found in 63% of a series of patients with extrinsic allergic asthma (Johansson, 1967). IgE appears to be produced in the lymphoid tissue of the respiratory tract, especially in the tonsils and in plasma cells in bronchial walls; as well as in the gastrointestinal tract (Ishizaka and Ishazaka, 1970). It has recently been shown that leucocytes capable of releasing histamine when challenged by an allergen are mainly coated with IgE immunoglobulin (Assem and McAllen, 1970). Stenius and his associates (1972) found no correlation between total IgE, amounts of specific IgE and the age of onset of asthma or with its severity and duration. Total IgE may also be within the "normal" range in atopic subjects in whom specific IgE is present.

There are innumerable allergens that have been implicated in reagin mediated asthma. They include such commonly encountered substances in the environment as pollens, animal dander and fur, and the recently described house dust mite (Voorhorst et al, 1964).

Besides the well established evidence for the role of immediate Type I allergy in bronchial asthma, it now seems probable that asthma may also be initiated by hypersensitivity mechanisms which do not involve reagin. Pepys (1972) thus subdivides extrinsic asthma into atopic and non-atopic types. Pepys and his co-workers (1968, 1969) have shown that precipitating, heat stable antibodies, which are complement dependent and known to be important in Type III reactions, may play a part in asthma developing slowly over several hours, becoming maximal about seven to eight hours after allergen exposure. In this type of extrinsic, non-atopic asthma it is the particular environmental exposure which is of primary importance, whereas in the Type I group it is the subject's constitution which is so (Pepys, 1970). Late asthma of this type has been associated with Aspergillus fumigatus infection and has also been shown in bird fanciers using avian protein extracts and in workers exposed to enzymes extracted from Bacillus subtilis. In certain circumstances, e.g. bronchopulmonary aspergillosis there may be a combination of Type I and III reaction. The patients when challenged with extracts of Aspergillus fumigatus develop immediate airway obstruction which rapidly resolves, only to recur after four to five hours, when it is more severe and persistent (Pepys et al, 1968).

Intrinsic asthma remains a very obscure form of the disease. There is no evidence in this form of asthma of any history of extrinsic allergy or of a Type I allergic reaction to skin or inhalation tests. IgE levels in this group have been reported to be either normal or low (Johansson, 1967) in contrast to the raised levels i

extrinsic asthma in which a direct relationship has been shown between the amount of IgE and the number of allergens to which the subject reacts (Wide et al, 1967). In the intrinsic asthma the blood eosinophilia tends to be higher than in the extrinsic form. Assem et al (1971) have reported that the white cells of some intrinsic asthmatics whose total IgE levels are within the "normal" range, seem to have more IgE attached, of a comparable degree to the IgE content of the white cells of extrinsic asthmatics. This appears to constitute some evidence of an IgE reaction in the intrinsic asthmatic. Hall et al (1966) first reported that women with intrinsic asthma appear to have increased amounts of autoantibodies especially to gastric parietal cells, thyroid and nuclear materials, compared with women with extrinsic asthma. Smooth muscle antibody has also been found in a small but significantly greater proportion of patients with intrinsic asthma (Turner Warwick and Haslam, 1970). It is unlikely that these antibodies are responsible for intrinsic asthma and probably only indicate an increased immunological responsiveness present in patients with this form of asthma (Turner Warwick 1971). Of course the possibility that non-immunological mechanisms may have a role to play cannot be discounted.

(iii) Possible role of pharmacological mediators in bronchial asthma.

Most of the knowledge at present available about the various chemical mediators and their possible role in bronchial asthma, has been obtained from experiments in the guinea pig, in which the respiratory tract is the first target organ to react, and react intensely, to anaphylaxis. Herrheimer (1967) wrote "guinea pig bronchi react in a similar way as human asthmatic bronchi". These experiments have served as a basis for a much narrower range of clinical investigations in man. Although pharmacologists point out that the chemical mediators released following an anaphylactic reaction are similar and their effects on trachea bronchial muscle comparable in the two species, immunologists have found out that the sensitizing mechanism of guinea pig anaphylaxis differs from that of atopy in man (Bonnerraf, 1968). Interpretation of results obtained in animal experiments must therefore be applied with great caution to the human situation. Thus although 5-Hydroxytryptamine is known to be an important chemical mediator in some species there is no direct evidence connecting it with human bronchial asthma.

When isolated lungs of sensitized guinea pigs are perfused with antigen in saline, various bronchoactive substances or their precursors appear in the perfusate. These substances include histamine (Bartosch, Feldberg and Nagel, 1932) slow reacting substance of anaphylaxis (SRS-A) (Kelloway and Trethewie, 1940), kallikrein (Brocklehurst and Lahiri, 1962; Jonasson and Becker

1966) and the prostaglandins E2 and F2 (Piper and Vane, 1969); Recently a factor able to attract eosinophils, called eosinophil leucocyte chemotactic factor of anaphylaxis (ECF-A) (Kay and Austen, 1971) has been identified. In man, definite evidence is now available that histamine, SRS-A and ECF-A are pharmacological mediators associated with anaphylaxis. No reports on the release of kallikrein or bradykinin from antigen-stimulated sensitized human tissue have been published; this is also true of the prostaglandins E1, E2 and F2 .

Histamine.

Since the identification of histamine by Barger and Dale (1910) and the determination of its pharmacological actions by Dale and Laidlaw (1911) there has been a great deal of evidence linking histamine release with hypersensitivity. Katz and Cohen (1941) first reported that histamine was released from the tissues of an allergic individual when they showed that whole blood of a patient with ragweed hypersensitivity liberated histamine when incubated with antigen. Histamine was later shown to be released by the antigen-antibody reaction from human isolated lung (Schild et al, 1951; Hawkins and Mongar 1964; Parish, 1967; Assem and Schild, 1968). The available data regarding blood histamine levels in asthma is often conflicting. Some authors have reported increased levels during attacks and normal or only slightly elevated levels in the asymptomatic period (Jimenez-Diaz et al 1955; Konoshita, 1963); others have found no increase in blood histamine levels in asthmatic patients (Eggleston and Welsmans, 1966) or in plasma histamine levels (Beall,

1963). Serafini (1948) measured blood histamine levels during asthmatic attacks over a period of 10 hours, samples of blood being with drawn at fixed time intervals. He reported an initial rise in blood histamine at the onset of the attack, quickly followed by a drop to below normal values. Porter and Mitchell (1970) have recently reported blood histamine lvels, in children with asthmatic symptoms which were significantly higher than in a control group. These levels fell to near normal values in the asymptomatic period and during long-term steroid treatment. The significance of histidine decarboxylase, the enzyme involved in the formation of histamine is still not sufficiently appreciated. It is known however, that its activity can be very quickly increased as a result of stress (Brocklehurst, 1968); and it is conceivable that this might well be one of the mechanisms involved in the triggering off of asthma during periods of particular stress.

(b) SRS-A

There is a great deal of indirect evidence indicating that SRS-A has a role to play in asthma, although the importance of such a role has not as yet been definitely evaluated. SRS-A was detectable when lung tissue from asthmatic subjects was brought into contact with the sensitizing antigen (Brocklehurst, 1960) and bronchoconstriction was induced in man when it was inhaled as an aerosol spray (Herxheimer and Stresemann, 1963). It is known that the contraction due to SRS-A is very long lasting, much more than that produced by histamine. All the evidence at present available seems to indicate that SRS-A is formed by enzymic processes activated by the union of antigen with

reaginic antibody, whereas histamine is released from a pre-formed store (Brocklehurst, 1970). However, although it is fair to conclude that SRS-A appears to have a role in asthma, because it is as yet very much an unidentified substance one can only speculate about its importance.

(c) Bradykinin.

There is very little evidence available in the literature about the formation and role of bradykinin in bronchial asthma. Austen (1971) showed that it had no action in the normal subject when administered by aerosol and that the response reported in asthmatics by Herxheimer and Stresemann (1961) could have been non-specific. There has been one report however, that the blood kinin level is raised in severe bronchial asthma (Abe et al, 1967).

(d) Prostaglandins

Prostoglandins are naturally occurring fatty acids that are widely distributed in a variety of tissues. Their chemical structure was first determined by Bergstrom and his co-workers in 1962. Small amounts of the prostaglandins E2 and F2 have been shown to be released from the guinea pig lung during anaphylaxis (Piper and Vane, 1969) but such observations have not yet been reported in man. Prostoglandins E2 and F2 have both been isolated from human lungs (Anggard, 1965; Karim et al, 1967). Sweatman and Collier (1970) found that PGE2 relaxes isolated human bronchial muscle whilst contraction results when PGF2 is applied. Neither atropine nor mepyramine decreased the response produced by

PGF_2 and therefore it does not appear to act by stimulating cholinergic nerves or by releasing histamine. Cuthbert (1969, 1971) reported that inhalation of PGE_1 and PGF_2 resulted in an increase in the FEV1 in asthmatics. Hedquist (1971) has shown a drop in SGaw in normal subjects after the inhalation of PGF_2 ; this decrease in SGaw was over in ten mimutes. The function of prostoglandins in the normal lung is unknown and their relationship with bronchial asthma remains to be proven. Horton (1969) suggested that overproduction of the bronchoconstrictor PGF_2 at the expense of the relaxants PGE_1 and PGE_2 might explain changes associated with bronchospasm. This, however, is still mere speculation and there is no evidence to support it. It has been claimed that PGE_1 and PGE_2 increase leucocytic cyclic AMP levels by stimulating adenyl cyclase (Lichtenstein et al, 1971).

(iv) Non-immunological mechanisms in asthma.

In addition to the immunological aspects of asthma it has been suggested that this condition may also be due to a functional imbalance of the autonomic nervous system. This hypothesis was first put forward by Eppinger and Hess in 1917 when they introduced their concept of vagotonia and suggested that asthma might be due to an excessive cholinergic activity.

More recently Williams (1950) claimed that "a consideration of allergy as a result of a dysfunctional prepondrance of the cholinergic portion of the autonomic nervous system seems to fit the available

evidence best". However, experimental support for these statements has been lac ing until comparatively recently.

An important advance in the study of the autonomic nervous system was made by Ahlquist (1948) who first suggested that the different pharmacological effects of adrenergic drugs on smooth muscle could be accounted for if one accepted the existence of two sets of receptors which he designed alpha and beta, in or near the target organs affected by these substances. Beta adrenergic action, as produced for example by isoprenaline, is associated with bronchial smooth muscle relaxation, myocardial stimulation and peripheral vasodilation. The beta receptors were further subdivided into the β_1 receptors which were concerned with the effects on the heart and the β_2 receptors which were mainly associated with bronchial smooth muscle relaxation (Lands et al, 1967). It is now generally believed that the beta receptor is an enzyme, adenyl cyclase, (Sutherland and Rall 1960; Belleau, 1967; Robison et al, 1967) which is thought to be located in the cell membrane, and indications are that it may be a lipoprotein, (Sutherland et al, 1962). Adrenergically activated adenyl cyclase catalyses the formation of cyclic 3,5 - A.M.P., an intracellular nucleotide, from adenosine triphosphate, in the presence of magnesium ions. Cyclic 3,5 - A.M.P. then functions as an intracellular mediator of adrenergic action (Sutherland et al, 1968). Stimulation of alpha receptors is claimed to cause bronchoconstriction but as will be discussed further on, there is still some controversy as to the existence of alpha receptors in the lung.

Weiss and his co workers (1929) reported that intravenously administered histamine produced a fall in vital capacity in asthmatic subjects at dosage levels which left pulmonary ventilation unaffected in normals. The hypersensitivity to histamine present in asthmatic subjects has now been demonstrated by a number of workers and shown to persist even in the asymptomatic phase. (Curry 1946; Bouhuys et al, 1960; Dowell et al, 1966). Parfenjev and Goodline (1948) showed that mice which are usually resistant to the effect of injected histamine, developed hypersensitivity to this drug after the injection of a vaccine prepared from Bordetella pertussis. Investigation of this phenomenon in mice and rats by Fishel, Szentivanyi and Talmage (1962) showed that the administration of dichloroisoprotrenol, a beta-adrenergic blocking drug, increased their sensitivity to histamine to the same extent as the injection of the Bordetella vaccine. These authors suggested that histamine hypersensitivity is the result of a functional imbalance between the alpha and beta receptors. Szentivanyi (1968) went on to propose the theory that partial beta-adrenergic blockade is the major cause of bronchial hypersensitivity in asthma.

These observations gained in importance when McNeill (1964) reported that propranolol, a beta adrenergic receptor blocking drug, reduced the vital capacity in asthmatics and that this was not reversed by isoprenaline. Similar effects on asthmatics given propranolol for cardiac conditions were reported by Besterman and Friedlander (1965). Using the FEV_1 as an index, Zaid and Beall (1966) were unable to show an increase in hypersensitivity to histamine in

normals, following the administration of propranolol. Using a body plethysmograph, McNeill and Ingram (1966), however, showed a 50 to 100 per cent increase in airway resistance in normal subjects within the first thirty minutes of administration of the beta blocker. Richardson and Sterling (1969) reported a mean fall of 34.9% in specific conductance in asthmatics following intravenous propranolol but showed no change in normals who were given the drug. MacDonald et al (1967) had also reported a rise in airway resistance following intravenous propranolol administration and showed that this effect was largely prevented by atropine. Langer (1967) similarly showed atropine antagonism of propranolol aerosol effect in asthmatic patients. McDonald and his co-workers concluded that this bronchoconstriction could be explained on the basis of unopposed vagal activity. Subsequent reports confirmed that atropine aerosol prevented a decrease in FEV_1 in asthmatic patients who had been given propranolol intravenously (Grieco 1970; Grieco and Pierson, 1971).

The effect of beta adrenergic receptor blockers has also been attributed to their unmasking of alpha adrenergic receptor activity in bronchial smooth muscle (Fleisch et al, 1970). The presence of alpha adrenergic receptors in bronchial smooth muscle is a matter of some controversy. Forster (1966) found no evidence of alpha receptors in the trachea of the guinea pig and the same conclusion was reached by Cabezas et al, (1971) who studied the airways of dogs. Giurgis and McNeill (1969) studying isolated human bronchial muscle also reported results suggesting that the adrenergic receptors in the human bronchi are of the beta type. Bronchial alpha receptors

have, however, been shown to exist in some animal species (Castro de la Mata et al, 1962; Everitt and Cairncross, 1969). Mathe et al (1971) have presented evidence, from their studies on isolated strips of human bronchi, that alpha receptors were present, although they appeared to be sparse.

Govendaraj and Kerr (1968) and Kerr et al, (1970) showed that in asthmatics, bronchoconstriction occurring after histamine administration could be inhibited by the alpha-blocking drugs phenoxybenzamine and phentolamine. Although these workers claimed that this effect was due to the alpha receptor blockade, their evidence for the presence of these receptors is inconclusive as both drugs are known to have additional effects which might have contributed to or even caused this effect. Thus phenoxybenzamine is known to have an anti-histamine action which is as powerful as many of the anti-histamines used clinically, and phentolamine has a direct action on the adrenal medulla leading to an increase of catecholamines, (Goodman and Gilman, 1970). Thymoxamine has been described as the most selective alpha adrenergic blocking drug available at present (Brownlee, 1966) and is known to be without effect on beta receptors (Birmingham and Szolcsanyi., 1965). It also lacks the mixed actions seen with other adrenergic blocking drugs. Bianco et al (1972) first demonstrated that thymoxamine prevented most of the decline in specific conductance caused by the inhalation of 400 g of histamine in four normal subjects. Gaddie et al (1972) using thymoxamine showed that it had a protective effect against histamine-induced bronchoconstriction in extrinsic asthmatics. They suggested that this was evidence for the presence of alpha adrenergic

receptors in human bronchial muscle.

The evidence for the existence of alpha receptors in human airways is based on the use of alpha adrenergic blocking drugs to protect against histamine-induced bronchoconstriction. However, the evidence is not quite conclusive as even thymoxamine, which is the most selective of the alpha blockers is known to have a weak antihistamine action., (Birmingham and Szolesanyi, 1965). Thus unopposed cholinergic impulses might be responsible for the bronchoconstriction resulting from beta adrenergic blockade, the mechanisms and relative importance of which in the aetiology of asthma are still to a great extent unknown.

Although the aetiology of bronchial hyperactivity in asthma and the mechanisms by which it is expressed are uncertain, (Cade and Pain, 1971) hypersensitivity of the bronchial tree seems to be the most basic functional defect demonstrable in asthma (De Vries et al 1962); Parker et al 1965). Hypersensitivity does not seem to be related to the type of asthma (Klein and Salvaggio, 1966) nor to sex, age, initial level of airways obstruction or treatment with corticosteroids (Cade and Pain, 1971).

(v) Other factors associated in asthma.

(a) Respiratory infection.

Acute respiratory infections are often known to trigger off attacks in asthmatic patients. These infections are also known to increase the reactivity of the bronchi to metacholine aerosol

both in asthmatic patients as well as in normal subjects, (Packer et al, 1965). The cause of this altered reactivity is unknown. There is some evidence suggesting a role for microbial products in the development of bronchial hyper-reactivity. Thus Cooke (1947) reported attacks of asthma developing in asthmatic patients following injections of autogenous bacterial vaccine. Similarly Hajos (1963) showed that attacks were provoked when asthmatics inhaled aerosols of influenza virus or bacterial vaccines, and Hampton et al, (1963) showed the same effects with an aerosol containing an extract of Neisseria catarrhalis. Ouellette and Reed (1965) noted that asthmatics were more sensitive to metacholine following an injection of killed influenza virus vaccine; normal subjects did not show this increase in sensitivity.

Various microbial products are known to be able to release some of the pharmacological mediators of bronchoconstriction. The nature of such a microbial activity is not known but is presumed to be a non-immunological direct effect on such cells as the mast cells (Szentivanyi, 1971). The exotoxin, toxin, from Staphylococcus pyogenes has been shown to liberate histamine (Brown et al, 1966) as have endotoxins from E. coli (Davies et al, 1963).

(b) Psychological factors.

It has been a long standing clinical observation that emotional factors and stress frequently precipitate attacks of wheezing in some asthmatic patients. Hippocrates wrote ' the asthmatic should guard himself against his own anger'. Dekker and Green (1956)

showed that attacks of asthma could be regularly produced in some of their asthmatic patients by inducing anxiety by discussing with them emotionally charged situations derived from their case histories. Luparello and his co-workers (1968) carried out some very interesting work showing that suggestion operated in asthmatic patients. They measured changes in airway resistance and showed that almost 5% of the patients studied showed an increase when given nebulized saline to inhale, and were told that it was the allergen which the patient had previously associated with his attacks. In a number of these an inhaled saline placebo reversed the attacks of bronchoconstriction which had developed. In a second study, Luparello et al (1970) gave their asthmatic patients isoprenaline and carbachol to inhale under double-blind conditions, suggesting to them that one was a bronchodilator and the other a bronchoconstrictor. The suggestions resulted in significant changes in the response to the drugs in the way that had been suggested. Rees (1967) reported major psychological stress immediately preceding the onset of asthma in 35% of 800 asthmatic patients. Zealley et al, (1970) investigating psychopathology in asthmatic patients concluded that traits of sensitivity, anxiety, obsession, dependency and low self-confidence were commoner in asthmatics than in normal controls. They pointed out however, that psychopathology need not be implicated as the cause of the asthmatic diathesis; it is as likely that concomitant psychopathology only determines the clinical presentation.

McFadden et al (1969) showed that the asthmatic response to suggestion could be abolished by atropine and suggested that it was

thus mediated via efferent cholinergic pathways. Hyperventilation is a common accompaniment of intense emotion and could possibly be another method by which stress could precipitate asthma since hypocapnia is known to lead to increased airway resistance (Newhouse et al, 1964).

It is worthwhile considering what Francis Rackemann had to say on asthma as far back as 1931; "The situation is somewhat analagous to that of a loaded gun. A good deal of knowledge is being obtained about the great variety of triggers which fire the charge, but why is the gun loaded ? And what constitutes the load ?" As shown in the preceding sections, his questions are still far from answered more than forty years later.

THE PATHOLOGY OF BRONCHIAL ASTHMA.

Most of the knowledge at present available about the pathology of asthma has been obtained from lungs of patients dying in status asthmaticus. Little is known about the pathology of the less severe forms of asthma. However, important information has also been yielded from bronchial biopsy material and sputum studies.

At post-mortem the striking feature is that the lungs often appear overdistended and fail to collapse. They have been likened to the lungs in fresh-water drowning (Gough, 1955). Small area of collapse involving a small number of secondary lobules are often seen and occur most frequently along the anterior margins of the lung. The cut surface of the lung shows the presence of occluding mucus plugs and occasional areas of bronchiectasis and there is a notable absence of destructive emphysema, the architectural pattern of the lung being well maintained. Both the large and the small airways may contain the mucus plugs but they occur typically in the segmental bronchi and in the bronchi of three or four generations distal to this. Any bronchiectasis is probably secondary to the absorption collapse following bronchial occlusion by the mucus plugs (Dunnill, 1971).

The outstanding finding in any section of asthmatic lung is the presence of a dense exudation in the bronchial lumen. The exudate consists of both mucus produced from the glands in the bronchial wall as well as a protein-laden serous exudate arising from the increased permeability of dilated capillaries in the sub-

mucosa. The presence of this serous component is thought to have an adverse effect on the ciliary action of the mucosal cells (Hilding, 1932). The cellular component of the exudate is made up of eosinophils together with normal or degenerate columnar respiratory epithelial cells. Shedding of ciliated mucosal cells has been described as a constant feature in any asthmatic lung; and it is considered by some workers to be due to the transudation of oedema fluid from the submucosa through the mucosa (Dunnill, 1971). Sanderkin and Evans (1965) have sectioned sputa from asthmatic subjects and have demonstrated that the non-mucoid elements of the exudate organize into the strips and laminae which become the basis of the spirals described by Curshmann in 1883. Autolysis of the cellular elements is thought to lead to the formation of Charcot-Leyden crystals. More recently Naylor, (1962) drew attention to the presence of compact clusters of columnar epithelium cells, known as Creola bodies, in the sputum of asthmatics.

A detailed description of the changes present in the bronchial mucosa of patients dying in status asthmaticus has been given by Dunnill (1960). Mucosal oedema with separation and shedding of the superficial ciliated columnar cell layer is a common finding. Metaplastic or regenerating epithelium is seen in all patients dying of asthma. Eosinophils are often present between the mucosal cells. The basement membrane is almost invariably thickened (Cardell, 1956, Rose and Radermecker, 1971; Dunnill, 1971). Electron-microscopic studies have shown that this thickening is due essentially to an increase of the collagen fibres (McCarter and

Vazques, 1966). The presence of immunoglobin deposition just below the bronchial epithelium of biopsy specimens from asthmatic lungs has been demonstrated by immunofluorescence and include IgG, IgA and IgM (Callarame et al, 1969). Since IgE seems to be the major immunoglobin implicated in extrinsic asthma it would be expected that it should have been found too. However, since only minute quantities of this highly active immunoglobin are required to induce symptoms, its demonstration may be difficult.

The capillaries in the submucosa are dilated and their endothelial cells often oedematous. A cellular infiltrate is frequently present in which eosinophils are prominent but which also contains lymphocytes and some mast cells. Mucus gland hypertrophy is generally thought to be present. Marked tissue eosinophilia is frequent in asthmatic patients (Glynn and Michaels, 1960; Salvata, 1968; Connel, 1971). Eosinophils were found more frequently in bronchial tissues than in the blood or sputum, and in general there was no relation between the numbers found in these three situations.

Salvato (1959, 1968) biopsied the bronchial wall of asthmatic patients before and during an asthmatic attack and found significantly lower mast cell counts in biopsy material removed from patients during an episode of asthma than in biopsy material obtained from the same patients during the asymptomatic phase of the disease. His findings were corroborated by the work of Connell (1971). It is suggested that the paucity of the mast cells is almost certainly due

to the fact that they are degranulated, and degranulated mast cells cannot be identified in tissue sections. It is well known that degranulation of mast cells occur following anaphylaxis (Mota 1963) and treatment with the histamine liberator 48/80 (Salvato 1961, 1963). It seems likely that mast cell degranulation in asthma has the same functional significance. Although it is known that mast cells are rich in biologically active substances such as histamine, heparin, hyaluronic acid and most probably slow reacting substance of anaphylaxis neither their precise physiological function nor the possible role they might play in conditions such as asthma has as yet been determined (Kahlson and Rosengren 1971).

Connell (1971) also observed an inverse relationship between the eosinophilic infiltrate and the mast cell content of the bronchial wall; the greater the number of eosinophils, the fewer the number of mast cells. Archer (1963) showed that the behaviour of mast cells might govern tissue eosinophilia. West (1959) pointed out that eosinophils appear in mastocytomas only when there is disruption of mast cells and Welsh and Greer (1959) describe phagocytosis by eosinophils of granules of mast cells disrupted by 48/80. Hence it is tempting to infer that in bronchial asthma the tissue eosinophilia is secondary to massive degranulation of mast cells (Salvato 1968). However, although it has been demonstrated that eosinophils are capable of phagocytosing antigen-antibody complexes, little is actually known of their action in asthma (Hansinger et al 1972), or of the inter-relationships between eosinophils and mast cells in this condition.

One other striking feature in the pathology of asthma is the presence of marked hypertrophy of the bronchial smooth muscle (Spencer 1968) which was first described by Huber and Koessler in 1922. Dunnill et al, (1969) found that 11.9 ± 3.4% of the segmental bronchial wall was occupied by smooth muscle in cases of status asthmaticus compared with 4.6 ± 2.2% in normals. The relative importance of bronchial smooth muscle hypertrophy mucosal oedema and plugs of tenacious mucus in the pathogenesis of airway obstruction is discussed more fully in the next section.

The role of smooth muscle in normal airways and in bronchial asthma.

Since Reisseisen's anatomical study of the bronchial musculature and the demonstration of airway smooth muscle in 1882, and Varnier's original observation in 1779 of its powers of contraction, there have appeared a number of fundamental papers reviewing its structure, regulation of tone and possible function (Toldt, 1888; Miller, 1921; Macklin, 1929; Wyss, 1952; Widdicombe, 1963; Olsen et al, 1967).

Reisseisen pointed out that the architectural structure of airway smooth muscle is such as to allow easily the adaption of the rhythmic changes in length and width of airways, which he recognised to be an integral part of the process of breathing. Toldt (1888) gives one of the earliest more detailed descriptions of the muscle layer in the bronchi; he described the muscle fibres as being arranged in a lattice-like form (gitterformige).

Miller (1921) in his classical paper on bronchial musculature confirmed Toldt's description that the musculature surrounding the bronchi and bronchioles is not in the form of distinct bands which encircle the airways but is in the form of a network. He described the muscle bands forming the network as "geodesic", i.e. lying along the shortest mural path between any two points. He stated that these "geodesic" bands prevented tangential motion, and in this way provided for the greatest amount of strength and at the same time permitting the greatest amount of extension and contraction of the airways. Macklam (1929) described the bronchial musculature as a contractile net embracing the mucosa of the entire bronchial tree. The prevalant view is that the smooth muscle extends from the trachea down to the alveolar ducts, (Widdicombe and Stirling, 1970). In the bronchioles and alveolar ducts the smooth muscle is thicker relative to the diameter of the lumen (Huckert,1913; Macklam, 1929; Widdicombe, 1963) and it is to be expected that changes in bronchomotor tone would affect the diameter of these airways more, both because of the greater bulk of smooth muscle and also because the centripetal force due to mural tension varies inversely with the radius - Laplace's law (Widdicombe, 1963).

The precise physiological function of airway smooth muscle is still unknown (Douglas et al 1966; Macklem, 1971), and there is as yet no general agreement on the role that it might play in airway obstruction. Studies performed to determine the effect of smooth muscle tone on the mechanical properties of airways have resulted in conflicting evidence. Radford and Lefcoe (1955) found that con-

striction of isolated bronchi did not alter the length-tension characteristics of the airways. Olsen and his co-workers (1967) however, found that this was only true of the trachea; constriction increased both the circumferential as well as the longitudinal tension in bronchi. Bronchoconstriction led to a decrease in bronchial compliance so that the airway became not only less distensible but also less compressible. This would seem to indicate that in the constricted state a greater compressing pressure is necessary to close the airway than in the relaxed state. Olsen attributed this to the presence of cartilaginous plaques in the airway wall that are pulled into an overlapping position when the bronchi are constricted extending the collagen fibres between the plaques and increasing the rigidity of the airway.

Widdicombe and Nadel (1963) have put forward the suggestion that smooth muscle tone helps to adjust the dead space and the airway resistance to optimal values at which the mechanical work of breathing is minimal. Bouhuys et al, (1959) have suggested that in small airways muscle tone may help to keep unequal gas distribution to a minimum. Bouhuys and Van de Woestyne (1971) measured lung volumes, air ay conductance, iso-volume pressure flow curves and static lung recoil curves in normal subjects before and after the administration of a bronchodilator aerosol. Their results - a marked increase in airways conductance with little change in the flow rates of the maximum expiratory flow volume curves - are in keeping with Olsen's suggestion that normal airway smooth muscle tone in man may help large airways to withstand dynamic compression

during forced expiration.

The relative importance of mucosal oedema and congestion, increased mucus secretion, the obstruction of small bronchioles by tenacious mucus plugs, bronchial muscle hypertrophy and muscle contraction in the pathogenesis of bronchial asthma is still a matter of some controversy. Laennec in 1819 wrote "On concoit tres bien que la contraction spasmodique de ces fibres puisse etre portee assez loin pour etrangler les conduits aeriens et empecher la penetration de l'air dans une grande partie des poumons".

But although "bronchospasm" has long been regarded as an important, if not the main, component of bronchial obstruction in asthma, there has been little direct proof of this. Frankland (1968) rightly makes a plea for the word 'bronchospasm' not to be used in reference to asthma as its use would seem to indicate a precise knowledge of the pathogenesis of asthma which we do not have. Unlike mammalian striated muscle, which is activated exclusively by a cholinergic effector system, mammalian smooth muscle can be activated by a variety of endogenous and exogenous agents (Somlyo and Somlyo, 1970). The causes of bronchoconstriction are numerous and complex and not fully understood. Thus various factors such as histamine, bradykinin, prostaglandins and slow reacting substance of anapylaxis are known to cause bronchoconstriction (Collier, 1968); besides it seems likely that changes in automatic balance play a part, for example in the effect of emotions on the bronchi. Schild et al (1951) exposed isolated bronchial

muscle from the lung of an asthmatic patient to a dilute solution of the specific antigen to which the patient was known to be clinically sensitive and showed that it contracted. Rosa and McDowall (1951) similarly showed contraction of a bronchial chain preparation, obtained from the lung of an asthmatic patient who underwent pneumonectomy for a bronchogenic carcinoma, when this was brought in contact with a flour-dust extract to which the patient was known to be allergic. Douglas et al (1966) demonstrated hyperactivity of the bronchi in asthmatics by measuring the "squeeze" pressure exerted by the bronchi during expiration by means of a balloon in a segmental bronchus.

Pharmacological results indicate that cholinergic, presumably vagal, nervous activity contributes to bronchoconstriction in some asthmatic patients, since atropine has been known for a long time to relieve airways obstruction in these patients (Herxheimer, 1959; Chamberlain et al, 1962; Altounyan, 1964). Hypocapnia, too may induce a bronchoconstriction in man, probably mediated by the vagus, (Newhouse, 1964; Pirnay et al, 1964) and may have a larger effect in asthmatic than in healthy subjects (Hafez and Crompton, 1968). Hypocapnia is not uncommon in asthma of mild to moderate severity, as a result of hyperventilation. Stirling (1968) showed that acute hypoxia causes an increase in airways resistance in normal subjects. He suggested that this is due to constriction of bronchial smooth muscle since it can largely be prevented by orciprenaline. He showed that hypoxia seems to act directly on the bronchial muscle as atropine had no effect on the bronchoconstriction response.

The dominant role of smooth muscle contraction in the pathogenesis of bronchial asthma is now being questioned by various workers (Dunnill, 1969), as the importance of mucosal oedema, increased mucus secretion and blocking of peripheral airways by tenacious mucus plugs becomes increasingly more recognised. Floyer (1698) pointed out the importance of mucus plugs in the pathology of asthma, when he wrote "If the Fits continue long, viz. two, three or four days, the first two days none or little phlegm is spit up, but on the third or fourth day it is cough'd up somewhat digested and less viscid". As early as 1950, Du Bois de Montreynaud reported seeing on direct bronchoscopy, a rapidly forming bronchial mucosa oedema in allergic subjects in whom asthmatic reactions were provoked by inhalation of specific allergens. Dunnill (1960, 1969) speculated that the smooth muscle hypertrophy found in asthmatic lungs, where ciliary action is often defective, was a response to increased clearance of exudate, possibly by a milking action; as suggested in the cineradiographic study of Holden and Ardran (1957). It is perhaps more likely that it represents work hypertrophy from bronchoconstriction (Takizawa and Thurlbeck, 1971).

It thus seems probable that in the earlier stages of an attack active bronchoconstriction is the major factor, since dramatic relief is obtained with sympathomimetic drugs, (Widdicombe and Stirling, 1970) but when an acute attack becomes protracted or the condition becomes more chronic, the situation is complicated by oedema of the mucosa and by retention of very viscid mucus.

The status of the hypothalamic-pituitary-adrenal axis in asthma.

Since it was established that corticosteroid therapy is frequently of great benefit in asthma, it has been tempting to postulate that failure of the adrenal cortex may be an underlying defect in some asthmatic patients. Recently there have been reports of asthma occurring in patients with Addison's disease and in one of these asthma appeared to be the presenting symptom of adrenal insufficiency (Green and Lim, 1971; Harris and Collins, 1971). The infrequency of asthma in Addison's disease, variously reported as 0.5% (Maranon et al, 1956) and 4% (Carryer et al, 1960), however, make the proposition most unlikely.

Several papers on adrenal function in asthma have been published, some reporting inadequate basal function or inadequate response to stress and others finding no evidence at all of such dysfunction. There has also been one report by Siegal et al (1956) in which increased levels of plasma 17-hydroxycorticosteroids (17 OHCS) were found. These workers reported that the plasma levels of 17 OHCS were significantly higher in a group of patients with moderate (13.0 ± 2.01 mcg%) or severe symptons (18.8 ± 7.61 mcg%) than in mild groups (3.3 ± 0.61 mcg%) or in an asymptomatic group (3.3 ± 0.61 mcg%).

Early workers using tests then available, reported reduced adrenal function in asthmatic patients (Rackemann, 1945; Eriksson-Lihr, 1951; Rose et al, 1955). Spaner et al, (1960) found re-

duced levels of urinary 11-hydroxycorticosteroids (11-OHCS) during an asthmatic attack. Vacarezza (1961) reported normal plasma cortisol levels and normal values of urinary 17-hydroxycorticosteroids (17-OHCS) in 22 adult asthmatics but a poor plasma cortisol response to corticotrophin stimulation. Robson and Kilborn (1965) found that although plasma cortisol levels were normal at rest, almost 70% of their asthmatic patients had a significantly diminished response to an intravenous infusion of A.C.T.H. Some evidence that the hypothalamic-pituitary-adrenal axis may be impaired in asthma has recently been reported by Collins et al (1971). Three of their eight patients with acute asthma, who had not previously received corticosteroids, had pretreatment plasma 11-OCHS levels of less than 10 g per 100 ml and all had levels of 23 g or less. They comment that such levels are well below the range expected in response to stress. Low levels of 11-OHCS could possibly represent depression of hypothalamic activity by hypoxaemia.

On the other hand, Kass and Appleby (1960) found no difference in the amounts of 17-OHCS excreted in the urine of asthmatic patients and normal controls, before and after corticotrophin stimulation. Similar results were published by Nelson et al (1966). Blumenthal and his co-workers (1966) measured plasma cortisol levels, urinary 17-OHCS and performed the oral metyrapone test and measured the response to intravenous A.C.T.H. in five patients with extrinsic asthma. They failed to find any abnormality either during the asymptomatic period or when attacks were induced with ragweed pollen.

Dwyer et al (1967) too, reported normal 11-OHCS response to intravenous hydrocortisone in three asthmatic patients with acute episodes who had never been given corticosteroids.

A number of explanations can be put forward to account for some of these discrepancies. The variety of methods used for measuring corticosteroids and their metabolites is an important factor which may have contributed to the different results. The bioassay procedures used in many of the earlier studies are known to yield rather variable results, especially when comparisons are made between different laboratories. The patient population studied also appears to be widely different. The type of asthma, its severity and the presence or absence of associated complications or diseases are but a few of the many ways in which the subjects of the various studies have differed. Each of these variables may affect corticosteroid levels. The nutritional status of the patient may also affect corticosteroid metabolism; thus even a low protein, high carbohydrate diet may result in a decrease of both plasma and urinary corticosteroid levels. Similarly, concomitant endocrine, renal or liver disease and drugs, such as phenobarbitone, may influence corticosteroid levels. Insufficient data is provided to ensure that some of these factors were not operative in a number of the patients studied.

It appears that dysfunction of the hypothalamic-pituitary-adrenal axis is not a necessary predisposing factor for the development of asthma. But one cannot exclude the possibility that it could well be a conditioning factor in some patients, although the

the relatively infrequent occurrence of atopic diseases in patients with Addison's disease lends little support to this conjecture.

ALTERED PULMONARY FUNCTION IN BRONCHIAL ASTHMA.

(i) Airways resistance in asthma.

Increased airway resistance may be said to be the physiological hallmark of bronchial asthma. This increase in resistance to the flow of air is well reflected in the physiological indices used as tests in its detection and monitoring. In general, the forced expired volume in one second (FEV_1); and the maximum mid-expiratory flow rate (MMFR) and the peak expiratory flow rate (P.E.F.R.) are found to be consistently decreased from the predicted and are usually well related to the severity of symptoms. However, it is now recognised that subjective improvement is not always necessarily reflected in a similar change in the tests mentioned above. The ratio of the forced expired volume in one second to the forced vital capacity is also found to be reduced. Airway resistance (Raw) as measured by body plethysmography provides a direct measurement of the resistance to the flow of air. Various studies using body plethysmography have now been carried out in asthmatic patients both during the symptomatic phase as well as following therapy. The Raw is always increased, frequently very considerably, and the specific conductance (SGaw), that is the conductance divided by the thoracic gas volume at which the airway resistance is measured, correspondingly decreased during the acute phase; both indices return towards normal values as the patient's condition improves (Lapp Le Roy and Hyatt, 1967; McFadden and Lyons, 1968, 1969; Herzog et al, 1968; Pelzer and Thomson, 1969; Fisher et al, 1970; Daly, 1971; Vassallo et al, 1972). An increased Raw has been found to be

present even during the asymptomatic phase in some asthmatic patients (Ruth and Andrews, 1959; Bernstein and Kreindler, 1963).

Cade et al, (1971) provoked bronchoconstriction in asymptomatic asthmatic subjects with nebulized metacholine. They found that pulmonary resistance increased within one breath of the metacholine inhalation and was the measurement of lung function which changed most in response to the drug.

(ii) Lung volumes

The vital capacity is generally decreased in asthma and is usually more severely diminished the greater the degree of airway obstruction. A decrease in vital capacity not infrequently persists during the asymptomatic phase of bronchial asthma. Levine et al, (1970) have reported values of vital capacity as low as 40% and 61% of the predicted in two asthmatic subjects who were clinically asymptomatic. Lowell et al, (1955) have used the vital capacity to follow changes in asthmatic patients, but, on the whole, it has proved a far less sensitive index for this purpose than dynamic ventilatory tests.

A number of reports have appeared in which measurements of Total lung capacity (T.L.C.) Functional Residual capacity (F.R.C.) or Residual Volume (R.V.) in asthmatics were found to be elevated, thus reflecting the presence of a certain degree of hyperinflation. In fact, a reversible increase in T.L.C. has been documented in asthma as early as 1934, when Hurtado and Kaltreider observed a

decrease in T.L.C. following the administration of epinephrine to patients with acute asthma.

During an exacerbation of asthma the F.R.C. is frequently elevated whereas the T.L.C. may remain unchanged, may increase or even decrease (Woolcock and Read, 1968). Before Engstrom's study of asthmatic children in 1964, no systematic study of the serial changes in the various subdivisions of the lung volumes occurring during the various stages of this condition had been reported. Engstrom found that the T.L.C. was above the predicted levels in nearly all his subjects even when the children were clinically asymptomatic. He suggested that there was an increased rate of growth of the lungs in these children; his suggestion is however, unlikely because when such children are maintained symptom free over a prolonged period, subsequent lung volume measurements are within normal (Kraepelin, 1959). Since then a number of papers reporting the changes in lung volumes that occur during acute asthma and the period of recovery have been published (Woolcock and Read, 1965; Woolcock and Read, 1966; Meisner and Hugh-Jones, 1968; Weng and Levison, 1969; Palmer and Diament, 1969; Staneson and Tetulescu, 1970; Mayfield et al, 1971).

In general, the more severe the degree of airway obstruction the greater the amount of hyperinflation present, as shown by elevated R.V. and F.R.C., and both indices tend to decrease following treatment. In some of the patients reported by Woolcock and Read (1965) the F.R.C. during acute asthma was greater than the T.L.C. after re-

covery. In these patients tidal breathing during severe obstruction was taking place at a higher level than the point of maximal inspiration after recovery. Mead, Milic-Emili and Turner (1963) hold the view that inhibiting reflexes normally limit the degree of voluntary lung inflation; if this is true, then one must presume that such reflexes are modified in asthma. Palmer and Diament (1969) similarly found that as the airway obstruction increases in asthma there is a progressive hyperinflation of the lung and that when the obstruction is reduced by a bronchodilator, hyperinflation becomes less. Of the indices of hyperinflation they found that only RV/TLC% correlated consistently with the dynamic lung volumes and regard it as the best single measurement of hyperinflation in asthma.

Cade et al (1971) have investigated the mechanical properties of the lungs of five asymptomatic asthmatics following provocation with nebulized metacholine. There was an increase in thoracic gas volume in four of their subjects; the changes reached maximum values in a few minutes.

Various studies have now been reported in which serial measurements of functional residual capacity by a helium dilution method and thoracic gas volume by body plethysmography have been carried out in asthmatics during the acute attack and in the subsequent recovery period (Corbeel, 1968; Meisner and Hugh-Jones, 1968; Stanescu and Teculescu, 1970; Woolcock et al, 1971). In general, plethysmography yielded significantly larger values than did the helium dilution method. The differences were greatest when the asthma was

most severe and decreased during clinical recovery. As the helium dilution method accurately reflects the volume of ventilating parts of the lung, there must be significant portions of the lung that fail to ventilate during the time allowed for helium equilibration.

Hyperinflation may persist in the asthmatic patient even in the asymptomatic phase, (Beale et al, 1952; Woolcock and Read, 1966; Gold et al, 1967; Levine et al, 1970). Weng and Levinson (1969) reported finding hyperinflated lungs in asymptomatic asthmatic patients despite normal measurements of airway resistance. Petit, Melon and Melic-Emili (1960) in a carefully controlled study in asthmatics concluded that airway resistance may be doubled without the occurrence of any significant change in F.R.C. There is as yet little direct information on the relationship between increased airway resistance and pulmonary hyperinflation in asthmatics (Bates, Macklem and Christie, 1970).

The increase in F.R.C. may be compensatory to the decreased bronchial calibre found in asthma, and to a certain extent this may have a guy-rope effect in maintaining the patency of the airways. This, however, is not obtained without considerable cost to the patient, for as the lung volume increases, compliance diminishes progressively so that the further inspiration of a given volume of air requires the production of a higher transpulmonary pressure difference because the subject is breathing on a flatter part of the pressure-volume curve. The elastic work of inspiration will be greatly increased and must make considerable contribution to the patient's

sensation of dyspnoea. Asthmatic patients thus often find as much difficulty with inspiration as with expiration (Woolcock and Read, 1966).

(iii) The Lung elastic recoil pressure in Asthma.

Macklem and Becklake (1963) and Ting and Williams (1963) have both reported mean inspiratory static pressure-volume (P-V) curves for normal subjects and for patients with asthma and those with emphysema. In both studies the P-V curves for their asymptomatic asthmatic subjects were shifted upwards and to the left as compared with the mean curve for normal subjects; i.e. it appeared that the lung elastic recoil was reduced. Macklem and Becklake (1963) corrected for the increased lung volume in some of their subjects by calculating the "over-all compliance" (Mead et al, 1955), i.e. the ratio of T.L.C. to the maximum negative intrapleural pressure. This correction reduced the difference between the normal group and the group of asthmatics but accentuated the loss of elastic recoil in the group with emphysema. Other studies had indicated that patients with asthma have normal pulmonary elastic recoil pressures (Wells, 1959; Tooley et al, 1965).

Several workers have since measured the lung elastic recoil pressure in asthmatics both during exacerbations as well as in asymptomatic phases (Gold, Kaufman and Nadel, 1967; Woolcock and Read, 1968, Finucane and Colebatch, 1969). Gold and his associates showed that the elastic recoil pressure was decreased at all lung volumes in seven of their twelve asthmatic subjects. After

a week's treatment with corticosteroids and bronchodilators, the increase in airway resistance and in lung volumes reversed to normal and their P-V curves moved back to the normal range in all the patients but one. In the latter, a further week of treatment finally reversed all abnormalities. Gold also induced bronchoconstriction in four asthmatics who had normal P-V curves and in one normal subject with a 0.03% histamine phosphate inhalation. Although this resulted in a mean airway resistance of 320% of the control, the lung elastic recoil remained normal. Acute hyperinflation of the chest in a normal subject for an hour by means of a negative pressure jacket surrounding the thorax also resulted in insignificant changes in the lung elastic recoil. It thus appears that loss of lung elastic recoil is slow to develop. In a further patient whose treatment was discontimued for a week, Gold and his co-workers found that the lung elastic recoil which had been reduced prior to treatment, remained normal, despite a recurrence of airway obstruction.

Woolcock and Read (1968) showed that during an exacerbation six out of their ten asthmatic subjects had a decreased elastic recoil. Unlike Gold's patients, however, after intensive therapy although the airway resistance returned to normal in almost all of the patients the loss of lung elastic recoil and hyperinflation persisted in five subjects.

Finucane and Colebatch (1969) assessed the elastic properties of the lung in patients with asthma, emphysema and in normals by

measuring the static P-V curves of the lung during deflation from T.L.C.after a standard volume history. The P-V characteristics of this study thus mainly reflect the elastic properties of lung tissues since the pulmonary retractive pressure was measured during deflation from T.L.C. when lung surface forces contribute least (Radford, 1964). They found that in asthma compliance was similar to that in normal subjects but elastic retraction was reduced. The P-V curves, showed that the retractive pressure of the lung was inversely related to T.L.C., being least in the subject with the highest T.L.C. relative to the predicted T.L.C. and greatest in the subject with a normal T.L.C. In three of the four patients restudied by Finucane and Colebatch, there was a persistent reduction of elastic recoil pressure despite relief of airway obstruction for six weeks or longer. This finding agrees with that of Woolcock and Read (1968) and it seems likely that some patients with severe asthma may have a more or less permanent reduction of elastic recoil pressure.

The cause of the loss of elastic recoil of the lungs in asthmatic subjects is unknown. According to Mead (1961) the static P-V curve is dependent on two factors; the tension exerted by surfactant and the elastic properties of pulmonary tissue. The tissue component of the elastic retraction of the lung resides in the intimate association and arrangement of collagen and elastin fibres in the respiratory bronchioles, alveolar ducts and alveoli (Pierce and Ebert, 1969). In emphysema this fibre network is disrupted (Wright, 1961) and elastic retraction of the lung would be expected to be and is, in fact, reduced. In asthma the fibre network is

intact (Gough, 1955) and hence other factors must be responsible for the loss of elastic recoil. Gold et al, have suggested that prolonged distension of the connective tissue of the lungs causing temporary structural deformation is a possible explanation. Other alternatives they put forward are that the changes could be related to the forces exerted by surfactant; or the changes may be due indirectly to changes in perfusion of some alveoli which affects their production of surfactant or some other product important to the normal retractile forces. Apparently surfactant is easily lost or destroyed when the segmental pulmonary arterial blood supply is compromised (Pattle, 1961; Fenley et al, 1964). Similar changes are reported to occur with disturbances in arterial pH (Bergofsky et al, 1962) and hypoxia (Bergofsky et al, 1963; Scarpelli, 1971). In general, however, such changes in surface tension would be expected to occur in short periods of time and will not require days or weeks to take place.

Finucane and Colebatch (1969) put forward the idea that the loss of elastic recoil could be the result of a reduction of tissue forces due to tissue stress-relaxation (Marshall and Widdicombe, 1961). In asthma, stress-relaxation may occur in those parts of the lung held inflated by airway closure. Theoretically, the reduced retractive pressure in asthma could involve increased recruitment of surface-active molecules consequent upon prolonged over-expansion of the lung (Tierney and Johnson, 1965). The surface tension of a liquid is known to be inversely related to the concentration of surface-active molecules in the surface (Davies and Rideal, 1961).

Woolcock and Read (1969) suggested that hyperinflation of the lung, may itself, cause a reduction in lung elastic recoil, in a manner in which they did not explain; they looked at the problem from the opposite point of view from that of Gold and his associates. The latter considered the loss of elastic recoil to be responsible for the hyperinflation in asthma. If hyperinflation of the lungs itself causes a reduction in elastic recoil, then a residual abnormality in the airways sufficient to maintain a degree of hyperinflation could accoutn for the apparent loss of lung elasticity in asymptomatic patients. This could possibly account for the differences in results reported by Gold et al, and the work reported by Finucane and Colebatch, and Woolcock and Read. The patients reported on by Gold et al, all had normal lung volumes when the lung elastic recoil was measured after a week's therapy, whilst those reported on in the other two studies had persistent hyperinflation. One other factor put forward by Woolcock and Read as a possible contributing factor to the decreased lung elastic recoil is the effect that prolonged corticosteroid therapy may have on pulmonary connective tissue. There is however, no evidence to support this possibility.

(iv) The pulmonary diffusing capacity (D_L) in asthma.

There is some degree of controversy in the literature regarding diffusing capacity values in bronchial asthma. Measurements of diffusing capacity in asthma have now been performed during the asymptomatic phase (Levine et al, 1970) during an acute attack and in the

ensuing symptom free period (Weng and Levinson, 1969) as well as in subjects in status asthmaticus (Stanescu and Teculescu, 1970).

In a number of papers the diffusing capacity in asthma has been reported as normal. Among the first to report normal values were Bates (1958) and Macklem and Becklake (1963) who used a steady state method. Macklem and Becklake reported that both the diffusing capacity and the elastic recoil were well preserved in asthma and contrasted this with the decrease in both parameters that occurred in the emphysematous patients they studied. They found a high correlation between diffusing capacity and elastance in the sixteen asthmatic patients whom they studied and interpreted this as reflecting normal alveolar tissue. They found that at equivalent values of conductance emphysema is characterized by a considerably lower diffusing capacity than asthma. Normal values for diffusing capacity have also been reported when this was measured by the single breath method (Burrows et al, 1961; Kanagani et al, 1961; McFadden and Lyons, 1968; Meissner and Hugh Jones, 1968; Daly, 1971). The diffusing capacity was found to be normal even when the FEV_1 was markedly decreased (Bedell and Ostiguy, 1967; McFadden and Lyons, 1968; Ogilvie, 1968; Meissner and Hugh Jones, 1968).

On the other hand, there are now a number of papers reporting diminished values for diffusing capacity in asthma. Palmer and Diament (1969, 1970) using the single breath method measured the diffusing capacity in all grades of severity of asthma and found that it fell significantly as the degree of asthma became more severe.

They reported a mean value for D_L CO of 16.2 ± 7.3 ml/min/mmHg when the FEV% was less than 40% (the predicted being 26.1 ± 2.70 ml/min/mmHg); this value improved when salbutamol was administered.

Weng and Levinson (1969) measured the diffusing capacity by the steady state method in thirty asthmatic children during an acute attack and repeated the measurements when they were symptom-free. They found that it was significantly reduced during an acute attack but returned to the normal range during the symptom free period. The indices D_L CO/TLC and D_L CO/FRC which were markedly reduced during the attack remained significantly lower than normal during the symptom free period. Levine et al (1970) using a steady state method report a lower than predicted value in two of six asymptomatic asthmatics.

Stanescu and Teculescu (1970) studying patients in status asthmaticus and measuring the diffusing capacity by the single breath method found this to be below normal in three out of eleven patients. Following treatment this index increased in six patients including two of those with a low initial value. They attributed the decrease in diffusing capacity in their patients to the reduced value of 'effective' alveolar volume. They considered this decrease of the diffusing capacity in their patients with status asthmaticus as 'apparent', that is, not representing a true impairment of diffusing capacity but merely reflecting a regional unevenness of function throughout the lung. The diffusion constant (D_L/V_A)

was normal in all their patients.

There have been a number of reports in which the diffusing capacity has been measured following the administration of bronchoconstriction aerosols. Bouhuys et al (1960) and Lewis et al (1961) found a diminished diffusing capacity measured by the steady state method following the administration of histamine and metacholine aerosols. Bjure et al, (1966), however, have shown that there is an increase in diffusing capacity following the infusion of histamine and attributed this to the increase in cardiac output that occurs. Stanescu and Teculescu (1969) using a single breath method measured diffusing capacity before and after inducing bronchoconstriction with an acetylcholine aerosol in eight asymptomatic asthmatics and in five normal subjects. The diffusing capacity was within normal limits and fell in all subjects, returning to normal in most of them ten to twelve minutes later despite a persistent decrease in FEV_1. It is presumed that this decrease is due to changes in the distribution of diffusion in the lung to the alveolar volume.

Pecora, Bernstein and Feldman (1966) measured the diffusing capacity by the single breath method in twenty six children with intractable asthma. They reported that in sixteen children with hyperinflated lungs the diffusion capacity was greater than predicted whilst in the ten children who had no pulmonary hyperinflation the diffusion capacity was normal. They suggested that this increase

is due to a moderate increase in surface area of the lung and a greater decrease in the thickness of the alveolar membrane. Ogilvie (1968), too, reports higher than predicted values in a number of asthmatics, and points out that an imbalance between ventilation and perfusion can sometimes result in erroneously high values. Kreulniet and Nisser (1962) showed that the steady state diffusing capacity may be erroneously high in asthma.

Forster (1957) in his classical review of the processes of pulmonary diffusion and their assessment refers to the errors which may be introduced by non-uniformity of various parameters. Although the concept of a diffusing capacity is not difficult to envisage, the details of its measurement and the interpretation of the results obtained by the various techniques are far from straightforward, especially in clinical conditions in which there is non-homogeneous distribution of alveolar gas. Bates, Macklem and Christie (1971) have ascribed the difficulty in sorting out the apparent discrepancy of the diffusing capacity values in asthma obtained by various workers to four main factors - patient selection, variation in degree of airway obstruction, differences in technique and the uncertain interpretation of results obtained from induced bronchoconstriction. Thus, there is not infrequently difficulty when selecting patients, in differentiating between those suffering from asthma and those with chronic bronchitis with a degree of emphysema.

However, the interpretation of reports on diffusing capacity

in bronchial asthma is perhaps most seriously hampered by the variety of methods used in its determination. It is obvious that each method measures something different and probably none measures the true diffusing capacity of the 'pulmonary membrane'. The accuracy of each method for measuring this index of pulmonary function depends on certain critical assumptions about the relative uniformity of blood flow, ventilation and alveolar volume and if one of these assumptions is incorrect the measurement becomes biased (Forster, 1957). Since the assumptions are different for each method of measurement, a given type of non-uniformity in the lung is apt to bias the diffusing capacity measured by one method more than by another. This possibility accounts for most of the discrepancy between the various reports. Ohman et al (1972) measured the diffusing capacity in ten symptomatic asthmatics by both the single breath and steady state methods before and after treatment. The diffusing capacity measured by the single breath method was greater than predicted on both occasions. The mean pre-treatment value obtained by the steady state method was 51% of the predicted and it went up to 66% of the predicted following therapy.

The severity of the disease during which the measurement is made is another important factor to keep in mind when assessing results. Tests of diffusing capacity must be to a greater or lesser extent influenced by ventilation - perfusion abnormalities (Apthorp and Marshall, 1961).

Thus although the single breath method is said to be less sensitive to ventilation - perfusion ($\dot{V}_A/\dot{Q}_C$) abnormalities, in severe cases an impaired distribution of inspired air, regional $\dot{V}_A/\dot{Q}_C$ variations and the $DL/\dot{Q}$ ratio can decrease the value of the diffusing capacity obtained by the single method (Piiper and Sikand, 1966).

The transfer of gas in bronchial asthma thus appears to be more impeded by failure to deliver inspired gas to the alveolar surface than by interference with diffusion through the 'pulmonary membrane'.

(v) Arterial blood gas tensions and pulmonary gas exchange.

Very little attention was paid to the changes that occur in blood gases during asthma until comparatively recently. Bates and Christie (1964) stated that, "the patient with moderately severe bronchospasm but not in status asthmaticus only rarely shows any significant abnormality of arterial oxygen saturation or carbon dioxide tension". It had been generally assumed that the $PaCO_2$ is usually normal or low, due to hyperventilation until the terminal stages of status asthmaticus, when the $PaCO_2$ rises rapidly and respiratory failure supervenes (Marchand and van Hasselt, 1966). Before the important paper of Tai and Read in 1967 there had only been occasional reports of blood gas disturbances in bronchial asthma (Herschfus et al, 1953; Williams an Zohman, 1960; Feldman, 1962). Herschfus et al, studied fifteen patients during attacks

of asthma and found arterial oxygen desaturation in only two patients. Similarly, Williams and Zohman found only slight desaturation - a mean of 89% - in eleven of their fifteen patients. In both series, none of the patients had a raised blood carbon dioxide level.

Tai and Read (1967) were the first to report carbon dioxide retention, with arterial PCO_2 values ranging up to 200 mmHg and marked respiratory acidosis, with a blood pH as low as 6.81, in twelve patients admitted to their care in status asthmaticus. Their data showed that in other patients with only moderate clinical severity considerable hypoxaemia could also be present. Similar results have now been reported by a number of different workers (Reis, Millar and Donald, 1968; McFadden and Lyons, 1968; Meisner and Hugh Jones, 1968; Miyamoto et al, 1970; Robuck and Read, 1971). Arterial PO_2 levels below 60 mmHg may be associated with PCO_2 levels varying between 30 and 80 mmHg; such a level of PaO_2 is commonly seen when airway obstruction is severe, with an FEV_1 below 30% of the predicted normal value.

Pimnley (1971) states that if milder cases are included the fall in PaO_2 seems to bear a roughly linear relation to the FEV_1; normal PaO_2 values being usual when the FEV_1 is above 2 litres. Tai and Read (1967) found a general correlation between the degree of reduction of the FEV_1 and the extent of disturbance of blood gas tensions in their study of sixty four patients with moderately severe

asthma. They pointed out that FEV_1 levels of less than one litre were especially associated with a significant reduction of arterial PO_2; at the same time they emphasised that the correlation was not good enough to make FEV_1 levels greater than a litre a reliable index of a fairly normal arterial oxygen tension. The same conclusion was reached by Rees et al (1968) who stated that since increases in FEV_1 were not always accompanied by a rise in PaO_2, such changes could not be relied upon to indicate improved oxygenation. Palmer and Diament (1968, 1969) reported a correlation between PaO_2 and the RV/TLC%, hypoxaemia becoming progressively more severe as hyperinflation develops.

Rees, Millar and Donald (1968) following the clinical course and arterial blood gas tensions of twenty four patients in status asthmaticus, found that hypoxaemia was invariably present, was frequently quite marked and persisted despite intensive therapy sometimes for weeks. Most patients were normocapnic or even hypocapnic. When severe hypercapnia was present the patients generally died. They found that changes in $PaCO_2$ were inversely related to changes in pH and patients with severe hypercapnia had also metabolic acidosis. The pulse rate correlated well with PaO_2 and in the severely hypoxaemic patients the frequency exceeded 130 beats/min. McFadden and Lyons (1968) studied ninety one patients during an acute asthmatic attack. All their patients had hypoxaemia but hypercapnia was only present in eleven patients and was not found till the FEV_1 fell to below 20% of the predicted value. Hence

despite the fact that CO_2 retention is a prominent feature in some asthmatics with marked airway obstruction, low PCO_2 values indicating hyperventilation are frequently encountered. Hypocapnia and respiratory alkalosis was present in about 80% of the patients studied by McFadden and Lyons.

These studies have determined the facts that hypoxaemia, often of dangerous degree, may be present in asthmatic patients, and that severe hypercapnia is not usually present except terminally. Feldman (1962) pointed out the grave prognostic significance of an increase in $PaCO_2$ in adults with severe asthma.

The accompanying disturbance in the acid-base balance as reflected in the arterial blood, shows that the hypercapnia in most of these patients probably develops acutely. Flenley (1971) analysing the data from various authors (Reed et al, 1968; Mithoefer et al, 1968 Tubb and Guerrant, 1968; Tai and Read, 1967; Downes et al, 1968; Simpson et al, 1968)concluded that chronic elevation of PCO_2 is relatively uncommon in asthma. The increased renal reabsorption of bicarbonate which is an important defence against respiratory acidosis both in adults (Refsum, 1969) and in children with acute lower respiratory tract infection (Simpson and Flenley, 1967) thus appears to be too slow a mechanism to be of great importance in acute asthma, in which dangerous hypercapnia may develop very acutely. Mithoefer et al (1968) have found that correction of the respiratory acidosis by infusion of sodium bicarbonate was valuable in treating in-

tractable asthma, but others seem to have had less success with this approach (Flenley, 1971).

The mechanism of hypoxaemia, with or without CO_2 retention implies a maldistribution of ventilation and perfusion in the lungs which is shown by increased alveolar-arterial tension differences for oxygen $(A-a)DO_2$ and higher ratios of physiological dead space to tidal volume (VD/VT). A higher than normal $(A-a)DO_2$ and VD/VT has been shown to be present both during the acute attack (Field 1967; Meisner and Hugh Jones, 1968; Valabhji, 1968) as well as during the asymptomatic phase (Levine et al, 1970; Waddell et al, 1967). Valabhji's data is at variance with that of Waddell et al (1967), for in all his patients clinical recovery was associated with return of $A-aDO_2$ and VD/VT ratio to normal levels despite spirometric evidence of persisting airway obstruction in about half of them.

Simpson et al (1968) reported a significant correlation between PaO_2 and $PaCO_2$ in children with acute asthma breathing air on admission , and suggest that alveolar hypoventilation might also at times make an important contribution to the hypoxaemia in acute asthma.

Although uneven distribution of pulmonary ventilation in asthma has been recognised for a long time in both the acute phase (Bates, 1952; Fowler et al, 1952; Herschfus et al, 1953; Malmberg et al, 1963; Bates et al, 1968) and in the sympton free period, (Beale et al, 1952), the effect of this on the distribution of pulmonary blood

and the ventilation - perfusion relationships had until comparatively recently received less attention. Single cases of asthma with $\dot{V}/\dot{Q}$ disturbances had been reported by Donald et al, (1952) and by West et al, (1957). Leadbetter et al, (1964) in a study of asthmatic children reported that an abnormally high percentage of the cardiac output perfused the 'slow' or poorly ventilated compartments in the lungs.

The presence of adaptive mechanisms to divert blood flow away from poorly ventilated regions of the lungs were postulated by Barcroft, (1930); Anthony, (1930); and Haldane, (1935). The observation that hypoxia causes an elevation of pulmonary artery pressure probably secondary to pulmonary vasoconstriction led von Euler and Liljestrand (1957) to suggest that pulmonary hypoxia might play a role in controlling the distribution of pulmonary blood flow. Recent work has in general confirmed these suppositions. It is now generally accepted that the concentration of gases in the alveoli determine the resistance to blood flow in the adjacent vessels, and that the chemical stimuli for this local vasomotor control are hypoxia and to a lesser extent acidosis (Liljestrand, 1958; Fishman, 1961; Bergofsky et al, 1963; Fishman, 1969). Lopez-Majano et al, (1966) produced unilateral hypoxia by means of a Carlens catheter using 100% N_2 for seven minutes. By means of radioactive scanning following the intravenous injection of I ^{131}M.A.A. they showed that this was followed by a marked decrease in pulmonary bloodflow to the hypoxic lung. Evidence has also been adduced by other workers that a decrease in bronchiolar PCO_2 will redirect ventilation, towards better perfused parts of the lung, away

poorly perfused areas (Severinghaus and Stupfel, 1957; Arborelius, 1965). However, other mechanisms besides hypoxia - induced pulmonary vasoconstriction might play a role in the reduction of perfusion to poorly ventilated areas of lung (Woolcock et al 1966).

Although it seems unlikely that local alterations in perfusion could possibly compensate for the unevenness of ventilation in bronchial asthma, there is a lot of evidence to suggest that such homeostatic mechanisms do exist in asthma, and that they tend to reduce the $\dot{V}/\dot{Q}$ defect by decreasing the blood flow of underventilated lung units. Factors disturbing these homeostatic mechanisms would be expected to result in an increased $\dot{V}/\dot{Q}$ abnormality. Thus the administration of oxygen presumably by abolishing pulmonary vasoconstriction in hypoxic regions resulted in a worsening of the ventilation - perfusion imbalance in asthmatics as shown by an increase in the $(A-a)DO_2$ and VD/VT ratio. Breathing pure oxygen has been shown to have no effect on the pattern of $\dot{V}/\dot{Q}$ inequality in normal subjects or in patients with chronic lung disease (Riley, Cournand and Donald, 1951; Larson and Severinghaus, 1962; Cole and Bishop, 1963). Such a deterioration occurred not only in the acute phase of their illness (Field, 1967) but also in the asymptomatic phase (Valabhji, 1968); suggesting that during the latter phase a compensatory reduction of blood flow to underventilated parts of the lung might still be present. Supporting evidence for the existence of pulmonary vasoconstriction in asthmatics when sympton free has been produced by Irnell and Nordgren (1966) who infused acetylcholine

into the pulmonary artery of nineteen asthmatics and observed a reduction in arterial oxygen saturation in all but one. Valabhji (1968) reports a very small contribution of veno-arterial shunt of 3.7 ± 1.4% to the hypoxaemia present in their acute asthmatics. This is perhaps surprising in view of the widespread mucous plugging of the small airways that has been reported in asthma. The absence of a significant veno-arterial shunt could perhaps be explained on the basis of a diversion of blood flow from non-ventilated areas of the lungs as a result of pulmonary vasoconstriction.

LUNG SCANS IN ASTHMA.

Since the introduction of radioactive gases in the study of pulmonary physiology a great deal of information about the regional ventilation and perfusion of the lungs has become available. The first gas to be used was Xe^{133} in 1957 by Knipping and his co-workers who measured local ventilation. Radioactive xenon can, of course, also be used to measure regional blood flow as well as ventilation (Ball et al, 1962; Dollery and Hugh-Jones, 1963).

Bentivoglio et al, (1963) studied regional ventilation and perfusion in asthmatics during remission using the radioactive xenon technique and reported the presence of hypoventilation but a normal distribution of perfusion. A large number of studies using lung scanning following the inhalation of radioactive gases such as Xe^{133}, intravenous injection of I_{131} macroaggregated albumin as well as the inhalation of an aerosol containing Tc^{99m} - iron com-

ple , have now been carried out in asthma both during the acute attack and in remission (Woolcock et al, 1966; Mishkin and Wagner, 1967; Mishkin et al, 1968; Heckscher et al, 1968; Wilson et al, 1970; Despas et al, 1970). Most measurements showed well demarcated local ventilation and perfusion defects. Although the areas of hypoventilation generally showed decreased perfusion, some workers (Wilson et al, 1970) reported that the perfusion was frequently less effected than ventilation. Lung scans showed that the $\dot{V}/\dot{Q}$ imbalance frequently appears to be widespread in asthma. In general, repeat studies during improvement of symptoms showed normalization of $\dot{V}/\dot{Q}$ in areas which were previously involved; however, defects arising in new areas have also been observed (Mishkin et al, 1968; Heckscher et al, 1968).

Novey and his associates (1970) have studied early ventilation - perfusion changes following the induction of asthma by means of pollen, metacholine and exercise. He reported multiple focal $\dot{V}/\dot{Q}$ abnormalities appearing within minutes of induction of asthma. The regional ventilatory abnormalities were greater than those of perfusion although similar in distribution.

Although hypoxia is generally accepted as being mainly responsible for local pulmonary vasoconstriction, other mechanisms may also be involved in the causation of regional pulmonary blood flow defects. These include mechanical occlusion of capillaries by high intra-alveolar pressure at sites where regional hyperinflation is present,

(Despas et al, 1970). Permutt et al, (1961) have shown that blood flow throughthe capillaries of the lung is controlled by alveolar pressure so long as alveolar pressure is greater than pulmonary venous pressure. Another possibility is the local release of vasoconstrictive substances in asthma (Middleton, 1965).

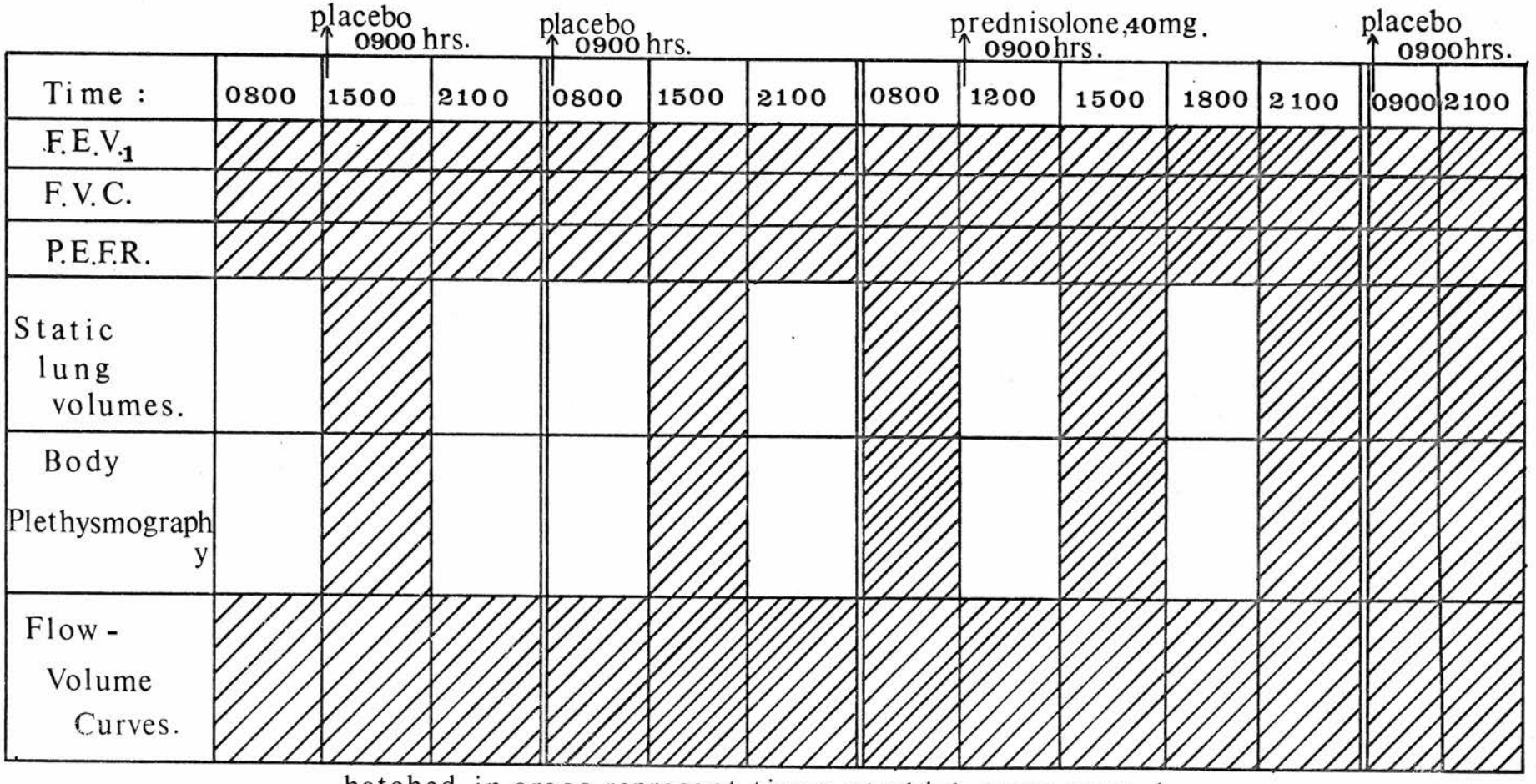
Plan of Study.

The study was carried out in two parts. In the first part the patients were studied over a period of four days. In order to obtain pre-treatment baseline measurements, to ensure that patients were in a stable clinical state and to assess diurnal variations, placebo tablets were given at 0900 hours on the first two days of the trial. The placebo tablets were supplied by Roussel Laboratories Ltd and contain Potato Starch B.P., Lactose B.P., Pregelatinised Starch, Talc B.P. and Magnesium Stearate B.P. They are indistinguishable in appearance and taste from the active drug. On the third day, 40 mg of Prednisolone acetate was administered as a single oral dose at 0900 hours and on the fourth day placebo tablets were again given at the same time. Repeated measurements of dynamic and static lung volumes, thoracic gas volume and airway resistance and maximum expiratory flow-volume curves were performed. Figure (1) shows the measurements and the time at which they were performed throughout the period of study.

The second part of the study was carried out over a period of five days. In this group of patients placebo tablets were given

Figure 1

Plan of first part of study.



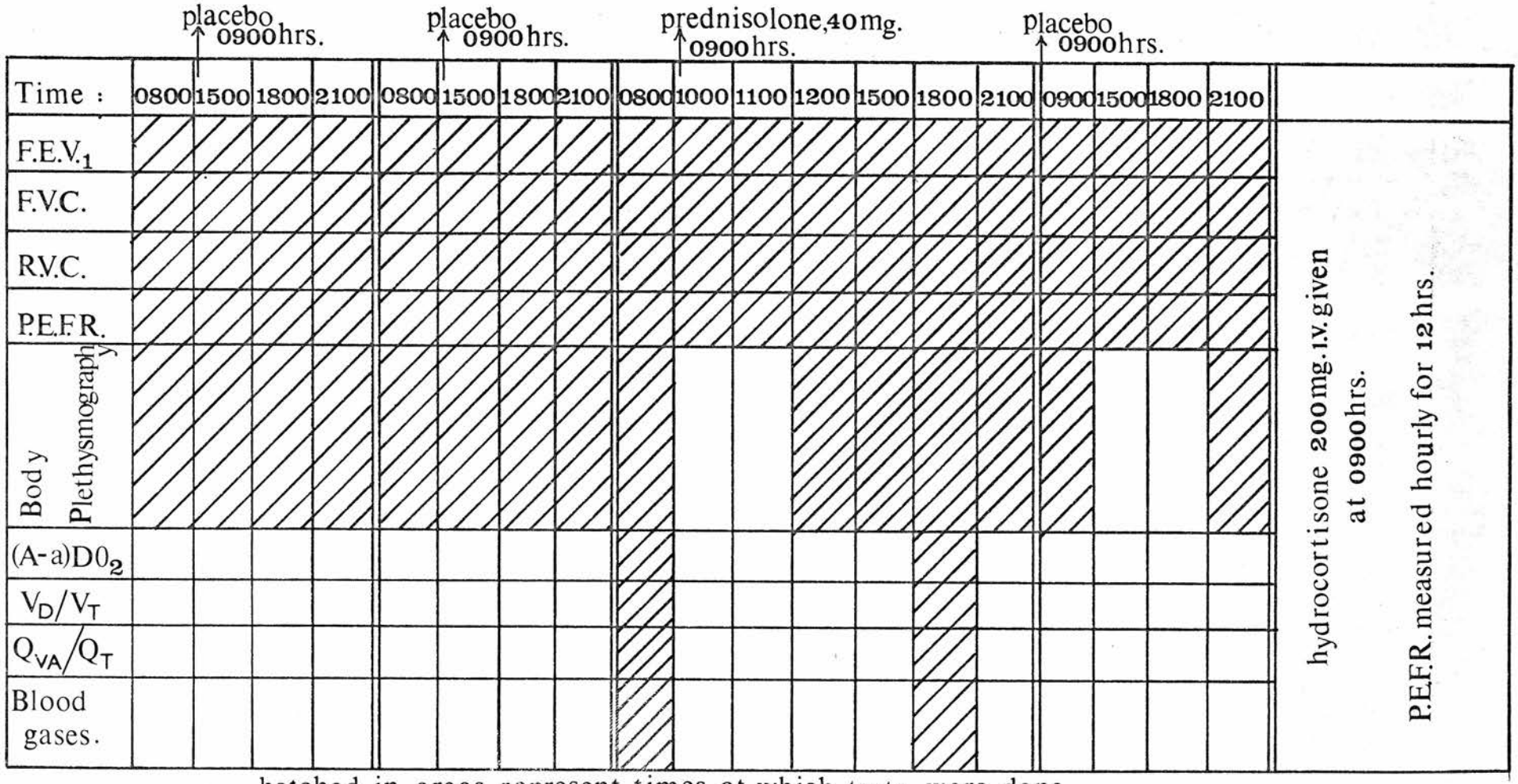
hatched in areas represent times at which tests were done.

on the first, second and fourth days and a single oral dose of 40 mg of Prednisolone acetate given on the third day. On the fifth day these patients received 200 mg of Hydrocortisone sodium succinate as a single intravenous injection. The way in which the measurements were altered from that in the first part of the study is shown in figure (2). Thus tests were performed hourly for the first three hours following administration of the active drug. Body-plethysmographic measurements were also more frequently performed. In this part of the study pulmonary gas exchange was investigated at the times shown in figure (2). The drugs in both parts of the study were administered with the patient in a fasting state.

At the time of admission the nature and purpose of the study were explained to the patients and informed consent was obtained. All drugs, including bronchodilators, were discontinued. A chest x-ray, an electrocardiogram and tests of hepatic and renal function were carried out. Three sputum specimens were examined for evidence of bacterial infection, Aspergillus fumigatus and eosinophils. Absolute blood eosinophil counts were carried out on three specimens of venous blood and serum precipitins to Aspergillus fumigatus were looked for. Immediate type skin hypersensitivity was tested to a wide range of allergies, including those derived from mites of the Dermatophagoides species. Reversibility of the airway obstruction to subcutaneous injections of 0.5 mg Adrenaline acid tartrate and 0.6 mg Atropine sulphate was also routinely performed.

Figure 2

Plan of second part of study.



hatched in areas represent times at which tests were done.

METHODOLOGY: DEVELOPMENT OF TESTS, PHYSIOLOGICAL BASIS AND PROCEDURE.

INTRODUCTION.

In order to carry out as complete a functional assessment as possible of the pathophysiological changes brought about by the administration of prednisolone to the patients in this study, a considerable number of pulmonary function tests was carried out. Bearing in mind that obstruction to the flow of air is the hallmark of bronchial asthma it was this aspect of pulmonary function that was particularly investigated. An essential factor that was kept in mind in choosing the tests was whether the subjects were likely to be able or willing to co-operate fully in their performance. This factor was of special importance because the tests were to be performed on a number of successive occasions to monitor the therapeutic effect of the drug. There is no definite answer at present as to which is the best pulmonary function test to perform in order to detect and be able to evaluate changes occurring in response to therapy in bronchial asthma. Ideally the test should however be valid, that is, truly measure the particular aspect of pulmonary function one sets out to test; and it should also be adequately sensitive and reproducible (Sobol, 1971).

Many studies reporting the correlation between various indices of airway obstruction both in normals and in patients with

chronic airway obstruction have been published (Kory et al, 1961; Pelzer and Thomson, 1966; Stein et al, 1966; Mitchell et al, 1967; Sobol and Emergil, 1968; Allen and Sabin, 1971). In general it has been found that correlations between such indices is significantly higher in subjects with airway obstruction than in normals. The ratio of forced expiratory volume in one second to the forced vital capacity (FEV_1/FVC) as well as the maximum mid-expiratory flow rate (MMFR) have been found to be highly correlated, on a cross sectional study, with the airway resistance. However, they have the disadvantage, that, on a longitudinal study, such as following the effect of corticosteroid therapy, any changes affect both the numerator and the denominator of the relationship; and under such conditions a change in airway resistance may go undetected (Cotes, 1971).

As previously discussed, an increase inbronchial contractility may lead to an increase in lung volume which has the effect of increasing the traction exerted by the lung parenchyma upon the airways, hence preserving, up to a certain point, their patency. Under these conditions, tests of forced expiration, such as the FEV_1, may remain normal or nearly so, but the F.R.C. and the R.V. are very often increased (Woolcock and Read, 1966). Such an increase in the RV/TLC ratio with an apparently normal FEV_1 has also been reported following clinical recovery in asthmatic patients (Weng and Levinson, 1969). Conversely, a diminution in lung volumes without an associated use in FEV_1 has been described by Woolcock and Read in

in 1965. The measurement of lung volumes thus forms an integral part of any investigation of pulmonary function in chronic airway obstruction.

It is of course realised that a considerable degree of disease in the small airways can be present without there being any definite abnormality of airway resistance or of the usual spirometric tests. Only about 10% of the total airway resistance is contributed by airways smaller than 2 mm in diameter in normal subjects (Macklem and Mead, 1967). The detection of changes in airway resistance contributed to by the small airways depends on the proportion of the total airway resistance which it forms and the degree of reversibility of each component. Thus changes in airway resistance occurring in the smaller airways following therapy could possibly go undetected.

Macklem and Mead (1967) showed that the time constants (resistance x compliance) of the lung units distal to airways smaller than about 2 mm were in the order of 0.01 sec. They concluded that under such circumstances a four fold difference in time constants between these units would be sufficient to cause a fall in dynamic compliance with increasing respiratory frequency. Woolcock et al, (1969) found frequency dependence of compliance in five bronchitics and four asthmatics in remission and interpreted their results as indicating obstruction in peripheral airways. Frequency dependence of compliance might be assumed to occur before there is any detectable abnormality in resistance.

It might therefore be expected that frequency dependence of compliance could possibly detect changes occurring in the smaller airways as a result of therapy before and to a greater extent than any of the more conventional tests. However, frequency dependence of compliance has also been reported in a number of normal subjects (Woolcock et al 1969; Ingram and O'Cain, 1971) and this test is also a technically demanding measurement (Flenley et al, 1971).

The closing volume (C.V.) may be defined as that lung volume above residual volume at which the airways begin to close, and it has been suggested that it might be a sensitive method of measuring airways obstruction. Its measurement is based on the fact that inspiration from close to residual volume produces uneven distribution of inspired air (Milic-Emili et al, 1966). Following the injection of a marker gas such as argon, during a slow inspiration, the subject is then instructed to expire slowly and smoothly. The concentration of the marker gas measured at the mouth is seen to rise to a plateau as the dead space is washed out. This plateau indicates emptying of mixed expired alveolar gas. As the residual volume is approached the concentration of the marker gas rises sharply. This sharp terminal rise is attributed to closure of the basal airways which are gravity dependent (Dollfus et al, 1967). It has been suggested that the index C.V./TLC might be useful in detecting minor airway obstruction. However, where there is marked regional inhomogeneity, as in asthmatics, neither a satisfactory plateau nor a clearly defined terminal rise

is likely to be obtained (Clarke, 1971). Insufficient information is as yet available about the use and validity of this test in airway obstruction. It was thus thought that measuring both the frequency dependence of compliance as well as the closing volume were unsuitable tests for use in this study.

The tests performed to assess the therapeutic effectiveness of prednisolone were therefore :

1. Direct measurements of airway resistance.
2. Measurements of dynamic lung volumes.
3. Measurements of static lung volumes.
4. Measurement of blood gases and assessment of pulmonary gas exchange.

MEASURING AIRWAY RESISTANCE

(a) Development of various methods of measuring resistance to breathing

One of the earliest attempts to measure airway resistance was the classical study of Rohrer in 1915. He made meticulous anatomical measurements on the tracheobronchial tree of a human lung obtained at post mortem, using calibrated bougies, which he inserted peripherally while dissecting proximal branches, and calculated the total resistance to airflow of the entire system using Poiseuille's formula. He erroneously concluded that the peripheral airways were responsible for about 90% of the total resistance. Gaensler

et al, pointed out in 1952 that Rohrer made an arithmetical mistake in calculating Reynold's numbers leading to a tenfold overestimation of the velocity at which the transition from laminar to turbulent flow would occur. More recently, Weibel (1963) showed that Rohrer had grossly underestimated both the number and total cross-sectional area of airways smaller than 4 mm diameter, probably because he studied deflated lungs. Macklem and Mead (1967) introduced the retrograde catheter technique and showed both in living dogs and excised human lungs that the peripheral resistance accounted for a very small proportion of total airway resistance.

The first experimental study of total pulmonary resistance in the living animal was made by Von Neergard and Wirz in 1927. They reasoned that because of the large alveolar volume relative to the airways, the pressure in the airway following interruption of the stream should equilibrate in a very short time to the pressure that existed in the alveolar prior to interruption. Their method was further developed by Vuilleumier (1944) and used by Otis and Proctor (1948) and Otis, Fenn and Rahn (1950). The assumption on which the 'interruption technique' is based is only partly valid. In practice the pressure measured during interruption is not exactly the same as the alveolar pressure before interruption becuase the energy of movement of the lungs, and to some extent that of the chest wall and diaphragm, is converted into pressure once the movement is interrupted (Mead and Whittenberger, 1954). This method was modified by Ainsworth and Eveleigh (1952) so that

flow was obtained from the pressure drop across an external resistance of similar airflow characteristics to the lungs, obviating a need for a flow meter. Later, Clements and Blam (1955) introduced a rapid repetitive interrupter that interrupted airflow about ten times a second. This gives satisfactory reproducible and accurate results for total pulmonary resistance.

Bayliss and Robertson (1939) first ventilated isolated animal lungs with gases of different density and viscosity. They used hydrogen and air, and based their investigations on the assumption that airway resistance but not tissue resistance would vary with the viscosity of the gases breathed. They mistakenly concluded that most of the 'lung viscance' is in the tissues. Fry et al (1954) using an argon-oxygen mixture on human subjects reached the opposite conclusion. McIlroy et al, (1955) pointed out that the previous studies based on this assumption had underestimated the effects of changes in the gas properties on Reynold's number and hence in the distribution of turbulence in the airways. They stressed the point that mixtures of equal kinematic viscosity should be used to ensure similar distribution of turbulence within the airways, as a given flow. They estimated tissue resistance to be about 30 - 40% of the total pulmonary resistance. More recent measurements using different techniques (Macklem and Mead, 1967; Bachofen, 1968;) indicate that tissue resistance is probably negligible. Probably a pressure difference due to static pressure volume hysteresis, which is not flow resistive in nature, was in-

cluded in earlier measurements.

Buytendijk (1949) employed an oesophageal balloon instead of an intrapleural needle to measure pressure changes in the intrapleural space. The introduction of the oesophageal balloon to estimate intrapleural pressure (Fry et al, 1952; Mead and Whittenberger, 1953) and the carefully worked out technique of Milic-Emili et al, (1964) were major steps in the measurement of lung mechanics and provided the physiologist with a safe measurement of trans-pulmonary pressure. Several techniques are now available for measuring non-elastic resistance from intra-oesophageal pressure, flow or volume tracings, but they all depend on the measurement of non-elastic pressure by subtracting or eliminating the pressure exerted against elastic resistance. Perhaps, one of the most satisfactory methods for the measurement of airway resistance from intra-oesophageal pressure and flow tracings is by the subtraction method of Mead and Whittenberger, (1953).

The introduction of body plethysmography in the study of human pulmonary physiology is generally attributed to Pfluger (1882). He measured his own intrathoracic gas volume by applying Boyle's law to relate changes in alveolar pressure to simultaneous changes in lung volume. Pfluger designed a wooden cabinet in which he could sit and voluntarily compress the gas in his lungs, the volume change being measured by a small spirometer attached to the chamber and the pressure at the mouth being simultaneously measured by a mercury man-

ometer.

The method of measuring alveolar pressure indirectly from measurements of alveolar gas compression and expansion was again proposed and attempted by Sonne in 1923, but its first practical application was made by Du Bois et al, (1956) who cleverly overcame the problems of measuring alveolar pressure. They have provided the only successful technique at present available for the measurement of alveolar pressure. With their method, alveolar pressure at any instant can be deduced from plethysmographic pressure changes. Several descriptions of modified techniques have since appeared in the literature (Bargeton, 1959; Bartlett, 1959; Comroe et al, 1959; Mead, 1960; Geubelle and Santerre, 1963; Jaeger and Otis, 1964; Sackner et al, 1964; Sobol, 1969; Smidt et al, 1969) attempting to make the measurements even more accurate. Mead (1960) revived the original volume-displacement plethysmograph of Pfluger with great success.

Another method which measured total respiratory resistance (airway, tissue and chest wall) is that in which forced oscillations are generated from a loud speaker at or near resonant frequency of the lung. The principle underlying this technique, which was also first introduced by Du Bois et al, (1956) is that, at the resonant frequency elastic pressures are exactly equal and 180 degrees out of phase with inertial pressures, thereby cancelling each other out. Pressure and flow are then in phase and their relationship describes the pulmonary flow resistance. It is of potential

value in measuring resistance to breathing of patients who cannot undergo body plethysmography, such as the acutely ill patient (Fisher et al, 1968). Goldman et al, (1970) have simplified the technique by using the fact that twice in every cycle the rate of change of flow is zero, therefore the inertial component of the pressure is zero. These points in time occur at positions of equal volume, and therefore equal elastic pressures. Hence the change in pressure over this time interval can be related to the change in flow to give the total respiratory resistance.

(b) Description and calibration of apparatus.

The construction and calibration of a constant volume body plethysmograph was personally supervised in our laboratory. It was also ensured that results obtained from it were reliable and reproducible. Perhaps, as suggested by Bargeton and Barres (1969) it should be called a 'closed box' type of plethysmograph as the terms constant volume and constant pressure plethysmograph are misleading since in both types the mass of air in the box undergoes a volume and pressure change.

The plethysmograph built in this laboratory is box shaped and made of Marine seven-plywood with a hingless door that has a glass window at face level. The door is clamped firmly to the box by means of twelve steel clips and made airtight by means of a rubber gasket around the periphery. Its volume calculated geometrically

is 347.2 litres. Communication between the operator and the subject is no problem as the usual speaking voice carries through the walls of the box.

Two M.D.C. micromanometers supplied by Furness Controls Ltd have been used to measure changes in flow and mouth pressure and changes in plethysmographic pressure. They are connected to the mouthpiece and pneumotachograph by non-compressible plastic tubing about 3 ft. long. The manometers are sensitive pressure measuring devices capable of measuring a gas pressure down to 10 dynes per sq. cm. for a full scale deflection. The micromanometers' measuring head consists of two symmetrically arranged cavities separated by a metal diaphragm. The diaphragm together with a fixed electrode on either side, forms two condensers which are part of the tuning capacities of two tuned circuits both equally coupled to an R.F. oscillator. Movement of the diaphragm causes a variation in the capacitance between it and each adjacent electrode, thus unbalancing the voltage across the tuned circuits. These voltages are compared by a differential rectified voltmeter, and the difference is shown on a meter calibrated directly in pressure.

The frequency response of the micromanometers was tested by comparing them with an Elma Schonander manometer (5 - 15 mmH20) which was known to have an excellent frequency response. The pressure in the plethysmograph, was measured by both the M.D.C. manometer and the Elma Schonander manometer simultaneously.

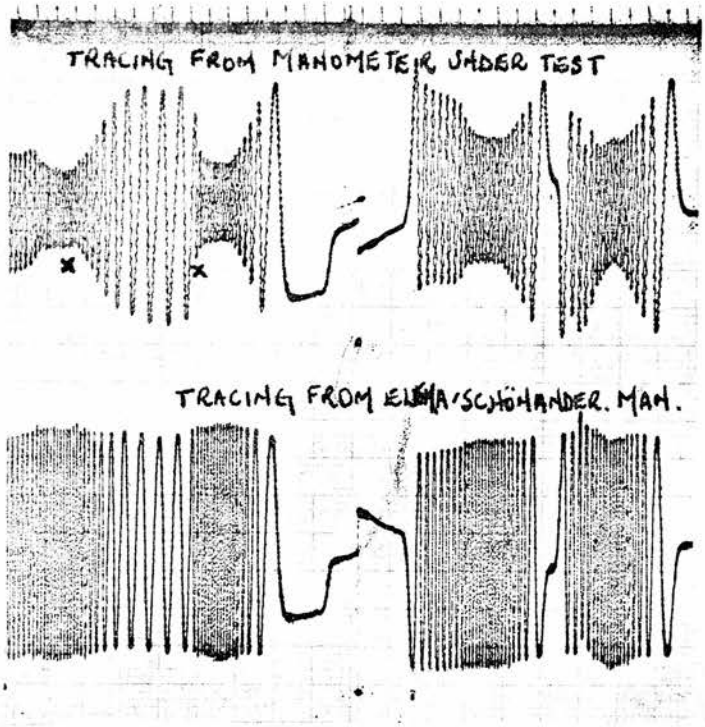

TRACING FROM MANOMETER UNDER TEST
TRACING FROM ELEMA/SCHÖNANDER. MAN.

fig 3

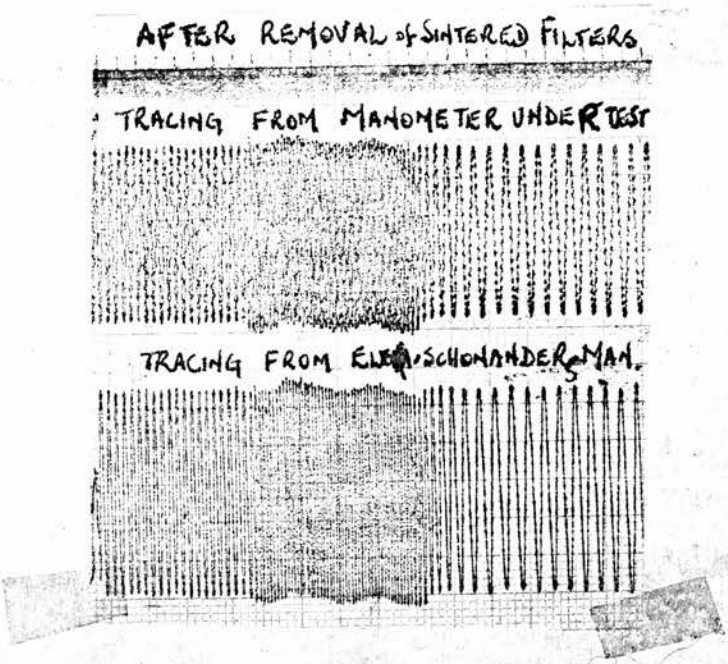

AFTER REMOVAL of SINTERED FILTERS
TRACING FROM MANOMETER UNDER TEST
TRACING FROM ELEMA/SCHÖNANDER MAN.

fig 4

Similar lengths of tubing were used to connect both manometers, the readings being fed into a direct writing multi-channel recorder (80 Elema Schonander Mingograf) and an oscilloscope. The M.D.C. manometer had originally a sintered filter on each side of the diaphragm which brings about a loss of frequency response by introducing a resistance capacitance filter. The latter induces phase shift between the transducers at increasing frequencies (Fig. 3).

The removal of the sintered filters corrected the M.D.C.'s loss of frequency response and phase shift shown by adding 35 ml at 1 - 5 Hz. (Fig. 4).

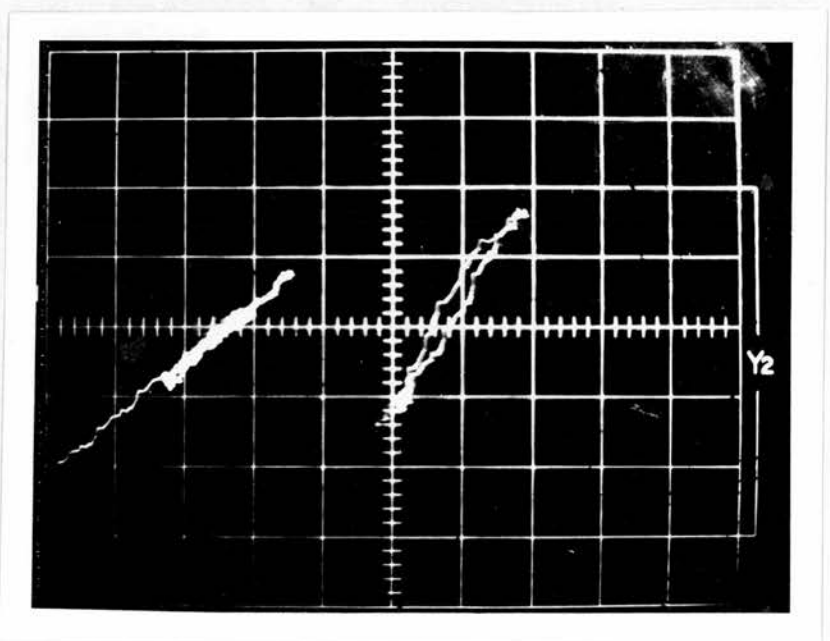
Flow was measured with a heated Fleisch pneumotachograph with a linear response between 0 and 2.5 l/sec.

The plethysmographic pressure signal was fed into the horizontal, and the flow and mouth pressure signals, in succession, into the vertical, axis of a cathode ray oscilloscope (Solartron C.D. 1400). The vector loops produced by the subject's panting manoeuvres were displayed on the oscilloscope screen (Fig. 5) and their slopes obtained by visual alignment with parallel lines ruled on a Perspex disc which rotated within a fixed protractor scale in front of the screen. The visual method was used for convenience since it has previously been claimed to agree adequately with the more expensive method of photographing the vector loops and then measuring their angles (Du Bois et al, 1956 b; Butler et al, 1960). This

fig 5

PLETHYSMOGRAPHIC VECTOR LOOPS

photographed from oscilloscope screen



θ_2 θ_1

method was found to be a very satisfactory one.

The body plethysmograph was calibrated by means of a simple pump with a stroke displacement of 35 ml of air. This was set to produce a deflection of 6 cm on the oscilloscope. The box calibration factor is therefore $\frac{35 \text{ ml}}{6\text{cm}} = 5.85$ ml/cm deflection.

As the plethysmograph was always calibrated when empty, the calibration is adjusted to the smaller volume of air which is present when there is a subject sitting in the plethysmograph, by means of the following relationship:

$$F_2 = F_1 \left(V_{\text{pleth.}} - \frac{\text{Wt(kg)}}{1.07} \right) / V \text{ pleth.}$$

where F_1 = initial calibration factor, 5.85 ml/cm deflection.

1.07 = Assumed average density of the human body.

V. pleth. = volume of body plethysmograph.

A problem that occurs in the measurement of the signal from the plethysmograph is outside pressure changes. There are different methods that are used to stabilise the measurement, of the pressure in a constant volume plethysmograph. If the input in the differential pressure transducer that is not connected to the plethysmograph is left open, all changes of the outside pressure, as can occur in opening and closing doors or in windy weather, will interfere with the signal (Comroe et al, 1959; Smidt et al, 1969). Thus to minimise such pressure disturbances from outside a 500 ml

TABLE I

Resistance offered by mouthpiece and pneumotachograph head to various rates of air flow.

$\dot{V}$(l/min)	P(mmH_2O)	R.(cm H_2O/l/sec).
50L/min	2.16 mmH_2O	0.260 cmH_2O/l/sec.
60l/min	2.60 "	0.262 "
75l/min	3.36 "	0.268 "
100l/min	4.30 "	0.258 "
150l/min	6.50 "	0.260 "
200l/min	8.65 "	0.260 "

Each value is the average of three consecutive measurements.

bottle was attached to the second input of the transducer as a closed reference pressure. All doors and windows in the laboratory were kept closed during the measurements.

Mouth pressure was calibrated by means of a simple water manometer; 4 cm of water pressure being used to give a deflection of 3 cm on the oscilloscope. The mouth pressure calibration factor (F_3) is thus, 4cm H_2O/3 cm = 1.33 cm H_2O/cm deflection.

Flow was measured by means of a Fleisch flow meter, which was previously calibrated by means of a rotameter. A flow rate of 60 l/min was set to give a deflection of 2 cm on the oscilloscope. The flow calibration factor is therefore:

1 l/sec/2cm = 0.5 l/sec/cm deflection.

The resistance offered by the mouthpiece and pneumotachograph head was found to be : 0.26 cm H_2O/l/sec. (see Table I).

(c) Principles involved in measuring airway resistance by Body Plethysmography.

Airway resistance depends for its calculation on the simultaneous measurement of the rate of the flow of air as well as the pressure difference between the alveoli and the mouth.

$$\text{Airway resistance (Raw)} = \frac{\text{Alveolar to mouth pressure difference (PA)}}{\text{Rate of air flow } (\dot{V})}$$

The rate of airflow can be easily measured by a pneumotachograph at the mouth. Alveolar pressure cannot however be measured during airflow; but it can be derived by making use of the compressibility of the air in the lung and applying Boyle's law, to calculate it from measurements of changes in plethysmographic pressure. The relation between alveolar and plethysmographic pressure is defined by measuring mouth and plethysmographic pressures during a panting manoeuvre against a closed shutter. During this procedure there is no airflow through the respiratory system and mouth pressure is assumed to equal alveolar pressure. With the subject sitting in an airtight chamber, the volume change owing to compression and expansion of air inside the thorax, occurring during expiration and inspiration, produces concomitant and reciprocal changes in the plethysmographic air outside the lungs. Hence, at any instant, the resulting pressure change in the box must be opposite in sign to the pressure change in the lung. Such changes in plethysmographic pressure can be quite easily measured continuously during the respiratory cycle. Changes in air flow are plotted simultaneously against plethysmographic pressure changes which in turn, as has been shown, are proportional to changes in alveolar pressure. Immediately after, changes in plethysmographic pressure are plotted against mouth pressure as the subject pants against a closed shutter; this step serves to relate changes in plethysmographic pressure to changes in alveolar pressure. Therefore, alveolar pressure is effectively measured during flow, since the alveolar pressure for a given plethysmographic pressure is the same whether or not flow is

interrupted provided the ratio of lung to plethysmographic gas volume is constant.

The difference between this method and previous interrupted methods is that the interruption of flow of the plethysmographic method is simply the means of calibrating the changes in plethysmographic pressure in terms of alveolar pressure; the values for airway resistance are always obtained during uninterrupted flow.

Boyle's law only applies if the condition of the human lungs can be assumed to be isothermal. If the conditions are adiabatic then the expression P.V. = k, no longer holds. Under adiabatic conditions P.V. = k, where = Cp/Cv (Cp = specific heat at constant pressure; Cv = specific heat at constant volume). Nolte (1968) investigating this problem found that there was no difference in F.R.C. when this was measured with subjects breathing air (= 1.40) and breathing a helium/oxygen mixture (= 1.61). He concluded that this was evidence of approximately isothermal conditions in the lungs, thus justifying the application of Boyle's law.

Panting may be considered as a rather unusual physiological manoeuvre to perform as far as spontaneous breathing patterns are concerned. It was the way, however, in which Du Bois et al (1956) solved the problem of thermal exchange which occurs when normal tidal volume breaths are used. Warming and wetting of the inspired air leads to an increase in the volume of thoracic gas and consequently to an increase in the plethysmographic pressure which is superimposed

as an artefact on the signal due to actual changes in lung volume. Cooling and condensation of the expired air also has an effect but to a lesser degree; the resultant effect of normal quiet inspiration and expiration being an increase in pressure inside the plethysmograph. Panting through a heated pneumotachograph reduces the size of this artefact.

There have been other attempts to overcome the artefact produced by thermal exchange to allow measurements to be made during breathing patterns rather than panting. Among these was the suggestion put forward by Du Bois et al, (1956) to make the subject rebreathe from a rubber bag containing hot water, this would tend to keep the respired air at constant temperature and saturation. Bartlett et al, (1959) designed a plethysmograph with elaborate air conditioning. Jaeger and Otis (1964) asked their subjects to rebreathe from a 13 litre rubber bag that was filled with 3 - 5 litres of a 5% CO_2/95%/02 gas mixture and shaken with 20 ml of hot water, the bag being used when its temperature was 40°C.

Du Bois et al, (1952) suggested on theoretical grounds that the rate of oxygen transfer across the alveoli is probably constant, whereas the rate of carbon dioxide elimination varies throughout the respiratory cycle. The two gases behave differently because of the different slopes of their dissociation curves. The cyclic variations of CO_2 production that take place during the respiratory cycle produce similar changes in the rate of volume displace-

ment of the plethysmograph (Jaeger and Otis, 1964). The latter authors found that a decrease in breathing frequency increased the amplitude of the variations of CO_2 transfer. The variations of the respiratory exchange ratio during the breathing cycle are minimized by panting (Du Bois et al, 1956; Jaeger and Bouhuys, 1969).

The resistance of the upper airways increase appreciably during an ordinary quiet expiration and contributes a substantial fraction to the total resistance. So, paradoxically, it seems that spontaneous breathing results in an increase in upper airway resistance. Such an increase can be avoided to a great extent by a panting manoeuvre when the upper airway resistance tends to decrease and become fixed. Therefore, measurements of airway resistance, are said to be more satisfactory and less variable than those made during spontaneous breathing (Mead, 1971). In order to get a truer value of airways resistance it is necessary to minimize the elastic and inertial components of total lung resistance. Panting results in a decrease of the elastic component and during this manoeuvre, the inertial component is small (McDermott, 1971). Hence the panting technique which started the development of body plethysmography, appears to be still the best practical approach for most applications. This has recently been confirmed by the work of Stanescu et al (1972) who found that the glottis was definitely wider during panting than during quiet breathing.

(d) Details of Method.

The subjects were instructed in the test procedure and were taught how to pant. They then entered the body plethysmograph and the door was clamped down. The subjects sat comfortably inside the box and could easily communicate with theoperator outside. They had the mouthpiece adjusted to their height; this ensured that there was no crouching, which can cause flexion of the neck and compression of the upper airways (Guyatt and Alpers, 1968). The rise in plethysmographic pressure that took place as the subject warmed and humidified the air around him was equalised to ambient room pressure by repeated venting by means of a large bore solenoid controlled valve until the pressure drift with the vent closed was so slight that it did not interfere with measurements. This usually took between two to three minutes. The subject was then asked to put on a nose clip, place the lips tightly round the mouthpiece, support his cheeks in order to minimise any variation in the volume of the buccal cavity and carry out a panting manoeuvre through an open glottis. The subjects were asked to pant through the heated Fleisch pneumotachograph at the end of a normal expiration, that is, as near F.R.C. as possible. Flow was plotted against body plethysmographic pressure and the angle produced on the face of the oscilloscope was measured as 1. The operator then actuated the shutter to block off the mouthpiece and the subject was asked to continue to make shallow panting efforts against it. During these efforts mouth pressure was plotted against the box pressure and the angle recorded as 2.

Five determinations were made for each subject, at a breathing frequency of about 1 - 2 cycles/sec and at flow rates of 0.5 l/sec. The initial reading was discarded and the mean of the last four taken. When body plethysmographic measurements were carried out during this study, these were always the first tests performed. This procedure was adopted because a forced inspiration, or a forced expiration, carried out, for example, during an FEV_1 manoeuvre, could possibly alter the values for airway resistance, as shown by Butler et al,(1960); Nadel andTierney,(1961); Lloyd,(1963.) Bronchial obstruction induced by spirometry has also been recently demonstrated by Gimeno et al, (1972) in patients with chronic airway obstruction. Woolcock et al, (1969) have recently shown that total pulmonary resistance at a given lung volume is higher when that volume is attained by inspiration than by expiration and that this difference is reduced by atropine. They suggest that the effect of volume history on the airways is dependent on efferent vagal impulses modifying smooth muscle tone. The subjects in this study were instructed and shown how to reach their F.R.C. through a normal quiet expiration. With a little training most subjects were able to produce clear and reporducible vector loops and changes in airway resistance and thoracic gas volume were easy to follow.

(c) Choice of an index to reflect changes in airway resistance.

The importance of the relationship between airway resistance

(Raw) and the lung volume (Vtg) at which it is measured is self evident, and Raw should be standardised for the Vtg at which it is obtained. Briscoe and Du Bois (1958) stated that when Raw is plotted against Vtg the relationship is a curvilinear one. When however Vtg is plotted against the reciprocal of Raw, i.e. airway conductance (Gaw), they claim that the relationship appeared to be linear and related Gaw, rather than Raw, to Vtg; obtaining specific conductance (SGaw) by dividing Gaw by the Vtg at which it was measured. The relation between Gaw and Vtg has been shown to be not so perfectly linear, and it has been suggested that Gaw is more linearly related to intra-oesophageal pressure (Butler et al, 1960; Linderholm, 1963). However, the validity of specific conductance has been examined and confirmed by various workers (Pelzer and Thomson, 1969; Guyatt et al, 1967, 1968, 1970; Bates, Macklem and Christie, 1971). No grounds for using more sophisticated corrections have been found.

Normally both the flow-plethysmographic pressure ($\dot{V}$/Pb) and the mouth pressure-plethysmographic pressure (Pm/Pb) relationships are rectilinear and can be displayed on an oscilliscope as linear closed loops. However, in some cases of marked airway obstruction, the Pm/Pb vector loop is splayed out. This is probably due to incomplete equilibration between alveolar and mouth pressure during the closed shutter manoeuvre. In such a case 'looping' would introduce inaccuracies in the measurement of the angle and the calculation of both Vtg and Gaw; but would hardly affect SGaw sinceiit can be calculated that the measurement of SGaw is obtained

from the $\dot{V}/Pb$ ratio along (Pelzer and Thomson, 1969).

Because of the systematic increase in Vtg in patients with poor Gaw, e.g. asthmatics, the fall in Gaw is proportionately smaller than the fall in SGaw. Consequently SGaw is the more discriminative index.

(f) Normal values obtained by body plethysmography.

In order to establish a set of normal values for our body plethysmography and to find out how these compared with values in the literature, measurements were carried out on twenty-six subjects. The latter were either members of the department or medical students, and were divided into three groups; females non-smokers; males smokers and males non-smokers. (see Table II). Individual values are included in Appendix (Table 1).

In order to try and discover how variable the body plethysmographic measurements may be, ten of the previous subjects had the procedure repeated on five different days, at approximately the same time of day. An analysis of variance has been carried out on the values obtained (Table III). Individual values are included in Appendix (Table 2). This shows that the source of variation within subjects is extremely small compared to that between subjects (F more significant than .001% level). Hence it may be assumed, that at least in normals, this test is quite repeatable.

TABLE II

Body plethysmographic values for 26 normal subjects.

Mean and Standard Error.

SUBJECTS	AGE	Raw cm H_2O/l/sec	Gaw l/sec/cmH_2O	Vtg. l	SGaw l/sec/cmH_2O
8 females non-smokers	18-32 yrs.	1.14±0.06	0.89±0.046	3.36±0.148	0.27±0.01
13 males non-smokers	19-45 yrs.	1.08±0.038	0.94±0.033	4.14±0.149	0.23±0.01
5 males smokers	21-35 yrs.	1.48±0.071	0.70±0.035	3.69±0.134	0.19±0.01

The individual values are included in the Appendix (Table 1). The values obtained were very similar to those obtained in other normal series (Pilzer and Thomson, 1966; Guyatt and Alpers, 1968; Guyatt et al, 1970 and Allen and Sabin, 1971). Values obtained from data reported by Allen and Sabin are reproduced overleaf for comparison:-

TABLE II

cont.

SUBJECTS	AGE	Raw	Gaw	Vtg.	SGaw
2 females non-smokers	16-19 yrs.	1.54	0.65	2.33	0.29
12 males non-smokers	22-44 yrs.	1.25±0.08	0.80±0.09	3.76±0.17	0.23±0.01
16 males smokers	21-59 yrs.	1.62	0.62	4.33	0.16±0.002

TABLE III.

Analysis of variance on repeated plethysmographic measurements.

	Source of variation	Sum of square	d.f.	Mean square	F	Variance.
Vtg	between subjects	14.3764	9	1.5974	133.1	0.3171
	within subjects	0.4788	40	0.0120		0.0120
	total (about mean)	14.8552	49			
Raw	between subjects	1.03	9	0.115	32.85	.0223
	within subjects	0.14	40	0.0035		.0035
	total	1.17	49			
Gaw	between subjects	0.81	9	0.09	30	.0174
	within subjects	0.11	40	0.003		.0030
	total	0.92	49			
SGaw	between subjects	0.0293	9	0.00325	20.96	.00062
	within subjects	0.0062	40	0.00015		.00015
	total	0.0355	49			

2. MEASURING STATIC LUNG VOLUMES.

(a) Development of Physiological Methods for Measuring Static Lung Volumes.

Borelli, in 1680, is said to be the first to have measured the inspiratory volume of the lung and to call attention to the residual volume. Davy, in 1800, measured his own residual volume, which he then described as "residual air", by introducing a method based on the dilution of a known volume of hydrogen, which he made himself, by the 'residual air' in the lungs. The subject was asked to take 5 - 7 deep and rapid breaths after forcibly emptying his lungs. In 1846, John Hutchinson, a surgeon, attempted to name the various sub-divisions of the lungs and measured vital capacity, using a spirometer. In 1860, Grehant calculated the volume of gas left in the lung at the end of a normal expiration - F.R.C., basing his study on Davy's method. Davy's method was modified by various workers during the following century, including Bohr (1907), but it was difficult to perform and poorly reproducible.

Van Slyke and Binger made the next real advance in 1923 by using hydrogen dilution without forced breathing, mixing being accomplished by quiet respirations from a spirometer, for from 5 - 7 minutes. Their method was thus more suitable for clinical application. Difficulties arose with the analysis of hydrogen, and moreover, the dangers of explosion and poisoning with arsine due to the impurities

in the zinc used in the production of hydrogen were serious drawbacks. Christie (1932) reviewed no less than forty-seven papers dealing with methods available up to that time for measuring lung volumes. He concluded that the method of Van Slyke and Binger was the best but suggested using nitrogen as the 'indicator gas' instead of hydrogen, the subject breathing from a spirometer with a known volume of oxygen - the oxygen dilution method.

Lassen, Cournand and Richards, (1937) pointed out an 'oxygen storage effect' which they believed introduced errors in the calculation of the volume of the lung by Christie's method. They modified the latter's calculation to allow for observed differences in the concentration of nitrogen between alveolar air and the spirometric circuit at the end of the rebreathing period. Herrald and McMichael, (1939) modified Christie's method by matching the oxygen consumption of the subject with a controlled inflow of oxygen through a calibrated needle valve, so that the volume of the lung - spirometer system remained constant during the rebreathing period. They proved that this alteration abolished the 'oxygen storage effect'. Christie's oxygen dilution method proved to be unsatisfactory in patients with uneven ventilation because equilibration between subject and circuit was delayed. McMichael (1939), continuing the constant volume feature of his earlier method, re-introduced the foreign gas principle, employing hydrogen the analysis of which was made rapid and simple by a thermal conductivity analyser.

Meneely and Kaltreider (1941) replaced hydrogen with helium because it had all the advantages and none of the dangers of the hydrogen method. Gilson and Hugh-Jones (1949) reported a similar closed-circuit method using helium with oxygen as the diluent; this requires a long period of oxygen breathing before the measurements were made. Meneely and Kaltreider (1949) used air instead of oxygen in the circuit. Weiner and Cooper (1956) comparing the methods of Gilson and Hugh-Jones (1949) with that of Meneely and Kaltreider (1949) showed that the latter's method is simpler, can be performed more readily, is easier for the patient and is as reliable as the Gilson and Hugh-Jones method.

In the closed-circuit helium dilution method, Meneely and Kaltreider (1949) recommended the subtraction of 110 ml from the determined value of the lung volume as a correction for absorbed helium. The authors, however, presented no data to support the derivation of this correction and were not convinced that it was correct. Holmgren (1954), on the other hand, claiming that the catharometer's sensitivity was too low to detect the small quantity of helium that would be absorbed, introduced no correction. Birath and Swenson (1956) again proposed a correction factor for the small amount of helium absorbed by the blood; this however has not been universally adopted (Bates, Macklem and Christie, 1971). No correction factor has been applied in the calculation of lung volumes carried out by closed-circuit helium dilution in this study.

A new principle for the measurement of lung volume had been introduced by Darling, Cournand and their associates in 1940. Their method known as the open circuit nitrogen clearance technique involves the displacement of nitrogen from the lungs by oxygen breathing, and calculation of the volume of nitrogen expired by analysis of the nitrogen content of expired air. As the method depends upon multiplication of a large gas volume by a value for nitrogen concentration, small analytical errors in measuring nitrogen concentration will result in considerable error in the calculated F.R.C. The open-circuit technique is simpler in the sense that it requires less in the way of equipment than the closed circuit method. The results of both methods have repeatedly been shown to be comparable (Gilson and Hugh-Jones, 1949; Motley, 1957; Boren et al, 1966).

Lamphier (1953) indicated that it would be useful to have a method that would require a single breath as the test procedure and therefore allow rapid and easy measurement of lung volumes. Forster et al, (1957) described a modification of the closed-circuit, helium dilution method. In this method, a maximal inspiration is taken, from residual volume, of a gas containing 10% helium. This breath is held for approximately ten seconds and then expired completely so as to provide a sample of alveolar gas for analysis. Ogilvie et al, (1957) considered the value obtained by this technique as unreliable. Mitchell and Renzetti, (1968) evaluating the single breath method for measuring T.L.C.

found that it correlated very well with the closed-circuit helium dilution method and body plethysmography in 22 normal subjects. In 52 patients with pulmonary disease, they found that both gas dilution methods measured similar volumes which were significantly less than those measured by body plethysmography.

As has been mentioned in the previous section on the measurement of airway resistance, body plethysmography also yields measurement of thoracic gas volume. In fact, when it was first used, it was measurements of lung volume that were obtained rather than measurements of airways resistance. Paul Bert (1868) seems to have been the first to observe changes in pressure simultaneously with pulmonary ventilation in a closed chamber containing an animal, which were described in a paper entitled "Changements de pression de l'air dans le poumon pendant le deux temps de l'acte respiratoire" read at the 'Societe de Biologie de Paris' under the chairmanship of Claude Bernard. In 1870 he wrote, "c'est un moyen fort commode d'enregistrer la respiration des animeax". In 1882, Pfluger in a paper entitled 'Das Pneumometer' re-stated Paul Bert's findings; he went on to measure his own intrathoracic gas volume by a 'decompression method'; whereas the voluntary compression method had been described by Gad, (1881) as cited by Bass, (1925). It is perhaps not sufficiently appreciated that Robert Menzies in his thesis, 'Tentamen Physiologicum Inaugurale de Respiratione' submitted for the degree of M.D. in Edinburgh had actually managed to measure tidal breathing in man, using a water filled plethysmograph, as early as 1790 (see Figs.6,7.

Fig: 6

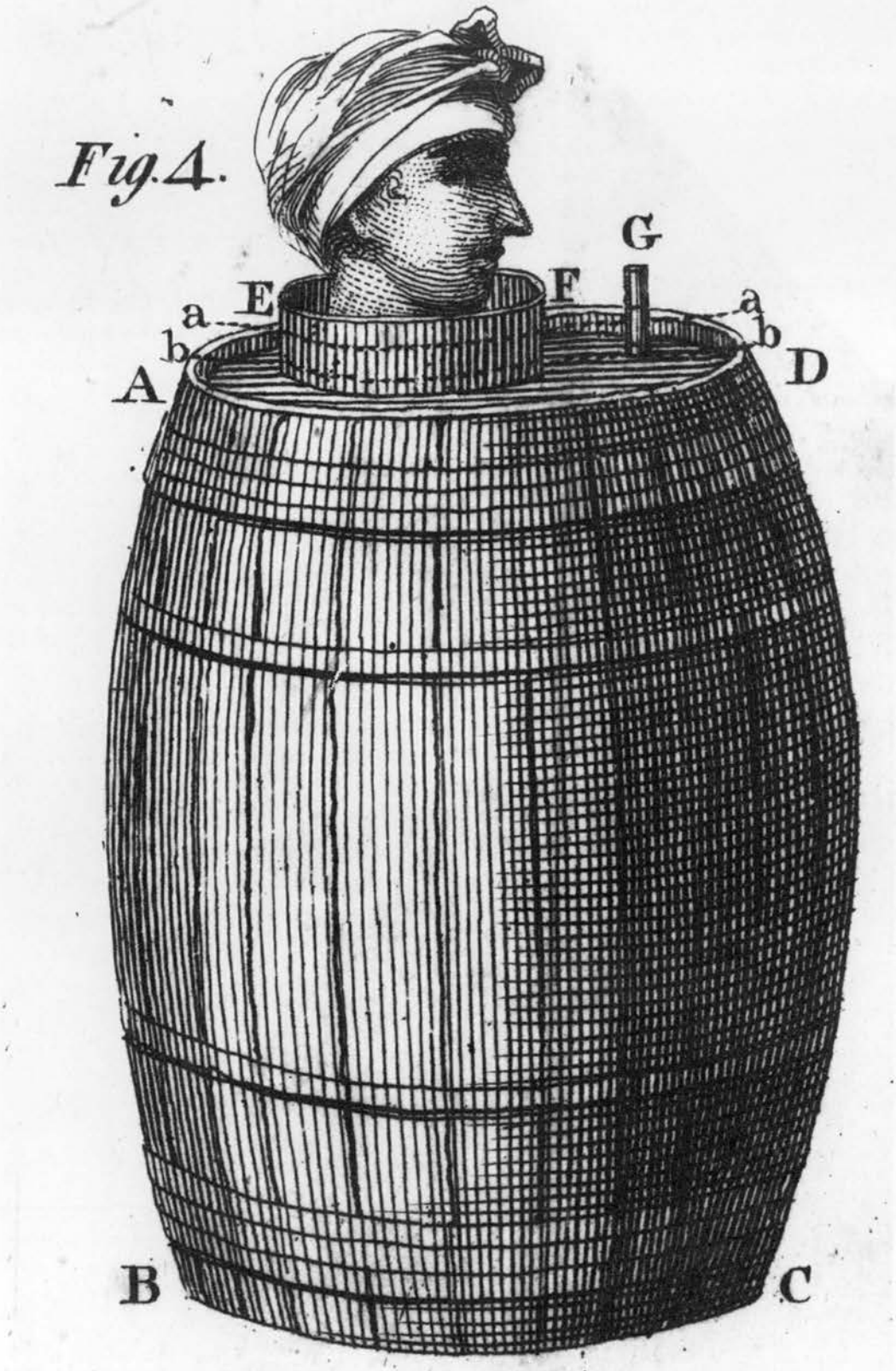


Fig: 1

EXPERIMENT. II.

HOMO ſanus et valens, pedes quinque digitoſque octo procerus, circuitu thoracis tres pedes treſque digitos explens, in dolium *A B C D*, uti in figura 4ta delineatur, arcte incluſus eſt, quod aqua gradum thermometri Fahrenheiteani nonageſimum temperie adaequante repletum eſt, donec ad eam colli, quae ad aſcenſionem et deſcenſionem metiendam maxime accommodabatur, partem aſcendit. Haec autem ex digitis 1.25 attingere notata eſt. Pulſus arteriarum, et ante et poſtquam immerſus eſt, 64 aut 65, et reſpirationes 14 vel $14\frac{1}{2}$, ut frequenter ante fuerat notatum, ſingulis minutis, fuerunt. Et omnino eadem duas horas et amplius manſerunt, per quod ſpatium in dolio moratus eſt, ne minimam quidem moleſtiam in ſpiritu trahendo vel emittendo, vel in re qualibet alia, ſentiens. Quinetiam, per omne id tempus aſcenſio et deſcenſio digitum unum parteſque ejus viginti quinque centeſimas, ad minimum, adaequare conſtanter reperta. Inſpiratione vero profunda facta, tantum aëris in pulmones irruit, quantum ut aqua vaſis cylindrici labra tranſgrederetur fecit. Cum area vaſis cylindrici fuerit 55.41 digiti quadrati, et area colli 18; $55.41 - 18 \times 1.25 = 46.76$ digitos cubicos, ut quantitatem, quae ab hoc viro reſpirari ſolebat, aëris habemus. Idem experimentum cum eodem fere exitu ter repetitum. Ne quis error vero ab aliqua cauſa ortus fuiſſet, reſpirationum ejus per allantoidem periculum facere duxi eſſe neceſſarium.

NB. E

Fig: 1

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NB. E

The lung volume measured by the body plethysmograph is known as the thoracic gas volume (Vtg). This is the total volume of gas that lies inside the thorax whether or not this is in communication with the airways. Body plethysmography thus yields higher values in some patients with lung cysts, emphysema or severe asthma, than do gas dilution methods. Such differences may however be reduced if the gas-dilution or gas-clearance methods are continued for a sufficiently long time (Emmanuel et al, 1961; Schmidt and Cohn, 1961; Tierney and Nadel, 1962). Though it may be thought that gas in the gastro-intestinal tract, especially a large gas bubble in the stomach, could possibly contribute an artefact in the measurement of the thoracic gas volume, Du Bois and his associates showed this not to be so (Du Bois, 1959). This was confirmed by Reichel (1969) who found no change in the Vtg in 11 subjects following the introduction of one litre of air into their gastro-intestinal system.

There was a long period of confusion in the nomenclature of the subdivisions of lung volume. Some, like Hutchinson's 'vital capacity' have been retained, whilst others like Davy's 'residual air' have been slightly modified to 'residual volume', and still others completely discarded. The confusion was brought to an end in 1950 with a suggested standardisation by the Federation of American Societies for Experimental Biology. Their definitions have been widely accepted.

(b) Details of methods used to measure static lung volumes.

Measurements of static lung volumes were carried out by

(i) constant volume body plethysmography - as described in the previous section.

(ii) closed-circuit helium dilution technique.

A Resparameter MK II (P.K. Morgan Ltd.) and described by Reynolds et al, (1965) was used to measure the various subdivisions of lung volume. A measured concentration of helium is introduced into the water spirometer section of the Resparameter, which has a seven litre bell. The dead space of the apparatus is determined by observing the dilution of helium after about 2 litres of air have been drawn into the spirometer. The Resparameter is equipped with a pump for circulating the gas through the helium catharometer, and a pen recording kymograph. The catharometer is a Cambridge indicator supplied by the Cambridge Instrument Co. Ltd. Initially, enough helium is added to give almost a full scale deflection on the catharometer. The gas flowing to the catharometer is first passed through soda lime and calcium chloride to absorb any CO_2 and water vapour, as the catharometer is slightly sensitive to these gases. The dead space of the apparatus was calculated each time before use :

$$\text{Dead space (D.S.)} = \frac{V \times He_2}{He_1 - He_2}$$

where V = volume of gas in system

He_1 = initial concentration of helium

He_2 = concentration of helium after addition of air.

The subject is then switched into the circuit at the end of normal expiration during quiet breathing with subject relaxed and sitting upright. During the procedure, the subject wears a nose-clip and is carefully watched to see that the mouthpiece fits snugly and that the lips are kept tightly sealed around it to prevent any leak. The Resparameter has a small rotameter for monitoring added oxygen and a soda lime canister for absorbing carbon dioxide. Enough oxygen is added to keep the expiratory baseline level without rising or falling. The end point of equilibration is taken when the catharometer reading remains steady and the reading does not alter after the subject is instructed to carry out a series of slow deep breaths. In some of the asthmatic patients studied this sometimes took over fifteen minutes. Before the subject is turned out of the circuit he is asked to perform two or three relaxed vital capacity manoeuvres.

The functional residual capacity is then calculated in the following manner:

$$\text{Functional residual capacity} = (V + D.S.) \times \frac{(He_2 - He_3)}{He_3}$$

Where He_3 is final helium concentration.

The volume of the mouthpiece being deducted from the final results.

Gilson and Hugh-Jones (1949) pointed out that there were five main sources of error in gas exchange methods for measuring F.R.C.:

(i) incomplete mixing of gases in the lung - this can only be completely obviated by body plethysmographic techniques. As has been shown by various workers, this factor is of special importance in patients with severe respiratory disease. In the present study, special attention was given to ensure that a true final equilibrium point was reached. Mixing of gases in the lung was aided by asking the patients to take a number of slow deep breaths before the final equilibration point was recorded.

(ii) inaccurate estimation of the resting expiratory level - this presented no problem, as this point could easily be determined by watching the subjects closely and switching them from breathing air into the Respirometer and the end of a quiet expiration.

(iii) the effect of specific physicial properties of the gas used as an indicator, especially in relation to those of blood.- Meneely and associates, (1949) estimated that 8 ml to 15 ml of helium would be absorbed in a seven-minute rebreathing procedure. Birath and Swenson (1956) suggested that 105 ml. BTPS from the lung volume measurement should be deducted to make up for the amount of helium absorbed. As has already been stated, it was not felt necessary to make this correction in the values presented.

(iv) the so-called "nitrogen lag" or "oxygen storage effect" - described by Lassen et al, (1957) and confirmed by Meneely et al, (1960). This refers to the assumption that when helium equilibrium is achieved, there is equality of gas concentrations in all parts of the lung-spirometer system; this assumption was shown to be incorrect in a closed-circuit system of decreasing volume during re-breathing. This source of error was overcome by keeping the volume of the system constant by adding oxygen at approximately the same rate as it was being taken up; thus ensuring that the resting expiratory baseline remained level.

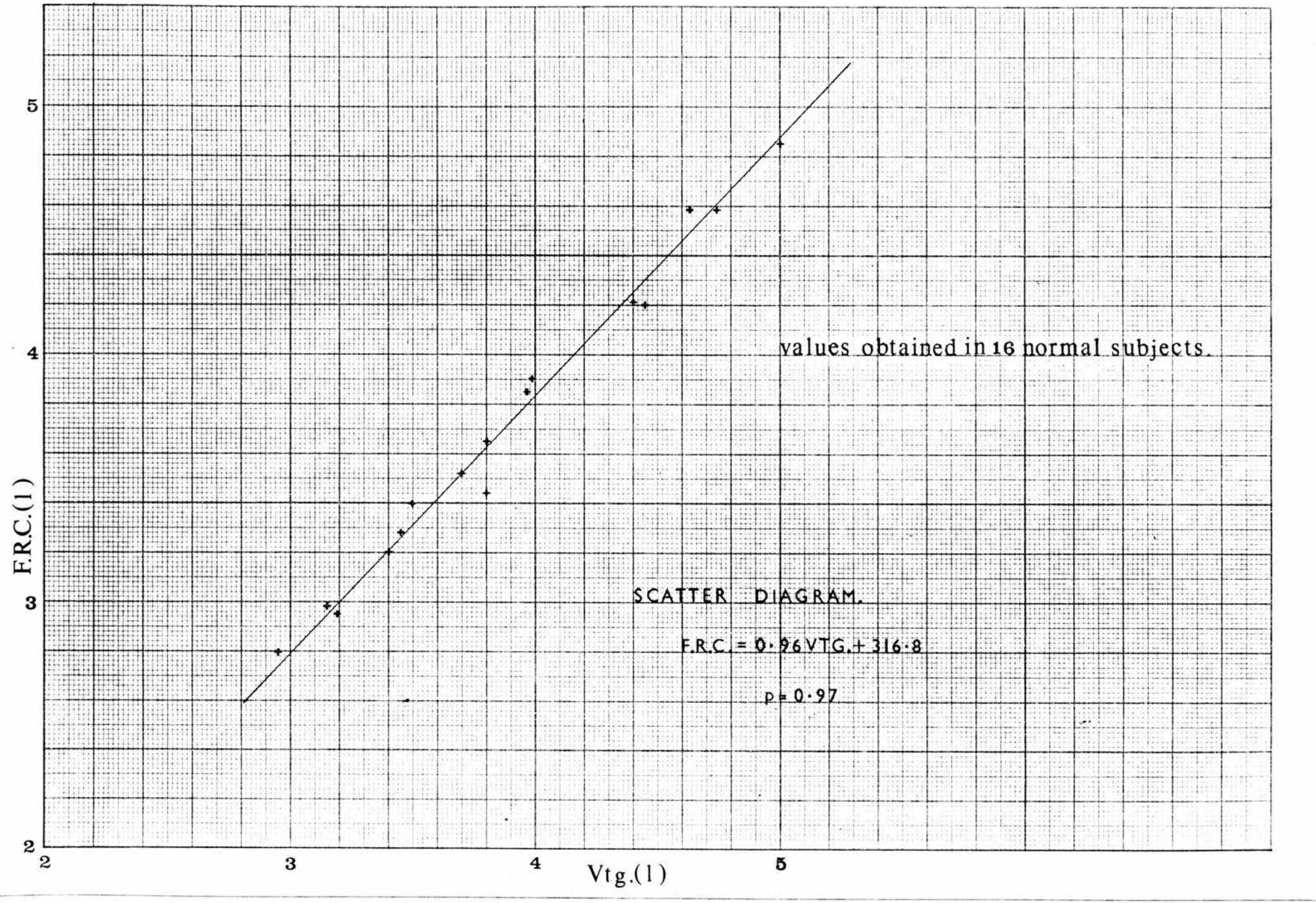
(v) faulty estimation of gas concentration - as has been previously mentioned, CO_2 and water vapour interfere with the correct estimation of helium concentration by the catharometer. These gases were removed by the addition of absorbers for these gases at the inlet of the catharometer. Besides interference from CO_2 and water vapour the thermal conductivity of the analytic cell in the catharometer has been shown to be affected by the presence of different concentrations of oxygen and nitrogen at the final reading compared to the intial reading. However, it has been shown that if the volume constancy of the system is maintained this should not introduce a significant error in the calculation (Hathirat et al, 1970).

(c) Comparing F.R.C. obtained by closed-circuit helium dilution with Vtg determined by constant volume body plethysmography:

TABLE IV.

Comparison between measurements of F.R.C. obtained by helium dilution with values of Vtg measured by body plethysmography in 16 normal subjects.

Name	F.R.C.(ml) B.T.P.S.	Vtg (ml) B.T.P.S.
1. J.S.	4850	4980
2. A.R.	3280	3450
3. A.M.	4580	4730
4. R.F.	3398	3500
5. M.F.	3850	3970
6. D.B.	3440	3800
7. J.R.S.	2950	3190
8. G.S.	3900	3990
9. R.C.B.	4209	4400
10. G.D.	4590	4630
11. A.T.P.	3520	3690
12. M.G.	3200	3400
13. F.W.	2800	2950
14. J.I.	2980	3150
15. P.F.	3650	3800
16. A.B.	4200	4450


F.R.C.(l)
Vtg.(l)
2
3
4
5
values obtained in 16 normal subjects.
SCATTER DIAGRAM.
F.R.C. = 0·96 VTG. + 316·8
p = 0·97

There have been a number of studies comparing FRC and Vtg both in normal and in patients with respiratory disease. In order to find out how Vtg obtained by body plethysmograph compared with F.R.C. by helium dilution method, values for the two methods have been determined in 16 healthy young volunteers who formed either part of the departmental staff or were medical students. Results are shown in Table IV overleaf, and in Fig. 8.

(3) DYNAMIC LUNG VOLUMES ---- SINGLE EXPIRATION MEASUREMENTS.

The single expiration measurements carried out in this study are:-

(i) Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC).

(ii) Relaxed vital capacity

(iii) Maximum expiratory flow volume curves

(iv) Peak expiratory flow rate.

(i) FEV_1 and FVC

(a) Development of test.

The origin of these tests may be traced back to Hutchinson, who invented the first spirometer and published the results of vital capacity measurements in 2130 subjects in 1846. Hutchinson's original test remained unaltered for a long time and no attempt

was made to relate it to time. Sturgis et al, (1922) put forward the idea that maximum ventilation was achieved in the last minute of exhausting exercise. Hermannsen, (1933) discovered that the highest ventilation was achieved by maximum voluntary effort and showed that this exceeded ventilation on exercise or in response to CO_2. He introduced the maximum breathing capacity test (M.B.C.) which was popularized by Cournand and his associates (1939, 1941). It became widely used following the establishment of normal values by Baldwin et al, (1948).

The M.B.C. however imposes a somewhat severe strain especially on the patient who is unwell (Shepherd, 1956). The search for an alternative and less exhausting procedure lead to the introduction of the timed vital capacity (Tiffeneau et al, 1947, 1949). The fast vital capacity manoeuvre as it was first known, was originally mainly considered as a means of predicting the maximum breathing capacity. Various factors were put forward for measuring the "indirect" M.B.C. Thus Tiffeneau et al, (1949) suggested multiplying the FEV_1 by 30; Gandevia and Hugh-Jones, (1957); by 35; whilst Cara (1953) multiplied the FEV_1 by 37.5 and Kennedy,(1953) used the $FEV_{0.75}$ and multiplied this by 40.

At the same time, however, there were also pleas for a more direct interpretation of the FVC tracings (Bernstein and Kazantzis, 1954; Shepherd, 1955). The forced expiratory volume in one second appears to have been introduced independently by Tiffeneau in

France and Gaensler in the U.S.A. The ideal time interval remained under discussion for a long time; Kennedy, (1953) suggested measuring the $FEV_{0.75\ sec.}$; Needham et al, (1954) $FEV_{2\ sec.}$ and Miller et al, (1956) preferred $FEV_{0.5\ sec.}$ The volumes which can be expired over times between 0.5 seconds and 3 seconds are highly correlated and $FEV_{1\ sec.}$ is now universally accepted.

In 1951, Gaensler introduced the concept of measuring the FEV as a fraction of the vital capacity, and showed in two separate papers that it could be used to differentiate between patients having "obstructive ventilatory insufficiency" and patients with "restrictive insufficiency"; two terms which had previously been introduced by Baldwin et al, (1948) to differentiate between underlying pulmonary patho-physiological mechanisms.

Terminology for measurements of the ventilatory capacity was introduced by Gandevia and Hugh-Jones in 1957, following which, the fast vital capacity became known as the forced vital capacity.

(b) Physiological basis.

The FEV_1, which is probably the commonest pulmonary clinical test in use, and is the simplest to perform, has perhaps the most complex underlying physiology of all the pulmonary function tests (Pride, 1971). It is what might be termed a polyvalent test and reflects very well the interdependence between the airways and the

parenchyma of the lung. It depends, especially, on the factors which determine:

(a) the maximum expiratory flow at a particular lung volume, i.e. lung elastic recoil pressure and airway resistance.

(b) the change in maximum expiratory flow with lung volume, which reflects pulmonary compliance and the change in airway resistance with change in lung volume.

The FEV_1 is thought to be relatively independent of the resistance of the upper airways and of the effort applied (Kemm and Kamburoff, 1970). It may be regarded as integrating a substantial amount of information about the mechanical properties of the lung (Pride, 1971).

PROCEDURE.

A Gaensler type water spirometer (Gaensler, 1951 b) which has a light bell and an automatic electrical timing device was used. The spirometer provides a direct reading without the necessity of analysing a paper record. All the patients could be considered as "experienced subjects", in that they had all previously undergone quite a number of spirometric tests. Each patient was instructed to take as deep an inspiration as possible, put the mouthpiece in his mouth in order to make a good seal with his lips, and then was actively encouraged to blow out into the spirometer as hard and as

far out as possible. Three measurements were carried out at intervals of about thirty seconds with the patient sitting down and not wearing a nose-clip. Meticulous care was taken to ensure that the patient started the manoeuvre from as near his total lung capacity as possible, as the FEV_1 is susceptible to the depth of the preceding inspiration, which determines the diameter of the airways at the start of expiration (Cotes, 1965; Kemm and Kamburoff, 1970).

Hutchinson in first describing his test in 1846 wrote "Each of these individuals breathed three consecutive times into the Spirometer because either from timidity or inexperience, the first observation is frequently not a correct experiment, but by three observations the point sought for is accurately determined. If more than three observations are consecutively made at one time the number of cubic inches of air will, from fatigue, generally be found to decrease". There has been some controversy as to which is the better estimate of the individual performance, the highest value of FEV_1 recorded or the mean of three technically satisfactory attempts. Cotes, (1965) suggests carrying out five measurements at 30 second intervals, of which, the first two are rejected, and the mean of the last three is taken as the definite reading. Freedman and Prowse, (1966) point out that in ill patients, the FEV_1 may fall off with successive expirations, as this makes them tired or because forced expiration makes them cough; this is often the case with asthmatics. They suggest in such cases, the peak value may be more relevant than

the mean. Kemm and Kamburoff (1970) found that there was no significant difference between the maximum and the mean FEV_1 when effort, as estimated by oesophageal pressure, was greater than 75% of maximum, and concluded that either value is acceptable. In the present study the best FEV_1 obtained from three successive efforts is chosen. All the patients had marked airway obstruction and were repeatedly submitted to a large number of tests. Submitting them to five forced expirations each time was considered unnecessary. Cough was not infrequently induced by forced expiration and a substantial number of the patients recorded peak values on their first attempt.

(ii) THE RELAXED EXPIRATORY VOLUME.

In normal subjects, increasing transpulmonary pressure during expiration tends to narrow the airways. Einthoven (1892) was the first to appreciate the importance of "dynamic compression" in the pathophysiology of airway obstruction disease. This narrowing effect has been shown to be increased in some patients with chronic obstruction (Mead et al, 1955; Dayman, 1956; Campbell et al, 1957). When excessive expiratory narrowing of the airways limits flow in patients with airway obstruction, changes in the peripheral airways, such as those produced by a bronchodilator, may not be detected by tests of maximum expiratory effort. This is because collapse of large central airways can mask the peripheral changes (Macklem, 1965).

The patients in the second part of the study were therefore asked to perform three relaxed expiratory manoeuvres, preceding the forced expiratory ones. The subject was asked to inhale as deeply as possible and then to let out all the air with a deep and heavy sigh. It was emphasized that force was not to be used but that the subject was to concentrate on a sigh or a relaxed expiration. The best reading was again taken as the final result. Some subjects found it more difficult to carry out technically satisfactory relaxed expiratory manoeuvres than the FEV_1.

(iii) MAXIMUM EXPIRATORY FLOW VOLUME CURVES.

Physiological basis and development of test.

(a) ISO-VOLUME PRESSURE-FLOW CURVES.

Fry and his associates in 1954, showed that a functional relationship exists between transpulmonary pressure, respiratory gas flow and the degree of lung inflation. These workers introduced isovolume pressure-flow (I.V.P.F.) curves to express the relationship between these variables. Isovolume pressure-flow curves have been used very successfully by a number of workers (Fry, 1958; Hyatt et al, 1958; Fry and Hyatt, 1960; Mead and Macklem, 1967; Mead et al, 1967; Pride, 1971)., to analyse mechanisms limiting flow during forced expiration. These curves are obtained by getting the subjects to

perform a series of expired vital capacity manoeuvres, slowly at first, and then more rapidly up to one of maximum speed and effort. The volumes are expressed as percentage of the vital capacity. Instantaneous values of oesophageal pressure - reflecting transpulmonary pressure, are plotted against simultaneous expiratory flows at the same lung volume. Each vital capacity manoeuvre yielding one point at a given volume. A family of isovolume pressure-flow curves can thus be obtained at different degrees of lung inflation.

Although this technique is too time consuming for routine use, the information obtained from such I.V.P.F. curves is absolutely fundamental to an understanding of what is happening during a forced expiration. I.V.P.F. curves show that at high lung volumes, usually above 75% of the vital capacity, flow goes on increasing as the alveolar pressure rises and no easily defined limit to expiratory flow exists at volumes around total lung capacity (T.L.C.). As lung volume is reduced below about 75% of the vital capacity, expiratory flow maxima can be shown , beyond which, a plateau is reached where flow no longer increases with increase in alveolar pressure. Plateaus of flow occur at lower and lower alveolar pressures with further reductions in lung volume.

Maximal forced expiratory flow has been shown to be determined by a number of factors, which include, the relationship between the degree of lung inflation and the transpulmonary pressure (Fry et al,

1960), the magnitude of small airway resistance (Macklem et al, 1965) as well as the lung recoil pressure (Stubbs and Hyatt, 1972) and, at times, the collapsibility of the large airways (Mead et al, 1967).

Although, as pointed out by Dayman as early as 1951, compression of large airways is responsible for limiting expiratory flow, it has been shown that it is not the only cause of an increase in resistance with increasing expiratory effort. The increase in the rate of flow of air will of itself bring about other changes. When Reynold's numbers exceed 2000, especially if airways are irregular, flow becomes turbulent (Mead et al, 1967); as turbulence develops, this increases the pressure drop from the airways. Besides the effect of turbulence, as the airstream moves from the alveoli, through the bronchioles and up to the larger airways, its linear velocity increases because the large airways have a smaller total cross-sectional area - this is known as convective acceleration of the flowing gas (Hyatt and Wilcox, 1963). Convective acceleration has the effect of reducing the pressure within the airways, the Bernoulli effect (Macklem and Mead, 1968), and this naturally increases the compressive effect of the high extra airway pressures found during forced expirations. The pressure drop associated with the components mentioned above will thus depend on the geometry of the airways andthe magnitude of flow (Mead et al, 1967).

(b) THEORIES EXPLAINING EXPIRATORY FLOW LIMITATIONS.

Fry (1958) was the first to attempt a detailed physiological explanation of the mechanisms limiting expiratory flow by applying aerodynamic principles to events occurring along the whole airway. He developed the concept of the "flow-limiting segments", which were the first to narrow sufficiently to limit flow. Analysis proved complicated due to the difficulties in accurately describing events occurring along the whole of the compressed segment.

Pride et al, (1967) suggested that when maximum expiratory flow is reached in an I.V.P.F. curve a "waterfall" or Starling resistor effect develops in the airways. This concept was first applied to pulmonary blood vessels by Permutt and his co-workers in 1962. Using the Starling resistor model they developed simple equations relating the roles of lung elastic recoil, airway resistance and bronchial collapsibility in determining maximum expiratory flow, driving pressure during this flow and airway resistance. They regard the airways as two rigid tubes connected in series by a collapsible tube. When the transmural pressure in the collapsible segment falls to a critical level, below Pleural pressure (Ppl) a "Waterfall" effect will develop and that part of the airway will form a flow limiting segment; i.e. flow becomes dependent on the difference between driving (alveolar) pressure and the surrounding (pleural) pressure and independent of the difference between the driving and outlet (atmospheric) pressure.

$$\dot{V}_E = \frac{Pel - Ptm'}{Rs}$$

where $\dot{V}_E$ = flow

Pel = elastic recoil pressure of lung

Ptm' = critical transmural pressure of collapsible segment at which a waterfall develops.

R_S = resistance of segment between the alveoli and the outflow end of the collapsible tube.

Mead et al, (1967) developed a different but complementary concept of events occurring during a forced expiration. They put forward the idea that during a forced expiration there must be some point or points in the airway where the intra-luminal pressure is equal to the pleural pressure. They referred to these points as the "equal pressure points", (EPP). Such a locus divides the airway into an upstream segment between the alveoli and the EPP, and a downstream segment between the EPP and the airway opening. The pressure drop from alveoli to EPP is the drop from alveolar pressure to pleural pressure, that is, the lung elastic recoil pressure. At maximum flow at any given lung volume, the lungs may be regarded as a fixed resistor (the upstream resistor) in series with a variable resistor (the airways dynamically compressed downstream from the EPP). Macklem and Wilson (1965) showed that the EPP were in the segmental bronchi on forced expiration in normal subjects.

Mead et al, formulated that:

$$\dot{V}_E \text{ max.} = \frac{Pel}{Rus}$$

where $\dot{V}_E$ max. = maximum expiratory flow

Pel = lung elastic recoil pressure

Rus = resistance of upper segment

Both Pride et al, and Mead et al, regard maximum flow as resulting from a fixed driving pressure operating through a fixed resistor in series with a variable resistor. In the equal pressure point theory, the fixed resistor is regarded as extending from the alveoli to the equal pressure points; in the analysis of Pride et al, it extends from alveoli to the flow limiting segment. Mead's concept has the advantage that fewer assumptions are made; it ignores the compressed segment and thereby simplifies the analysis further. In practice Rus is much simpler to measure than R_s (Pride et al, 1967). Pride's work takes into consideration the exact mechanism by which flow, is limited and the use of their equation would allow an estimation of Ptm' which might provide information about the collapsibility of the airways and possibly, the magnitude of smooth muscle tone.

In many respects the analysis carried out by Campbell, Martin and Riley, (1957) is similar to Pride's, but Campbell and his associates did not use the simplifying assumptions of the waterfall phenomenon. They used oesophageal pressure at which peak flow was reached during forced expiration, "Pt max. eff." - the maximum

effective intrathoracic pressure in an attempt to distinguish differences in mechanisms of airway obstruction in patients with emphysema and asthma.

(c) MAXIMUM EXPIRATORY FLOW VOLUME CURVES.

As from can be seen from I.V.P.F. curves, during forced expirations, the rate of air flow cannot increase beyond certain maximum values. At large lung volumes, these maxima are mainly set by the amount of expiratory effort, that is, by the force developed by the expiratory muscles which, in turn, depends on their speed of contraction and velocity of shortening (Agostoni and Fenn, 1960). This driving pressure, is opposed by the total flow resistance of the entire airway, as well as that of the tissues, chest wall and any resistance of the measuring equipment. As flow rises, the EPP move rapidly upstream. As has already been indicated, at lower lung volumes, flow is independent of muscular effort as long as this is above certain levels, and may be considered as being determined by the lung elastic recoil and the resistance between the alveoli and the EPP.

Since the degree of lung inflation is a main determinant in flow-limiting mechanisms, maximum expiratory flow rates are perhaps best studied as a function of lung volume. Maximum expiratory flow volume curves (M.E.F.V.) were introduced with this aim by Hyatt, Schilder and Fry in 1958 and have proved to be a

very useful tool in a number of physiological and clinical studies (Takishima et al, 1967; Lapp and Hyatt, 1967; Bouhuys et al, 1969; Van de Woestijne and Zapletal, 1970).

Maximum expiratory flow volume curves can be derived from iso-volume pressure-flow curves by plotting the maximum flows against the volume at which each was measured.

The plotting of I.V.P.F. curves, however, remains a laborious procedure, certainly not one that lends itself easily for frequent and repeated measurements on asthmatic patients. Fortunately, M.E.F.V. curves are easily obtained by plotting instantaneous flow against lung volume, instead of time as in the $F.E.V._1$, during a vital capacity manoeuvre. In normal M.E.F.V. curves, flow increases rapidly to reach a maximum at about 80% of the vital capacity, and then decreases, reaching a value of zero at the residual volume. The curve consists of essentially two parts, an effort dependent portion, which as indicated is that part at higher lung volumes, and an effort independent portion. According to Hyatt (1961) the effort independent portion extends to 60% of the vital capacity. Later studies by Mead et al, (1967) showed that it extended to at least 70% of V.C. Mellins et al, (1968) reported that I.V.P.F. curves of healthy children reach plateaus at lung volumes up to 90% of V.C. These data at first seem to suggest that children might reach the effort independent portion of the M.E.F.V. curves at higher lung volumes than

adults. It is now however, known that there is not a consistent relationship between lung size and the volume at which I.V.P.F. curves first reach a plateau. Van de Woestijne and Zapletal, (1970) showed that the effort independent portion extended to an average level of 82% of V.C. in normal subjects. Many adults achieved a plateau at lung volume levels which were similar to those at which children achieved theirs. Thus, maximum expiratory flow in about the lower 75% of V.C. is thought to reflect the physical properties of the lower airways and is determined by the lung elastic recoil, the resistance of these airways and the collapsibility of the flow-limiting segments.

Recent work by Clement and Van de Woestijne,(1971) has however cast some doubt on the "effort independence" of M.E.F.V. curves. They measured maximum flows in the "effort independent" portion of flow-volume curves and showed that these had a coefficient of variation of 9%. This lack of reproducibility was looked at by means of a polynomial analysis, and they showed that it was not only related to technique and to slight differences in volume at the maximum inspiratory level preceeding each expiration; but that a third source of variability can be attributed at least in part to effort dependency. Clement and Van de Woestijne (1971) claim that linear regressions constructed in the plateau region of I.V.P.F. curves (at 55% T.L.C.) do not demonstrate real horizontal flow plateaus; but that flow rates slightly increase with increasing transpulmonary pressures.

(d) PROCEDURE.

A Wedge Spirometer (Model 170 Med-Science Electronics Incorp; St. Louis Missouri) with a maximum volume of ten litres; was used to obtain both flow and volume. It is a waterless spirometer and does not depend upon a water chamber to maintain an air seal, instead an extremely compliant bellows is employed to allow motion of the output member with absolute assurance of zero leakage. Both volume and flow parameters are available as electrical signals, each generated as a function of the instantaneous rate of displacement of a core in a transducer. Each core is coupled to the moving output member of the spirometer. Its frequency response is claimed to be flat within 5% up to 10 cycles/sec for both volume and flow. Extremely low resistance characteristics are achieved in this instrument. The signals from the spirometer were fed into a direct writing multichannel recorder(80 Elema Scholander Mingograf). The spirometer was carefully calibrated for both volume and flow immediately before each set of measurements were performed. Hyatt et al, (1958) originally suggested a method using multiple expirations of varying effort to 'fill in' the flow-volume curve with true maximal flows at each volume. It was Branscomb, (1960) who introduced the idea of using a maximum forced effort in plotting flow against volume.

Three forced vital capacity efforts were recorded with the subject seated, with a nose-clip attached, at intervals of about

thirty seconds. The effects of flow and volume history on maximal expiratory flow rates are complex and not well understood (Bouhuys and Jonson, 1967; Bouhuys et al, 1969). All the subjects studied had an identical flow and volume history before attempting this procedure. The best of the three efforts was later analysed.

As can be shown by analysing I.V.P.F. curves the maximum flow especially over the lower half of the M.E.F.V. curve does not correspond to the greatest transpulmonary pressure produced by maximum effort. In this respect, the curves obtained from the subjects in this study are really maximum effort flow volume curves as first described by Fry and Hyatt in 1960. However, by making the subjects carry out F.V.C. efforts, an identical volume history was ensured and the tests were repeatable and comparable, each subject serving as his own control.

The significance of alveolar gas compressibility and its effect on the static pressure-volume diagram was described as early as 1946 by Rahn and his co-workers. Jaeger and Otis, (1964) studied the effect of gas compressibility on the dynamic pressure-volume relationship by simultaneously measuring changes in thoracic gas volume and volume displacement at the mouth. They found that the volume displacement at the mouth was less than the volume change of the thorax and this difference increased with increased airway resistance, respiratory rate and lung volume.

Their work was confined to the study of slow and rapid cyclic respiration.

In their original I.V.P.F. curves Hyatt and his associates (1958) represented flow as decreasing from maximum levels as pleural pressure increased. Ingram and Schilder (1966) studied the effect of gas compressibility on the forced vital capacity manoeuvre and the flow-volume relationships. They showed that the decrease in flow from maximum levels reported by Hyatt (1958), is, at least in part, an artefact related to the fact that, a spirometer at the mouth was used to measure volume. During forced expirations the gas in the lungs is compressed and lung volume decreases progressively below that shown by the spirometer. In this case, reductions in flow are to be expected since as lung volume decreases maximum flow also decreases. If a volume-displacement body plethysmograph is used, where all volume changes, including those of gas compression are measured, the I.V.P.F. curves usually show flatter plateaus. The larger lung volumes and high airway resistance found in patients with airway obstruction, will of course, magnify the effects of gas compression when flow and volume are measured by a spirometer at the mouth. Although ideally, as shown above, changes in flow should be plotted against absolute changes in thoracic gas volume, as no volume displacement body plethysmograph was available, both flow and volume had to be measured at the mouth. The effect of gas compression on M.E. F.V. curves however, is said to be less than on I.V.P.F. curves

(Bouhuys, 1970).

(e) Indices derived from flow-volume curves.

There have been various suggestions regarding the data that can be derived from flow-volume curves and the indices to be used. Cander and Comroe (1955) suggested measuring mean maximal expiratory flow between 0.2 and 1.2 litres of a forced expiration. The mean maximal expiratory flow between 25% and 75% of a forced vital capacity effort (MMEF 25 - 75%) was first put forward by Leuallen and Fowler, (1955). Franklin and Lowell, (1961) suggested using the expiratory rate during the third quarter of a maximal forced expiration, (MMEF 50 - 75%), as an index. Lloyd and Wright, (1963) measured maximum flow rate at a lung volume 1 litre above the residual volume; this describes the average slope of the last portion of the MEFC curve. The ratio $\Delta V / \Delta \dot{V}$ over the volume range 50% - 75% of the vital capacity was used by Lapp and Hyatt, (1967); this ratio has the dimension of time and represents the reciprocal of the MEFV curve slope over the volume interval chosen. Lapp and Hyatt considered this index as a measurement of the time constant of lung emptying. Hyatt, (1965) suggested that when comparing subjects of different size, it may be worthwhile dividing the maximum expiratory flow rate at 50% V.C. by the thoracic gas volume corresponding to 50% of the vital capacity. Bouhuys et al, (1969) studying the bronchoconstriction changes induced by inhalation of pharmacological agents and cotton dust,

showed that maximum flow rate measured at 60% of T.L.C. was the most sensitive index in detecting relatively slight degrees of bronchoconstriction. The maximal expiratory flow rate (MEFR) is another index obtainable from an M.E.F.V. curve.

Evidence has been produced that a maximum inspiration, which is such an important step in performing a forced vital capacity manoeuvre, alters lung compliance (Ferris and Pollard, 1960) and may change airway resistance (Nadel and Tierney, 1961; Lloyd, 1963). Frank and his co-workers (1962) first suggested that expiratory flow measurements after a less than maximum inspiration may be very useful. Bouhuys et al, (1969) introduced partial expiratory flow volume (PEFV) curves, made after inspiration to mid-vital capacity instead of the T.L.C. and reported that changes of flow rates on P.E.F.V. curves were usually larger than those of flow rates on M.E.F.V. curves, in a series of patients in whom bronchoconstriction had been indiced. Interpretation of P.E.F.V. curves however requires the measurement of thoracic gas volume to establish their volume level.

The indices that have been derived from the M.E.F.V. curves in this study include M.E.F.R. and maximal expiratory flow rate at 50% V.C. Maximal flow rates obtained at 80%, 60%, 40% and 20% of the vital capacity were also compared.

Hyatt, (1965) suggested that in chronic airway obstruction

where increases in residual volume are an integral feature of the disease process, the value of maximum expiratory flow volume curves may be decreased by analyzing the forced vital capacity manoeuvre on the basis of vital capacity alone. He suggested that it would be more logical to relate maximum expiratory flow to absolute thoracic gas volumes, and this should relate more directly to the underlying anatomical and physiological abnormalities.

Boulnays et al, (1969) believe that the maximum expiratory flow rate at a defined, absolute level of lung volume is a more satisfactory measure of expressing changes of M.E.F.V. curves than indices proposed by previous authors. They showed that changes in M.E.F.V. curves are most impressive when the curves are plotted on an absolute volume scale. As no volume-displacement plethysmograph was available, the absolute volume scale was obtained from separate measurements of total lung capacity obtained by the closed-circuit helium dilution technique. As shown further on, relating maximum flow rates to an absolute level of lung volume, made the changes in flow rates obtained, more striking and more meaningful, than when the same changes in flow were related to percentage of vital capacity.

(iv) Peak expiratory flow rate

Following the introduction by Wright and McKerrow in 1959 of a new portable instrument for measuring maximum forced expiratory

flow in litres per minute, the peak expiratory flow rate (P.E.F.R.) has become another popular single-expiration measurement.

According to Donald (1953): "The physician of the last century who asked a patient with respiratory disease to whistle or blow a candle out was crudely assessing the maximum respiratory velocities". He suggested that a "simple whistle-like instrument" might be developed and might become a standard clinical tool. There had been previous attempts in the past to measure flow rate on expiration. Thus, Hadorn, (1942) used an aneroid manometer connected across a simple orifice, the deflection of the manometer level being judged by eye. Wyss, (1950) used the same type of orifice but recorded the pressures photographically. Hildebrandt and Hanke, (1956) used a "pneumometer", incorporating an aneroid manometer fitted with a device for recording the maximum flow rate.

The Wright peak flow meter has a variable orifice which is initially closed by a vane. The latter is deflected during expiration, through an angle which is a function of the rate of flow. This instrument is calibrated in litres per minute and records flow over the first ten milliseconds of a forced expiration.

As the peak flow rate is a measurement occurring very early on in the vital capacity, it depends to a great extent on full co-

operation from the subject. A position of full inspiration was carefully ensured and the subject was coaxed to empty his lungs in a short, sharp expiration of maximum effort. The best of three efforts was accepted as the final value. The Wright peak flow meter was calibrated against a rotameter and the values obtained were well within 10% of the values reported by Cotes, (1965).

ASSESSMENT OF PULMONARY GAS EXCHANGE.

(1) Arterial blood gas analysis.

Development of methods.

(a) Arterial oxygen tension (PaO_2)

Direct estimation of the partial pressures of gases in whole blood was first attempted by Pfluger in 1872 who introduced blood into a tonometer containing gases of known concentrations and analysed the gas phase after equilibration between the blood and gas had taken place. Haldane (1898) first noted the ability of ferricyanide salts to displace oxygen from its chemical combination with haemoglobin. This led to a rapid improvement of vacuum extraction methods which had been introduced by Magnus in 1845, culminating in the manometric method of Van Slyke and Neill, (1924).

Riley and his associates in 1945, introduced a method in which

a small volume of blood is equilibrated with a gas bubble. The gaseous composition of the bubble being determined by chemical absorption in a capillary tube where the length of the bubble is proportional to its volume before and after absorption of each constituent. In their latest development, Riley et al, (1957) were using 1 ml. of blood and a bubble of 5 - 10 microlitres. The Riley method is slow and tedious and requires variable, empirical correction factors.

Of course, PaO_2, may also be determined by interpolation of the saturation in the oxy-haemoglobin dissociation curve, once the pH and the PCO_2 are known and the body temperature is not significantly different from 37°C. The oxygen content and capacity of the blood may be obtained by the manometric method of Van Slyke and Neill (1924); but this is too time consuming. A quicker determination of oxygen saturation could be obtained by the spectrophotometric method (Nilsson, 1960).

Danneel (1897/1898) was the first to use the platinum cathode for oxygen tension measurements; demonstrating a linear relationship between oxygen tension and the recorded current. However, its use was somewhat limited, because when immersed in biological media, it rapidly lost its function because of the deposition of a protein film on the surface of the electrode.

Modern methods of measuring arterial oxygen tension are based on the principle of Polarography introduced by Heyrovski in

1925. Essentially the system consists of an anode and a cathode made of a relatively non-ionisable metal, such as mercury or platinum, in an electrolytic cell; oxygen being reduced at the cathode when a negative potential is applied across the anode and cathode, causing a current to flow. The current which flows is a function of the rate of reduction of oxygen at the cathode. Baumberger, (1938) first used this principle to determine the dissociation curve of oxyhaemoglobin. The cathode of this electrode was formed of drops of mercury. This dropping mercury cathode was later used by Berggren, (1942) for his classical experiments on venous shunting in the lung. However, the technique was difficult to master and had to be carried out on anaerobically separated plasma, and not on whole blood. Contamination by films of protein and variation in mercury drop size produced unreliable results.

The problem of deposition of protein films on the electrode was finally solved by Clark in 1953, who isolated the platinum cathode by covering it with a cellophane membrane, which only allowed access to oxygen and carbon dioxide. It was further improved by incorporating the platinum cathode and silver anode in a solid cell, isolating the exposed electrode by a hydrophobic membrane (Clark, 1956). This type of electrode required active motion of the blood sample to ensure a continuous and adequate supply of oxygen to the electrode surface. There have been many ways in which stirring has been produced, such as the use

of a stainless steel blade (Rooth et al, 1959) and a glass coated, soft iron slug (Bishop, 1960). Elimination of the stirring or motion of the electrode has now been obtained by reduction in size of the platinum cathode and increasing the thickness of the covering membrane. The introduction of the Clark membrane - covered polarographic oxygen electrode has enormously facilitated the measurement of PaO_2 making it a routine laboratory investigation; no other method is now in regular use.

(b) Arterial carbon dioxide tension ($PaCO_2$)

Several of the original methods described above for the determination of PaO_2, e.g. the Van Slyke technique and the Riley bubble method, also yielded values for $PaCO_2$. Another method of determining the carbon dioxide tension in arterial blood makes use of the linear relationship between pH and log PCO_2 - the Astrup procedure (Astrup,, 1956, 1958, 1960). In this technique the sample of blood is divided into three parts, the pH of the first part is read directly with a pH electrode; the other two portions being equilibrated with two gas mixtures of known PCO_2 in small tonometers. The pH of the two equilibrated samples is measured and plotted against log PCO_2, the points being joined by a straight line. The PCO_2 of the original sample being obtained by interpolation on the line at its measured pH. Siggaard-Andersen et al, 1960 introduced a micromethod based on the Astrup procedure, using a microtonometer and a micro pH electrode for the determina-

tion of pH, PCO_2, base excess and standard bicarbonate using capillary blood.

A method which has gained a great deal of popularity since its introduction is the direct determination of PCO_2 with a CO_2 electrode. The principle of this electrode was discovered independently by Stow and his co-workers (1957) and Gertz and Loeschcke, (1958) and the method has been extensively developed by Severinghaus, (1958, 1960, 1962). The electrode consists essentially of a glass pH electrode with a reference electrode surrounded by a bicarbonate buffer and separated from the blood sample by means of a Teflon membrane which is permeable to CO_2 but impermeable to other ions. CO_2 diffuses from the sample across the membrane altering the pH of the bicarbonate solution. The change in pH is detected by the electrode; the voltage output of the electrode is directly related to pH and is therefore a log function of PCO_2. The pH is a linear function of the logarithm of the blood PCO_2 over the range from at least 7 to 700 mmHg (Severinghaus, 1960).

(c) <u>pH of blood.</u>

Sorensen (1909) introduced the logarithmic pH notation for expressing the concentration of hydrogen ions. He developed electrometric methods for determining the pH of the blood. Using these methods, Hasselbalch and Lundsgaard made the first accurate measurements of blood hydrogen ion concentration in 1912. A capillary

glass electrode was first used for measuring pH in the 1930's. This type of electrode enclosed in a water jacket for temperature control was re-introduced by Sanz, (1957) and has virtually replaced the bulb glass electrode for blood analysis which had been used before. Micro-electrodes, such as that described by Siggaard-Andersen and his co-workers (1960) have also been introduced in the measurement of blood pH.

A potential difference is set up when fluids of different hydrogen ion concentrations are on either side of a thin glass membrane. The potential difference is measured by combining the glass electrode with a reference electrode, such as a calomel electrode and measuring the voltage of the system.

(ii) Procedure.

The oxygen electrode used in this study is a Radiometer PO_2 electrode type E5046. It is a Clark type O_2 electrode and consists of a platinum cathode and silver/silver chloride anode placed in an electrolytic solution behind a polypropylene membrane. The electrolytic solution is a phosphate buffer to which some potassium chloride is added to stabilise the potential of the anode. A polarising voltage of about 650 m.V is applied across the two electrodes. The electrode was carefully calibrated before each blood sample was put in. "White spot" nitrogen was used as the zero reference point and atmospheric air was used as the high reference

point. Tonometry, using a tonometer of the swirling flask type, (Schoeller and Co., Elektrotechn. Fabrik, Frankfurt) was regularly carried out to check the oxygen electrode over the PO_2 range 15 to 120 mmHg and the values obtained from the electrode were suitably corrected by use of calibration graphs.

The carbon dioxide electrode used is a Radiometer PCO_2 electrode type E5036. It is a Severinghaus CO_2 electrode consisting of a combined glass electrode and silver/silver chloride electrode mounted in an electrode jacket surrounded by a $NaHCO_3$-NaCl solution and separated from the sample by means of a Teflon membrane. Calibration of the electrode was carefully carried out, before each blood sample was put through, with two gases of different CO_2 concentrations; mixtures of approximately 3% CO_2 in 17% O_2 and 9% in CO_2 in 17% O_2 were used.

The composition of all the gas mixtures used either in the calibration of the O_2 and CO_2 blood electrodes or in the calibration of the infra-red CO_2 and paramagnetic oxygen analysers which were used to measure expired O_2 and CO_2 concentrations was carried out using a Lloyd-Haldane (Lloyd, 1958) or a micro-Scholander (Scholander, 1947) apparatus. Analyses were duplicated to within 0.03%. These electrodes, if scrupulously calibrated, have a high degree of accuracy, as shown by Flenley and his co-workers (1967).

The pH electrode used is a Radiometer pH electrode type E5021 with a pH meter type PHM 27. The unit consists of a glass elec-

trode that is made of a pH-sensitive glass capillary sealed into a glass tube with a reference liquid , and an AgCl inner electrode is mounted in this reference liquid. The electrode is mounted in a glass water jacket through which heated water from a circulation thermostat, flows, keeping the electrode at a constant temperature. The glass electrode is connected to a saturated calomel reference electrode also surrounded by a glass water jacket. The interior of the calomel electrode is connected through a porous pin to a small pool of saturated KCL solution, which is used as a salt bridge. The pH electrode was carefully standardised just before use by a prepared buffer solution of known pH. Although it is realised that red blood cells create a potential at the boundary between blood and saturated KCL, equivalent to about 0.01 pH units, making the blood pH appear lower (Severinghaus et al, 1956; Siggaard-Anderson, 1961), no correction for this was applied to the pH values reported.

(2) Pulmonary Gas Exchange.

Geppert and Zuntz in 1886 were the first to suggest the effect of uneven ventilation on pulmonary gas exchange. Advances in the field were held up for a time because of the controversy over how oxygen entered arterial blood. Bohr (1891) originally proposed the hypothesis that pulmonary epithelium actively secreted oxygen under certain circumstances, such as during exercise and at high altitudes. Haldane and Lorrain-Smith (1896) supported his view.

On the other hand, August and Marie Krogh firmly believed that diffusion was the only process concerned with the pulmonary exchange of oxygen and carbon dioxide, and published their work in a series of papers (1910a; b, c, d, e, f). They stated: "The absorption of oxygen and the elimination of carbon dioxide in the lung takes place by diffusion and by diffusion alone". (1910, e) However, Haldane and his colleagues (1912), in an expedition to Pike's Peak (14,100 ft.), obtained evidence that the alveolar oxygen tension was about 35 mmHg lower than the arterial during exercise at this altitude. They again concluded that under such conditions oxygen must be secreted by the pulmonary epithelium. The 'Diffusion' versus 'Secretion' controversy was shown to be the result of methodological problems and was finally laid to rest by Barcroft in 1920, in the "glass chamber" experiment which he carried out on himself. He showed that under similar conditions of hypoxia and exercise to Haldane's 1912 expedition, the oxygen saturation of arterial blood was always less than that of blood exposed to alveolar gas obtained simultaneously. These findings were later confirmed in the Cerro de Pasco expedition.

Krogh, (1910, d) clearly established that unevenness of ventilation is important only as related to pulmonary blood flow and that both the absorption of oxygen and the elimination of carbon dioxide depend on the ratio of alveolar ventilation to perfusion. Haldane and Priestley, (1935) subsequently recognised and emphasised the effect of ventilation-perfusion ($\dot{V}_A/\dot{Q}$) inequality on the oxygenation of arterial blood. A quantitiative approach assessing the

effect of $\dot{V}_A/\dot{Q}$ inhomogeneity on the overall gas exchange in the lung was brilliantly worked out in a number of fundamental papers by Riley and Cournand, (1949, 1951); Rahn, (1949); Riley, Cournand and Donald, (1951) and Donald et al, (1952). They finally established the role of uneven distribution of pulmonary ventilation and blood flow as a major factor determining the partial pressures of oxygen and carbon dioxide in arterial blood. Fenn, Rahn and Otis, (1946) had earlier introduced the O_2 - CO_2 diagram for the graphic representation of the total effects of lung gas exchange, which proved to be a very useful analytical tool. It relates the tensions of oxygen and carbon dioxide to the haemoglobin saturation and the total content of CO_2 in the blood and is constructed from the dissociation curves for oxygen and carbon dioxide. Two sets of co-ordinates, representing the respiratory exchange ratio (R) and alveolar ventilation are superimposed on this diagram. A curved distribution line demonstrating the various combinations of O_2 and CO_2 tension which occur for different $\dot{V}_A/\dot{Q}$ ratios is also drawn up. The distribution line is defined at its upper end by the composition of mixed venous blood ($\bar{v}$) and at its lower end by that of the inspired gas. Riley and Cournand (1951) in their analysis of factors affecting the oxygen and carbon dioxide partial pressures in pulmonary gas and blood extended the O_2 - CO_2 diagram into a four quadrant system in which thepartial pressures and concentrations of oxygen and carbon dioxide in alveolar gas and capillary blood can be visualised simultaneously. The four quadrant diagram was again used by Riley and Permutt, (1965) to discuss the distribution of gas and blood in

two and three compartment models of the lung.

(b) Indices used to assess efficiency of pulmonary gas exchange.

The difference in partial pressure between alveolar gas and arterial blood is regarded as the simplest index of impaired gas exchange (West, 1970); and it is now universally accepted that the alveolar to arterial oxygen tension difference, $(A-a)DO_2$; and the determination of the physiological dead space to tidal volume ratio (VD/VT) are sensitive indices of the efficiency of pulmonary gas exchange.

(i) $(A-a)DO_2$

Farhi and Rahn in their classical paper in 1955 reviewed the theoretical causes resulting in an $(A-a)DO_2$. Three possible factors are recognised; a distribution component due to imperfect matching of alveolar ventilation and perfusion; a diffusion component, resulting from incomplete equilibration of end-capillary blood with alveolar gas; and a shunt component due to blood flow bypassing gas-exchanging alveoli - the venous admixture effect. The determination of the proportional contribution of these three factors to the total $(A-a)DO_2$ difference has been attempted by various workers. Haldane in his Silliman Memorial Lectures fifty years ago clearly reasoned that uneven distribution of ventilation or blood flow or both would produce an $(A-a)DO_2$. Lilienthal et

al, (1946) tried to determine the diffusion component of $(A-a)DO_2$ by studying the effects of breathing 11 - 13% oxygen. Their work was based on the assumption that the diffusion component would become easier to demonstrate at a lower PIO_2 and also that the ratio of venous admixture would be unaffected by breathing the low oxygen mixture. However, it was later shown that if the PIO_2 is decreased by breathing a low oxygen mixture, the increased proportion of the inspired inert gases may increase the distribution component of the $(A-a)DO_2$ (Farhi and Rahn, 1955; Overfield et al, 1969). Their conclusions have therefore not been generally accepted. Haab et al, (1960) using anaesthetised dogs tried to measure the distribution component, but their results are inconclusive. Farhi, (1965) showed that the diffusion factor becomes of any importance only at low oxygen tensions. Lenfant, (1963; 1964) measured simultaneously the A-a, oxygen, carbon dioxide and nitrogen differences. Canfield and Rahn (1957) had earlier demonstrated that the sum of the O_2, CO_2 and N_2 differences due to $\dot{V}_A/\dot{Q}$ distribution would be zero if it were not for the non-linearity of the oxyhaemoglobin dissociation curve. Lenfant raised the inspired PO_2 and by using O_2 - enriched mixtures under hyperbaric conditions was able to bring the PAO_2 in all alveoli to a point where haemoglobin is completely saturated. As a result, the oxyhaemoglobin dissociation curve will reflect only the quantity of dissolved oxygen and become linear. He showed that the $(A-a)DO_2$ exceeded only by a small amount the sum of $(A-a)DN_2$ and $(A-a)DCO_2$; proving that the normal $(A-a)DO_2$ is due mainly to the distribution of $\dot{V}_A/\dot{Q}$. Lenfant's

conclusion is supported by the calculations of West (1962, 1963, 1967, 1969), based on regional measurements of ventilation and perfusion. Overfield and Kylstra, (1969) and Cohen et al, (1971) have been able to estimate the (A-a)DO_2 components attributable to diffusion and distribution in unanaesthetised men. They compared the (A-a)DO_2 in the presence and absence of N_2 by getting their subjects to breathe 100% O_2, thus virtually eliminating the distribution component and any shunt component was minimised by lowering the pressure in an altitude chamber in which the subjects were seated. They concluded that in healthy men at rest, breathing 13 - 14% oxygen, there is no measurable diffusion component. They showed however, that during hypoxic exercise at 100 watts a component attributable to diffusion limitation was present. Their work bears out the theoretical predictions which had been earlier worked out by Staub, (1963) using a 'forward integration' procedure which was the reverse of the classical approach. He started at the arterial end of the pulmonary capillary and calculated the PO_2 of the capillary blood progressively along the capillary until he could estimate the remaining alveolar/capillary PO_2 gradient at the end of the capillary. Mellemgaard, (1966) had estimated the shunt component to be about 3% of the cardiac output in normal subjects.

(ii) VD/VT.

The concept of pulmonary dead space is said to have been originally introduced by Zuntz in 1882 (Haldane and Priestley, 1935).

Several workers estimated the anatomical dead space directly from casts of the tracheo-bronchial tree. Loewy, (1894) was the first to determine this. He found a value of 144 ml in a Plaster of Paris cast of the tracheo-bronchial tree in collapsed lungs. Rohrer, (1916) reported a value of 162 ml for a similar specimen. Munn et al, (1959) measured the volume of the extra and intra thoracic portions of the anatomical dead space by filling the airways with water. They found an average dead space of 138 ml of which about 50% was due to the extra thoracic airways. In 1890, Bohr introduced his equation for calculating respiratory dead space based on the concentrations of gases in alveolar and expired gas. Another controversy followed, between Douglas and Haldane, (1912) who found that the dead space increased by up to six times during exercise, and Krogh and Lindhard, (1913) who failed to find such an increase. The difference in results was once again due to discrepancies related to the problem of sampling alveolar gas. In the Haldane and Priestley alveolar sampling technique the measured alveolar $FACO_2$ is much higher than that in the alveoli at the start or end of a normal expiration, as CO_2 output con tinues into a rapidly decreasing lung volume. Since the alveolar $FACO_2$ is too high, the calculated V_D value is also too high.

The physiological dead space is thought of as representing "wasted" ventilation and the deadspace to tidal volume ratio is another index that can be used to indicate impaired gas exchange. The difference between the physiological deadspace and the anatom-

ical dead space is a direct relation of "wasted" ventilation and had been termed "Parallel dead space" by Falklow and Pappenheimer, (1955) and now usually known as "alveolar dead space" (Severinghaus and Stupfel, 1957).

The apparent change in physiological dead space that occurs in disease was developed by Rossier et al, (1955) as a test of pulmonary function. He used the term "functional dead space" for physiological dead space and early recognised that an increase in V_D could result from uneven $\dot{V}_A/\dot{Q}$ ratios. V_D is increased when there are significant volumes of the lung with a high $\dot{V}_A/\dot{Q}$ ratio, i.e. with a ventilation that is disproportionately higher than the corresponding perfusion.

(iii) Venous admixture effect (Q_v/Q_t).

Impaired pulmonary gas exchange may also be described in terms of "wasted" perfusion, termed venous admixture or shunt. Venous admixture effect reflects both the true right to left shunts as well as the shuntlike effects resulting from blood that is inadequately oxygenated by going through poorly ventilated areas of lung, i.e. regions with low $\dot{V}_A/\dot{Q}$ ratios. In normal subjects the true shunt is mainly due to communications between bronchial and pulmonary veins (Verloop, 1948) and the Thebesian veins which drain from the myocardium directly to the left ventricle (Thebesius, 1708). Bronchial pulmonary venous communications drain a fraction of the bronchial

circulation that is distributed to the more peripheral parts of the lung (Marchand et al, 1950). Potential communications, in the form of pre-capillary anastomoses, between bronchial and pulmonary arteries, known as "sperr arteries" have also been described (Von Hayek, 1960). Ravin et al, (1965) calculated that in normal subjects the component due to Thebesian veins is about 0.3% of the total cardiac output. The contribution of the bronchial- pulmonary venous anastomoses is probably less than 1% of the cardiac output (Munn, 1971). Mellemgaard, (1966) has estimated the true shunt to be about 1 - 2% of the cardiac output in normal seated subjects, whilst the total shunt is about 5% of the cardiac output.

(c) Procedure and calculation.

The subjects sat comfortably in a chair with the left arm supported and breathed through a low resistance valve for five minutes before the procedure was carried out. Each estimate involved a two minute collection of mixed expired gas into a Tissot spirometer and simultaneously a collection of arterial blood from a previously sited needle in the brachial artery, the site having been carefully anaesthetised. The blood was withdrawn in heparinised 10 ml glass syringes. Immediately after collection the syringe was sealed and the blood and heparin were mixed by rolling the syringe. The first few millilitres of blood were discarded before the sample was analysed. The disappearance of oxygen from shed blood is a well recognised phenomenon

and has been the subject of a number of studies. It is thought to be due to the metabolic activity of the cellular components of the blood, (Rooth et al, 1959; Asmussen et al, 1961; Hedley-White et al, 1964; Elridge and Fretwell, 1965; Greenbaum et al, 1967). The samples of blood obtained from the subjects during this study were therefore analysed as soon as collected.

Expired air was automatically collected and continuously analysed and recorded on a direct writing multi-channel recorder (80 Mingograf Schonander). Carbon dioxide was analysed by a rapid infra-red CO_2 analyser (Uras 4; Hartmann and Braun) and oxygen, by a paramagnetic analyser (Servomex O_2 analyser Type OA 150). Calibration of the instruments was carried out by gases previously analysed using a micro-Scholander gas analyser. The whole procedure was performed very carefully with a view to ensuring as steady a state as possible. As anaemia has been shown to cause an increase in $(A-a)DO_2$ (Sproule et al, 1960; Housley, 1967) this was excluded in the subjects studied. They all had normal haemoglobin concentrations and haematocrit values.

(d) Calculations.

(i) $(A-a)DO_2$

The determination of the arterial oxygen tension presented relatively few problems as better and quicker techniques for its

measurements were evolved. The measurement of the alveolar oxygen tension, however, proved to be a different matter. Haldane and Priestley, (1905) used end-expiratory air, making their subjects expire quickly and forcibly down a long tube with a side arm and collecting the last portion of gas for analysis. Rahn, (1949) pointed out that the alveolar gas exchange continues during the prolonged expiration resulting in a higher PCO_2 than average, the PO_2 being correspondingly lower. The alveolar gas composition so analysed, will also depend on the depth of the preceding inspiration. Rahn and Otis, (1949) developed a method by which a few millilitres of gas were withdrawn at the end of each normal expiration. The accuracy of such a method is obviously limited by the unevenness of gas distribution in the lungs, a feature which becomes even more prominent in the presence of airways obstruction.

Two groups of workers tried to get around this problem by deriving an average value for PAO_2 indirectly. Riley and his colleagues in the U.S.A. (1946, 1949) and Rossier, (1949, 1953) in Switzerland explored this possibility at about the same time. Their work was based on the assumption that the carbon dioxide tension of arterial blood is equal to the alveolar carbon dioxide tension and substituting $PaCO_2$ for $PACO_2$ in the alveolar gas equation. There is evidence from the work of Lenfant, (1963) that a small $(A-a)DCO_2$ may exist in normal subjects; if this were the case, the PAO_2 calculated, assuming equality of $PACO_2$ and $PaCO_2$ would be lower than the true PAO_2, resulting in an underestimation of the $(A-a)DO_2$. Because of the shape of the blood dissociation curves the error introduced

in using the arterial PCO_2 is generally very small. Riley and Cournand (1949) called the alveolar oxygen tension so obtained "ideal" because it represents the value present if the V_A/Q ratios were equal throughout the lung and no diffusion limitation was present. The PAO_2 used in the computation of the $(A-a)DO_2$ in this study, was therefore obtained from:

$$PAO_2 = PIO_2 - \frac{PaCO_2}{R} + (0.2093 \times PaCO_2 \frac{(1-R)}{R}$$

(ii) VD/VT.

The ratio between dead space and tidal volume was first introduced by Enghoff in 1931. In 1938, he suggested that the dead space be measured by substituting $PaCO_2$ for $PACO_2$ in Bohr's equation, introducing the modern concept of physiological dead space. He used the term "Volumen inefficax" to stress its functional nature. The physiological dead space reported in this study was calculated:

$$VD = VT \times \frac{(PaCO_2 - P_ECO_2)}{(PaCO_2)} - V_D\,(App)$$

A correction was made for the dead space of the mouthpiece which was measured by water displacement and all volumes corrected to B.T.P.S.

(iii) Venous admixture (shunt)

The shunt was calculated from the standard equation:

$$\frac{\dot{Q}}{\dot{Q}t} = \frac{CcO_2 - CaO_2}{CcO_2 - CvO_2}$$

assuming an a - v oxygen content difference of 3.5 and 5 ml.

Where $\dot{Q}/\dot{Q}t$ is the ratio of venous admixture to total blood flow; CcO_2 is the oxygen content of pulmonary end capillary blood and is in practice calculated on the basis of end capillary PO_2 being equal to ideal alveolar PO_2; CaO_2 and CvO_2 being, the arterial and mixed venous oxygen contents respectively.

RESULTS.

The patients studied all fulfilled the definition of chronic asthma on clinical grounds. The duration of their illness ranged from six months to thirty-four years (see Tables V and VI) Their disease could no longer be controlled by bronchodilator drugs and they were admitted to the Department of Respiratory Diseases for a trial of corticosteroid therapy. In none of these patients had such drugs been used previously. The study was conducted in two stages, eleven patients being initially admitted to the study in the first stage and twelve patients to the second stage. Besides the

TABLE V

Clinical and Spirometric data on patients studied during the first stage of the investigation.

Patient	Age	Sex	Ht.	Duration of Disease.	Initial FEV_1	Predicted FEV_1
M.T.	41	M	1.75m	34 yrs.	700 ml.	3150 ml.
S.D.	39	F	1.62m	13 yrs.	1060 ml.	2050 ml.
B.R.	62	M	1.75m	2 yrs.	1400 ml.	2600 ml.
M.E.	43	F	1.73m	12 yrs.	825 ml.	2750 ml.
M.J.	76	F	1.59m	6 mths.	950 ml.	1800 ml.
R.M.	73	F	1.62m	5 yrs.	625 ml.	1800 ml.
H.N.	24	F	1.55m	4 yrs.	2550 ml.	2650 ml.
S.B.	47	M	1.72m	5 yrs.	2430 ml.	3400 ml.
D.M.	51	F	1.57m	6 yrs.	880 ml.	2200 ml.

Predicted values for the forced expiratory volume in one second for males are derived from Kory, R.C. Callahan, R.,Boren, H.G. and Syner, J.C. (1961)., Amer. J. Med. 30: 243 and from Ferris B.G., Anderson, D.O. and Zickmantel, R. (1965)., Amer. Rev. Resp. Dis., for females.

TABLE VI

Clinical and Spirometric data on patients studied during the second stage of the investigation.

Patient	Age	Sex	Ht.	Duration of Disease	FEV_1(initial)	FEV_1(predicted)
B.H.	14	F	1.57m	10 yrs.	2000 ml	2850 ml
K.H.	38	F	1.54m	9 mths.	600 ml	2620 ml
M.V.	50	F	1.52m	4 yrs.	625 ml	2200 ml
M.N.	44	M	1.78m	3 yrs.	2300 ml	3650 ml
A.L.	25	F	1.53m	14 yrs.	1600 ml	2700 ml
F.G.	43	M	1.59m	24 yrs.	700 ml	2900 ml
G.W.	14	M	1.47m	11 yrs.	950 ml	2350 ml
S.J.	47	M	1.58m	6 mths.	1175 ml	2800 ml
B.W.	38	M	1.64m	1 yr.	1600 ml	3400 ml
G.A.	68	M	1.58m	15 yrs.	540 ml	2250 ml
L.R.	63	M	1.58m	10 yrs.	1635 ml	2500 ml
M.R.	32	F	1.52m	3 yrs.	2350 ml	2500 ml

patients with chronic asthma, two patients who were known to suffer from chronic bronchitis (Medical Research Council, 1965) were also studied during the first stage. They were shown to have a degree of reversible airway obstruction when tested to subcutaneous injections of Adrenaline and Atropine and they were therefore given corticosteroids to find out whether these drugs would be of any therapeutic benefit to them. All the patients had normal hepatic and renal function (Tables VII, VIII) & normal electrocardiograms. Their chest x-rays revealed a mild to moderate degree of hyperinflation but no other abnormal features. The results of sputum oesinophils, and absolute blood eosinophil count are shown in Table IX. Precipitins to Aspergillus fumigatus were absent in all cases. Prick skin tests were positive in five of the fourteen patients who completed the study (M.B., M.T., G.W., H.B., and A.L.) These patients all demonstrated hypersensitivity to some or all of a wide variety of pollens, house dust mite, animal fur and Dermatophagoides pteronyssimus.

Stage I

In the first part of the study, two patients H.N. and S.B. improved spontaneously soon after admission to the trial and were therefore excluded from it. Patient D.M. became extremely wheezy and dyspnoeic on the second pre-treatment day and immediate therapy for acute asthma was instituted. The two bronchitic patients (A.M. and A.N.) showed no response to the corticosteroids, their results are included in the Appendix. The results of the

TABLE VII

Liver function tests

	Serum bilirubin	S.G.P.T.	Alk. Phosphatase
M.T.	0.6 mg	12 units	7 K.A. units
S.D.	0.5 mg	10 units	6 K.A. units
B.R.	0.6 mg	15 units	10 K.A. units
M.E.	0.4 mg	16 units	12 K.A. units
M.J.	0.8 mg	13 units	7 K.A. units
R.M.	0.3 mg	17 units	9 K.A. units
H.N.	0.3 mg	6 units	9 K.A. units
S.B.	0.5 mg	10 units	10 K.A. units
D.M.	0.4 mg	11 units	9 K.A. units
B.H.	0.4 mg	10 units	12 K.A. units
K.H.	0.2 mg	12 units	7 K.A. units
M.V.	0.4 mg	14 units	7 K.A. units
M.N.	0.4 mg	14 units	11 K.A. units
A.L.	0.6 mg	12 units	8 K.A. units
F.G.	0.6 mg	10 units	13 K.A. units
G.W.	0.8 mg	8 units	12 K.A. units
S.J.	0.8 mg	12 units	11 K.A. units
B.W.	0.8 mg	11 units	10 K.A. units
G.A.	0.6 mg	9 units	11 K.A. units
L.R.	0.7 mg	16 units	19 K.A. units
M.R.	0.5 mg	12 units	6 K.A. units

TABLE VIII

	Serum Urea mg/100 ml.	Serum Sodium meq/l.	Serum Potassium meq/l.	Serum Chloride meq/l.
M.T.	25	140	4.1	106
S.D.	23	140	3.8	107
B.R.	25	139	4.1	108
M.E.	33	139	4.3	107
M.J.	40	143	3.9	110
R.M.	39	141	3.9	107
H.N.	23	136	3.6	103
S.B.	30	142	3.8	106
D.M.	28	138	4.2	107
B.H.	25	135	3.5	98
K.H.	36	142	4.2	106
M.V.	39	140	4.0	103
M.N.	24	141	3.6	103
A.L.	21	140	4.2	107
F.G.	29	140	3.4	102
G.W.	21	135	4.3	100
S.J.	37	143	4.1	103
B.W.	24	139	4.1	101
G.A.	4	141	3.8	103
L.R.	29	141	4.9	103
M.R.	30	140	3.8	105

TABLE IX

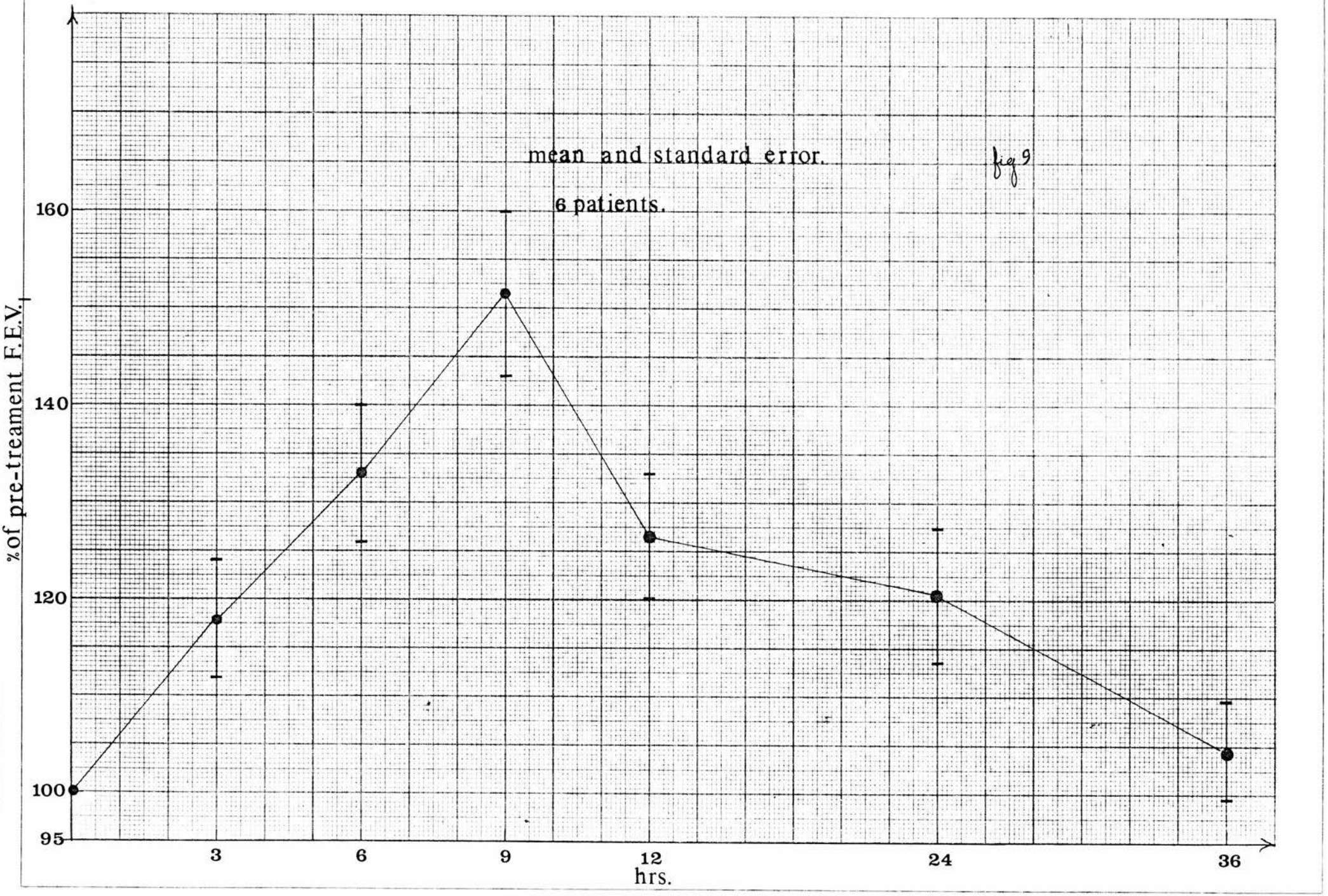
	Sputum		Blood eosinophils			Asp. f. precipitins
	Eos.	Asp.Fum.				
M.T.	---	+--	1170	600	660	-
S.D.	---	---	860	720	880	-
B.R.	---	---	1400	750	800	-
M.E.	+--	++-	440	430	624	-
M.J.	++-	---	500	710	540	-
R.M.	---	---	350	400	320	-
H.N.	---	---	1000	700	960	-
S.B.	---	---	300	250	280	-
D.M.	-+-	---	250	280	300	-
B.H.	---	---	250	200	400	-
K.H.	---	---	660	605	500	-
M.V.	---	---	200	300	250	-
M.N.	---	-+-	300	340	194	-
A.L.	--+	---	460	400	480	-
F.G.	---	---	200	310	280	-
G.W.	-+-	---	940	870	850	-
S.J.	---	---	666	620	936	-
B.W.	---	---	120	580	450	-
G.A.	---	---	180	200	250	-
L.R.	---	---	960	1000	940	-
M.R.	---	---	550	220	280	-

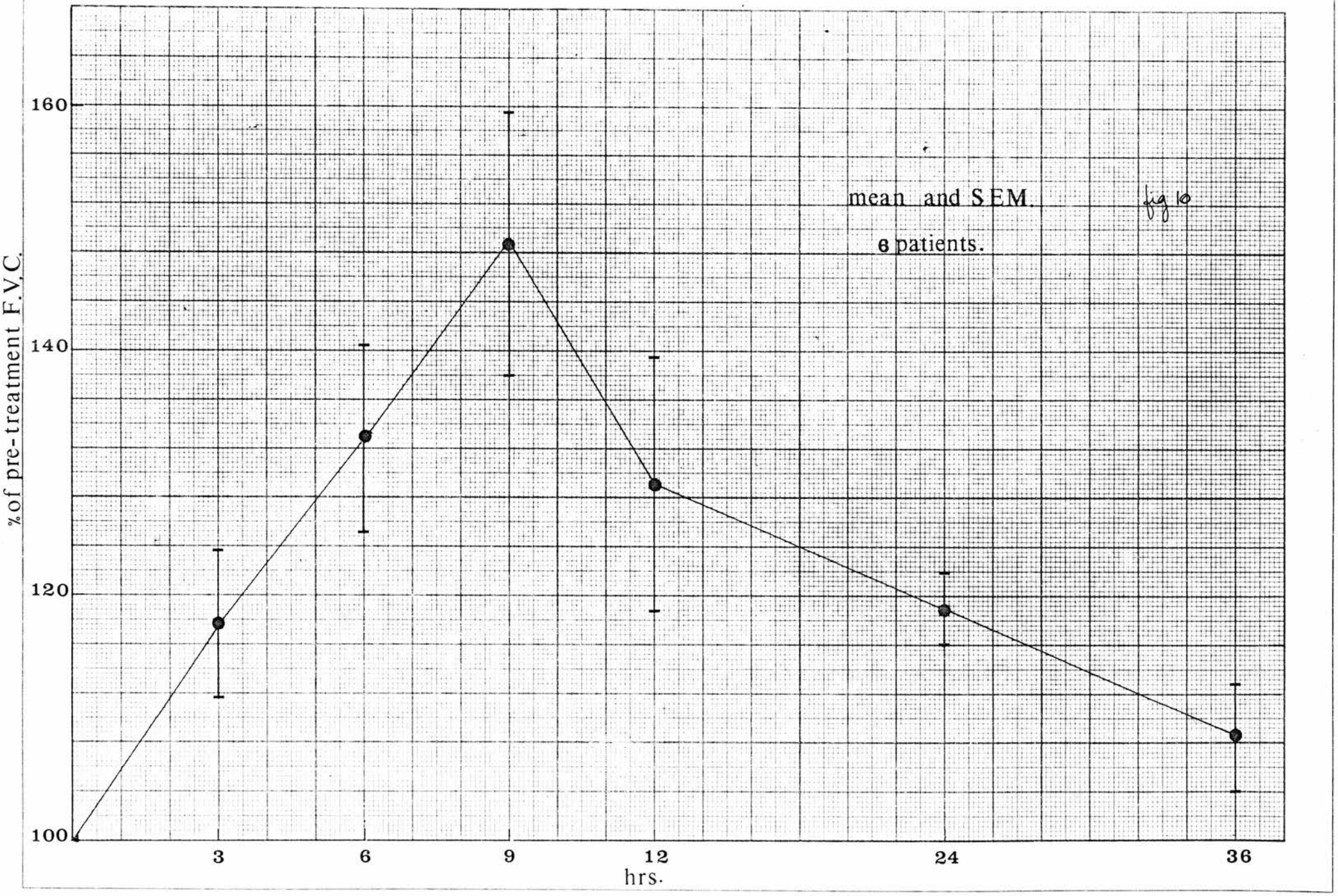
pulmonary function tests presented in this part of the study, therefore, refer to the first six patients shown in Table V . T.M. was unable to perform the last set of measurements 36 hours after Prednisolone administration because of an acute attack of breathlessness.

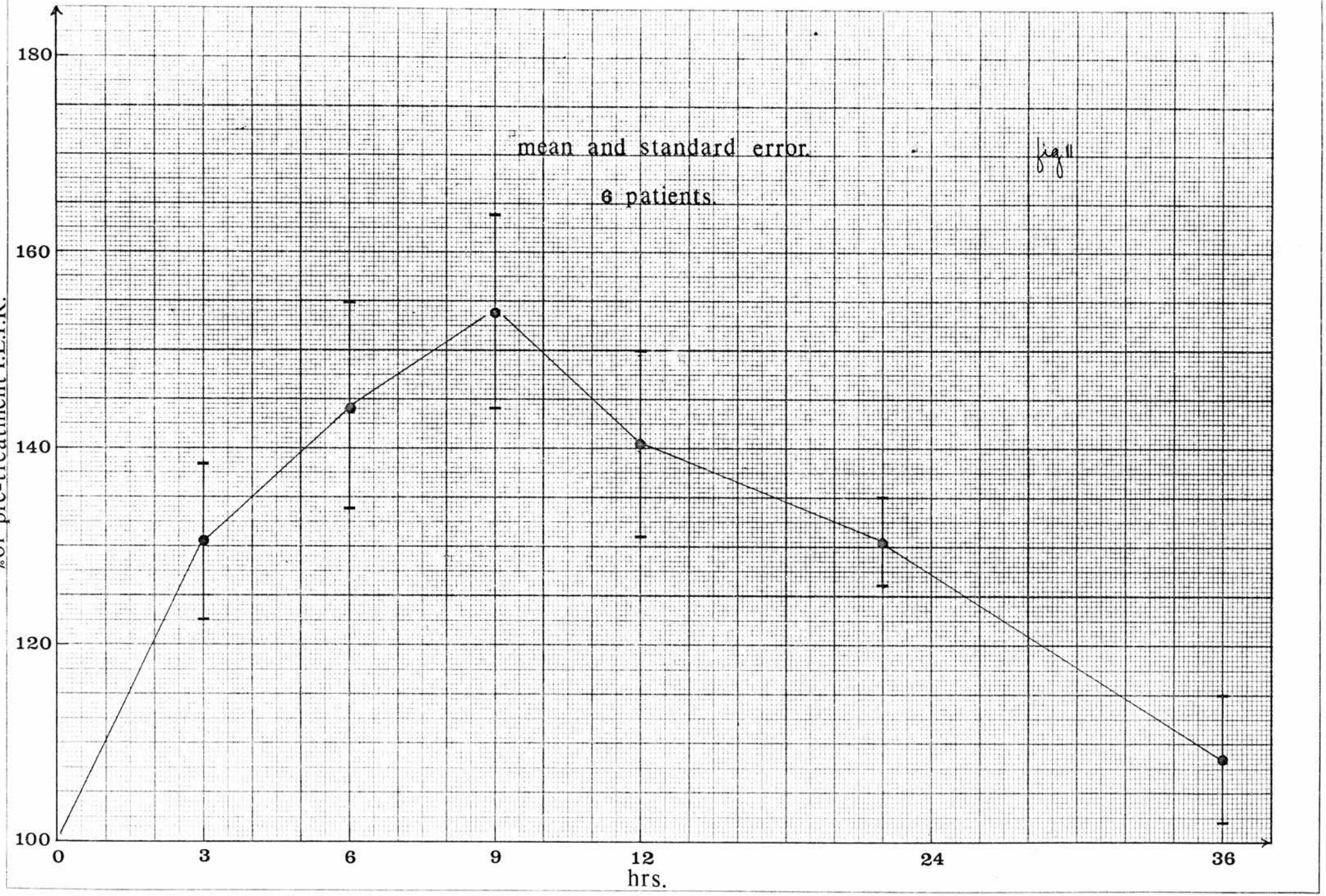
Minor fluctuations in all the measurements were observed during the first two days of the trial, but no consistent pattern was seen. In particular, no significant diurnal variation was observed, nor could any response to placebo tablets be demonstrated either within individuals or the group as a whole. This applies to both groups of patients studied in the two parts of the investigation. Individual results are included in the Appendix. In order to reduce the effect of individual variation all measurements were expressed as a percentage of the pre-treatment value. Statistical significance was tested in all instances by means of Student's "t" test (Snedecor and Cochrane, 1971).

Prednisolone produced consistent changes in dynamic lung volumes ($F.E.V._1$; F.V.C.; P.E.F.R.) which were evident and statistically significant from the pre-treatment measurements within three hours (P 0.05; P 0.05; P 0.25). In the group as a whole the peak effect was observed at nine hours, after which there was a decline towards pre-treatment levels, as shown in Fig. 9, 10, and 11.

Static lung volumes (T.L.C., F.R.C., R.V., and R.V./T.L.C.)

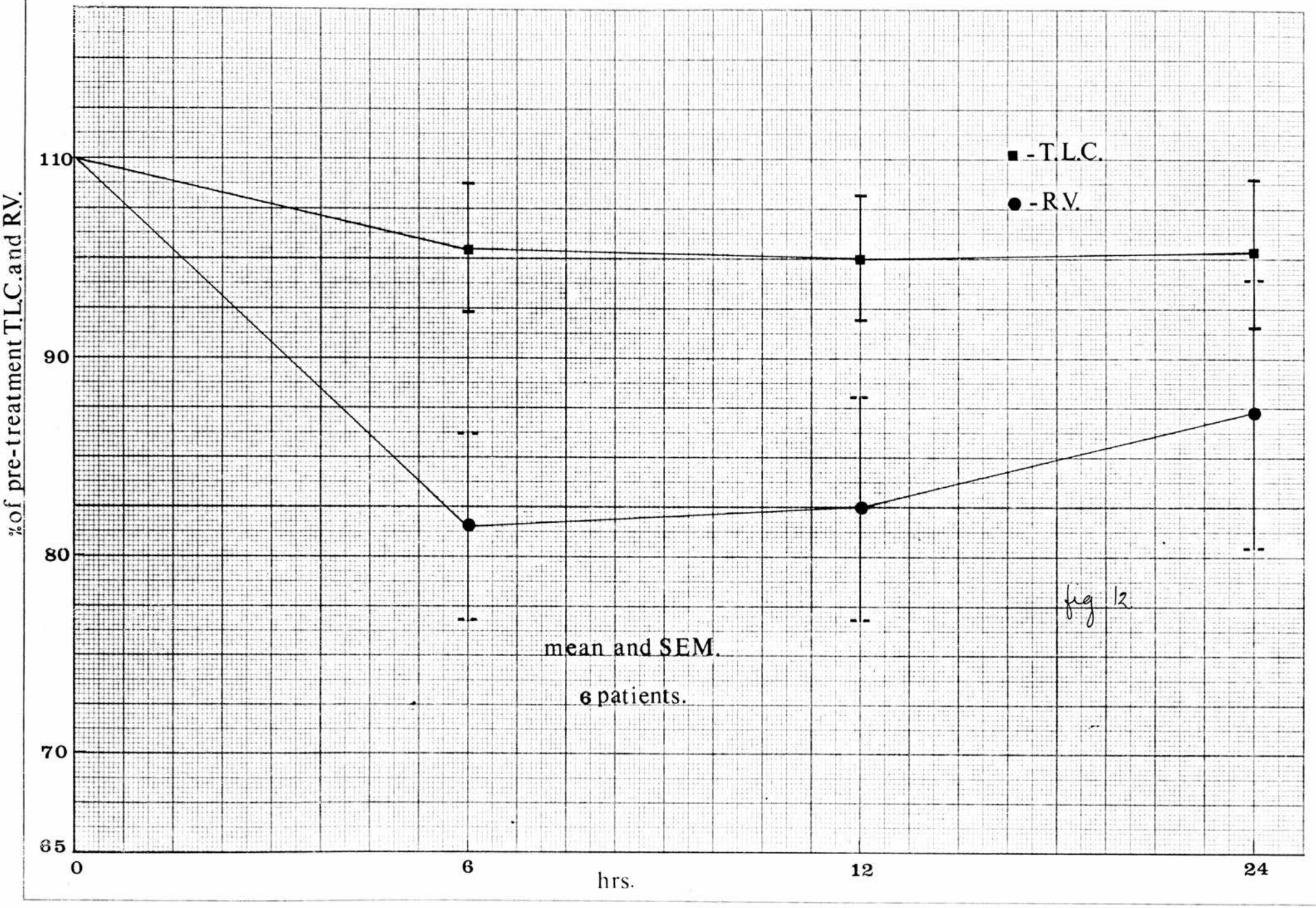

mean and standard error.
6 patients.
fig 9
% of pre-treament F.E.V.
160
140
120
100
95
3
6
9
12
24
36
hrs.

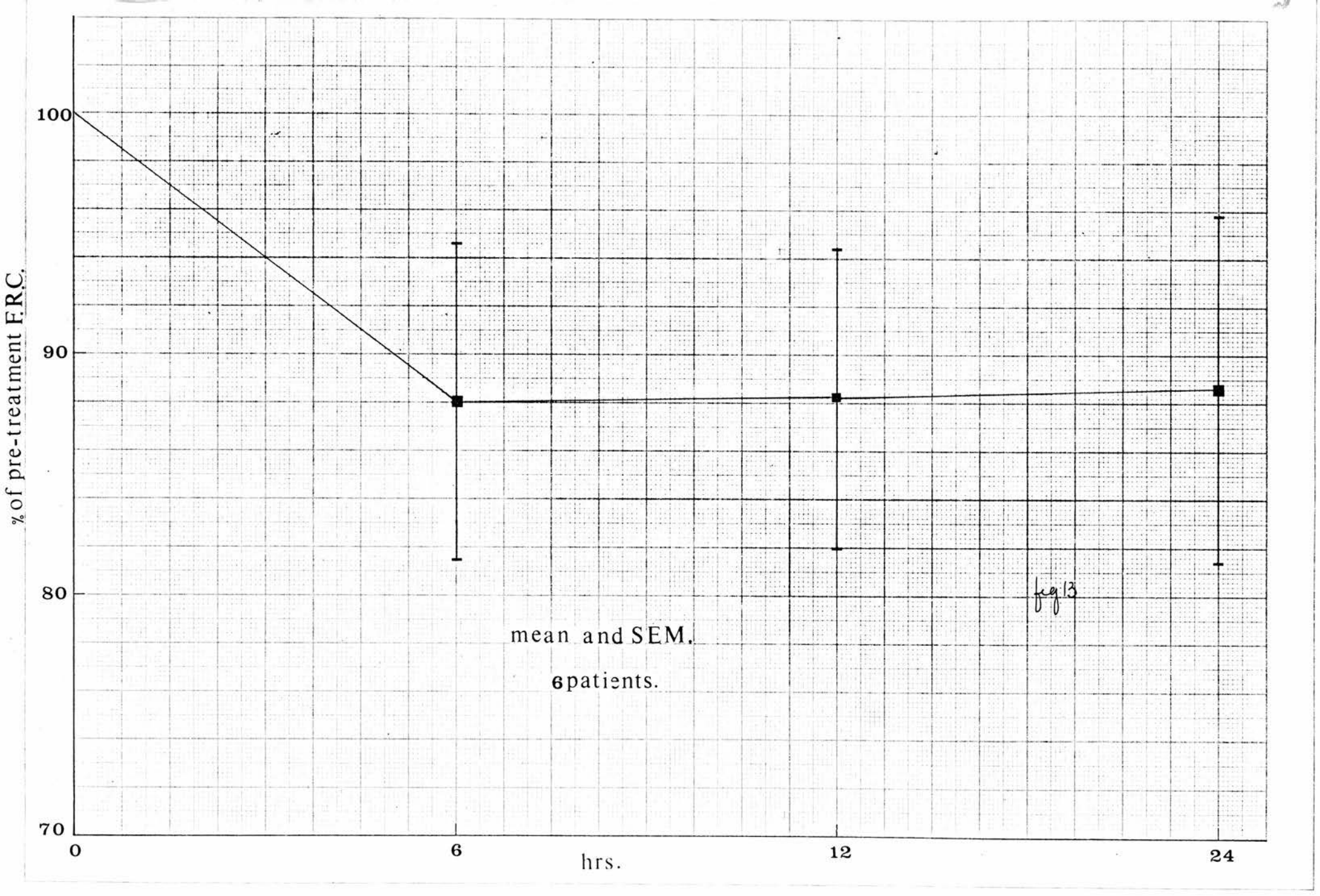

mean and SEM.
6 patients.
fig 10
% of pre-treatment F.V.C.
160
140
120
100
3
6
9
12
24
36
hrs.

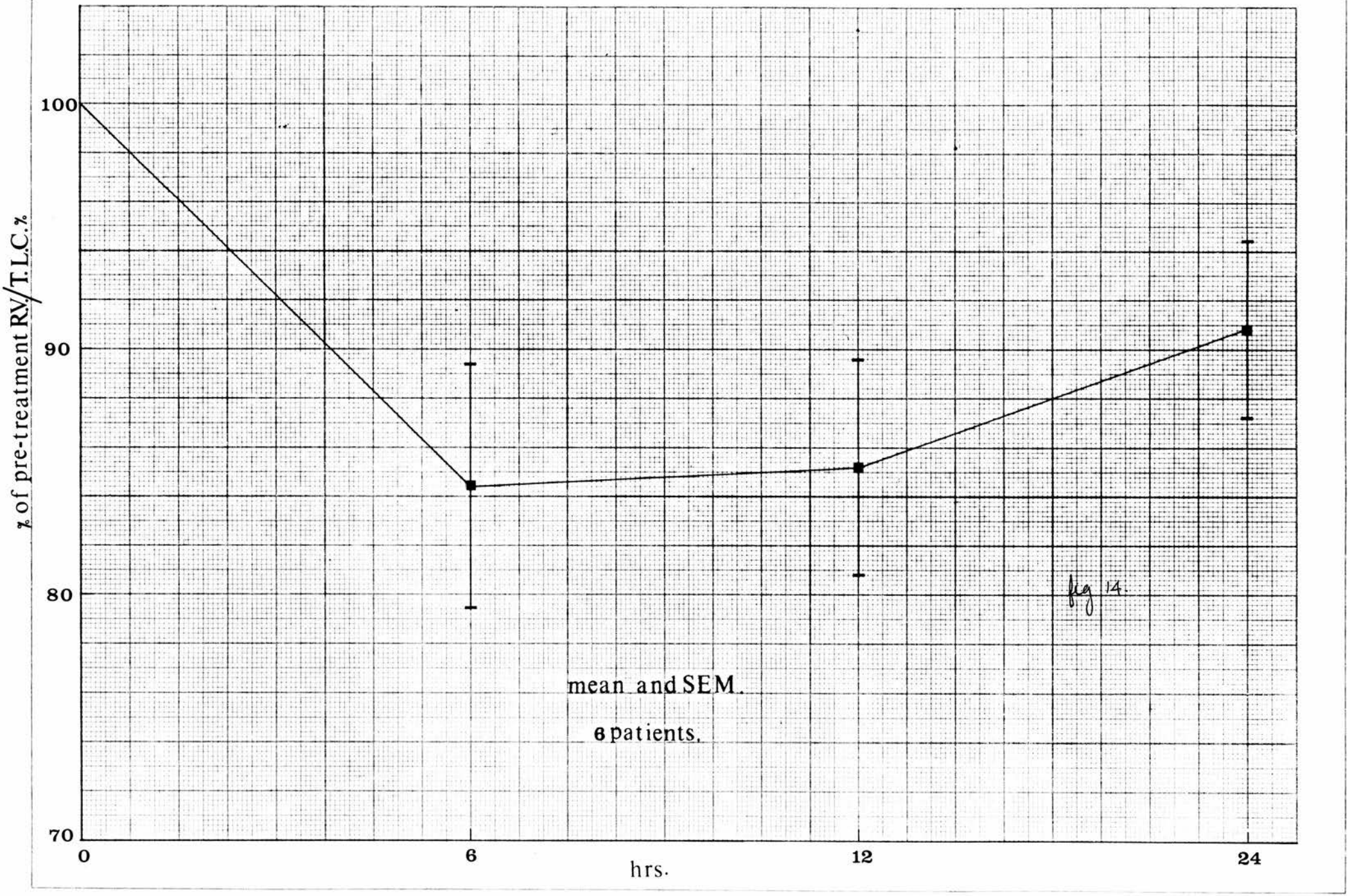

mean and standard error.
6 patients.
fig II
%of pre-treatment P.E.F.R.
180
160
140
120
100
0
3
6
9
12
24
36
hrs.

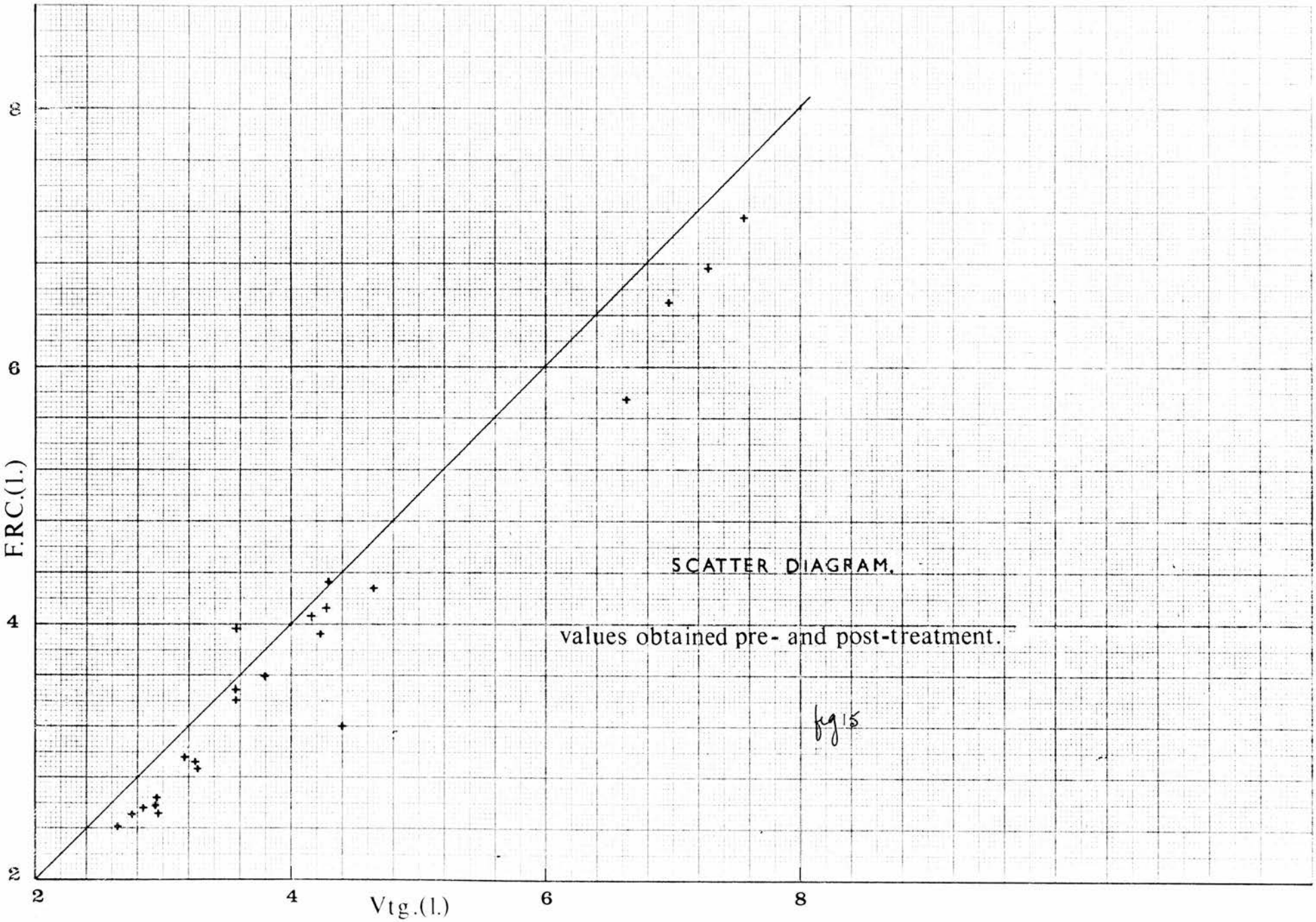
fell by six hours of prednisolone administration as shown in Fig. 12,13,14. At this time in the group as a whole the fall in R.V. and R.V./T.L.C. was significant (P 0.025; P 0.05) but the changes in T.L.C. and F.R.C. were not. In one patient, S.D., the F.R.C. and T.L.C. did however fall to 55.4% and 79% of the pre-treatment values. When the next measurements were performed, twelve hours after the drug had been given, there was a slight deterioration in all the lung volumes in the group as a whole, which continued over the next twenty-four hours. Two of the patients, M.E. and M.T., however, showed a further improvement at twelve hours. In general , the majority of patients, found that this test was the most difficult to perform. All patients had evidence of hyperinflation, their pre-treatment F.R.C. ranged between 115% and 216% of the predicted, the mean and standard error being 156% and 16%. Although their Vtg was consistently and significantly greater than their F.R.C. (P 0.001), the difference between the two indices was not very big (Fig. 15).

Body plethysmographic measurements showed marked changes at the time of their first measurement, six hours after Prednisolone (Fig.16,17), SGaw rising and Vtg falling compared with their pre-treatment values. The most noticeable change was found twelve hours after the drug had been given. The changes in Raw and SGaw were significant at six hours (P 0.01; P 0.05) but the change in Vtg was not (P 0.1). The latter was however significantly decreased by twelve hours. Measurements performed twelve hours after the administration of Prednisolone showed a return of all these parameters towards pre-


% of pre-treatment T.L.C. and R.V.
110
90
80
70
65
0
6
12
24
hrs.
■ - T.L.C.
● - R.V.
mean and SEM.
6 patients.
fig 12


100
90
80
70
% of pre-treatment F.R.C.
0
6
12
24
hrs.
mean and SEM.
6 patients.
fig 13

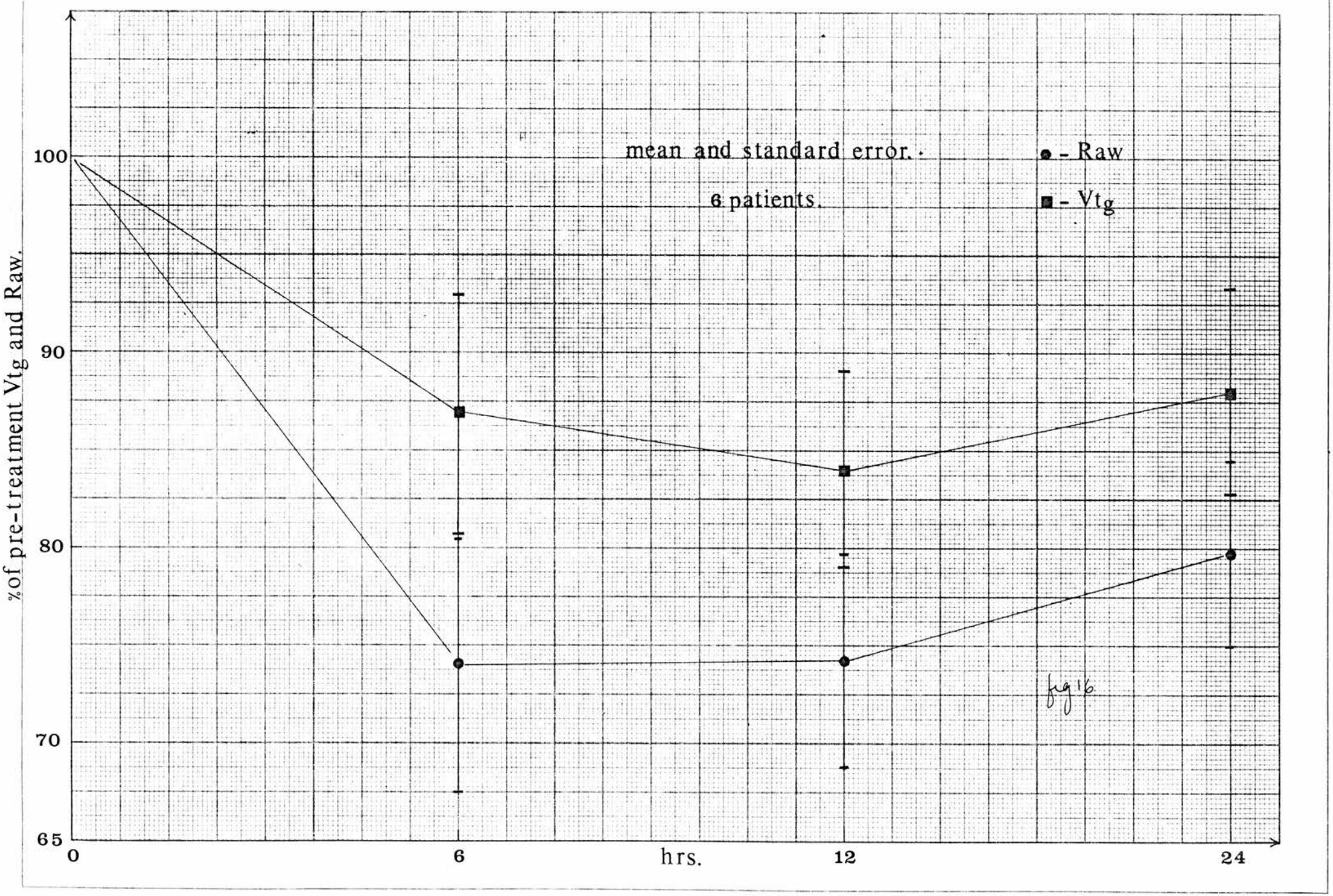

100
90
80
70
% of pre-treatment RV/T.L.C.%
0
6
12
24
hrs.
mean and SEM.
6 patients.
fig 14.

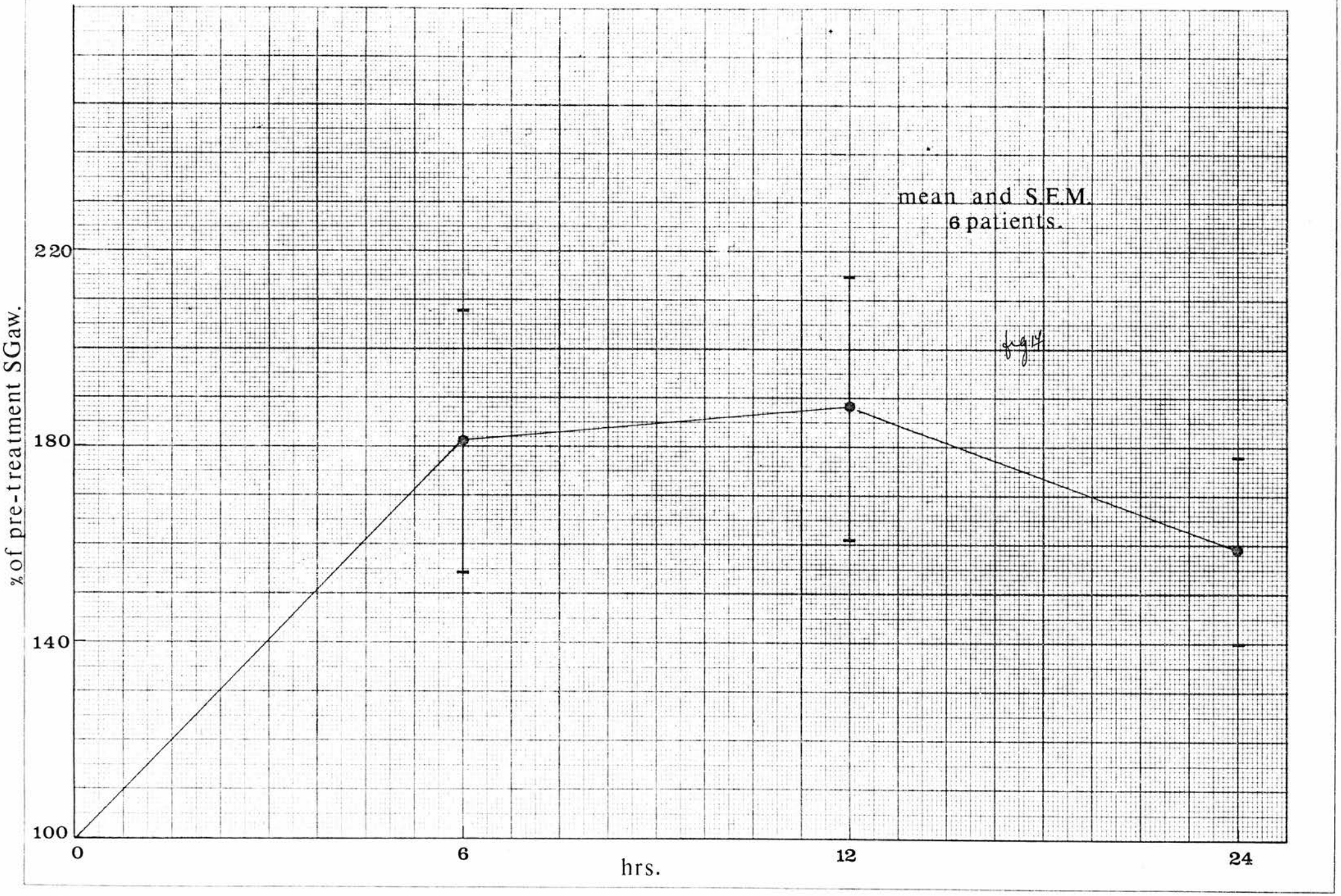


SCATTER DIAGRAM.

values obtained pre- and post-treatment.

fig 15

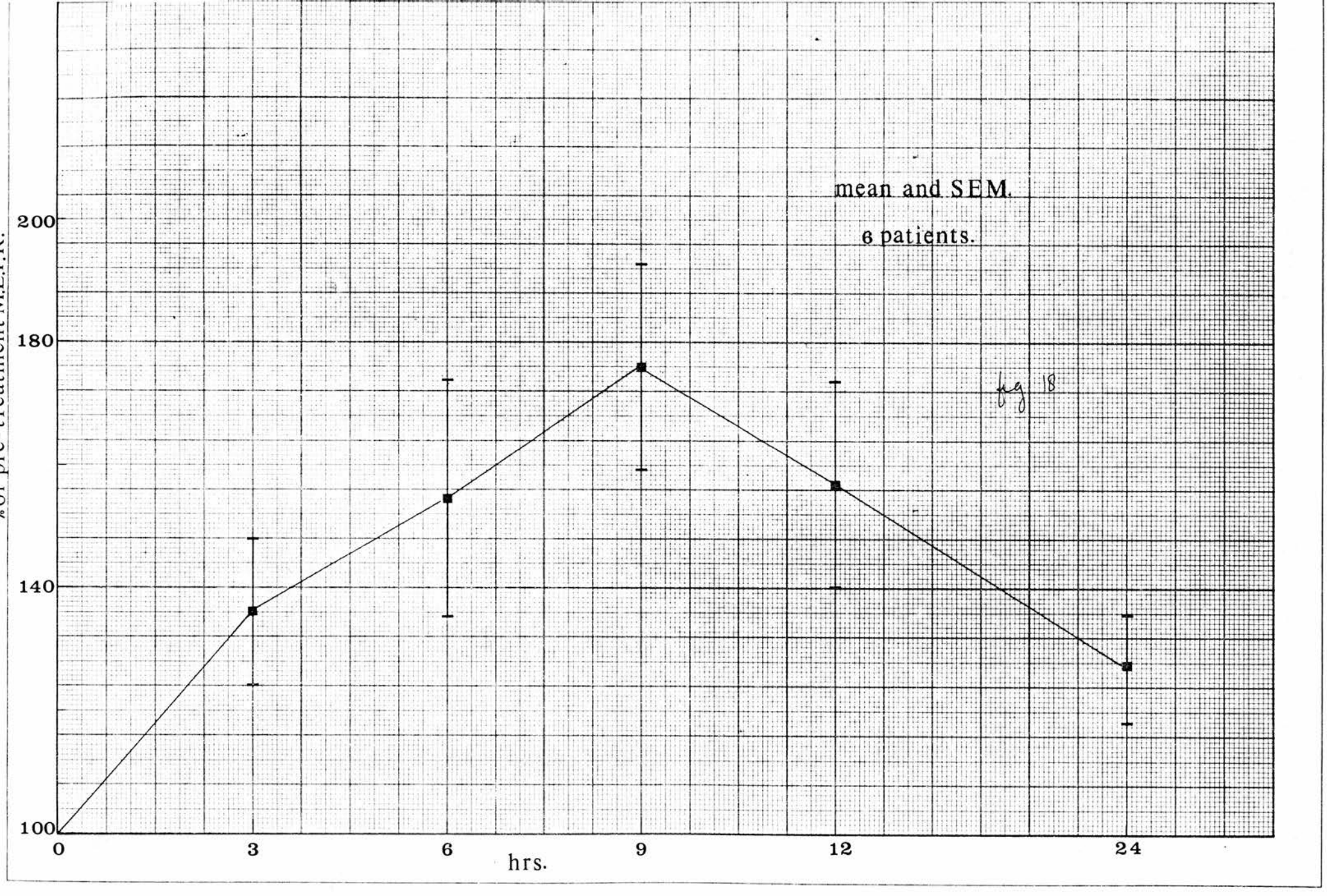

mean and standard error.
6 patients.
- Raw
- Vtg
%of pre-treatment Vtg and Raw.
100
90
80
70
65
0
6
hrs.
12
24
fig 16

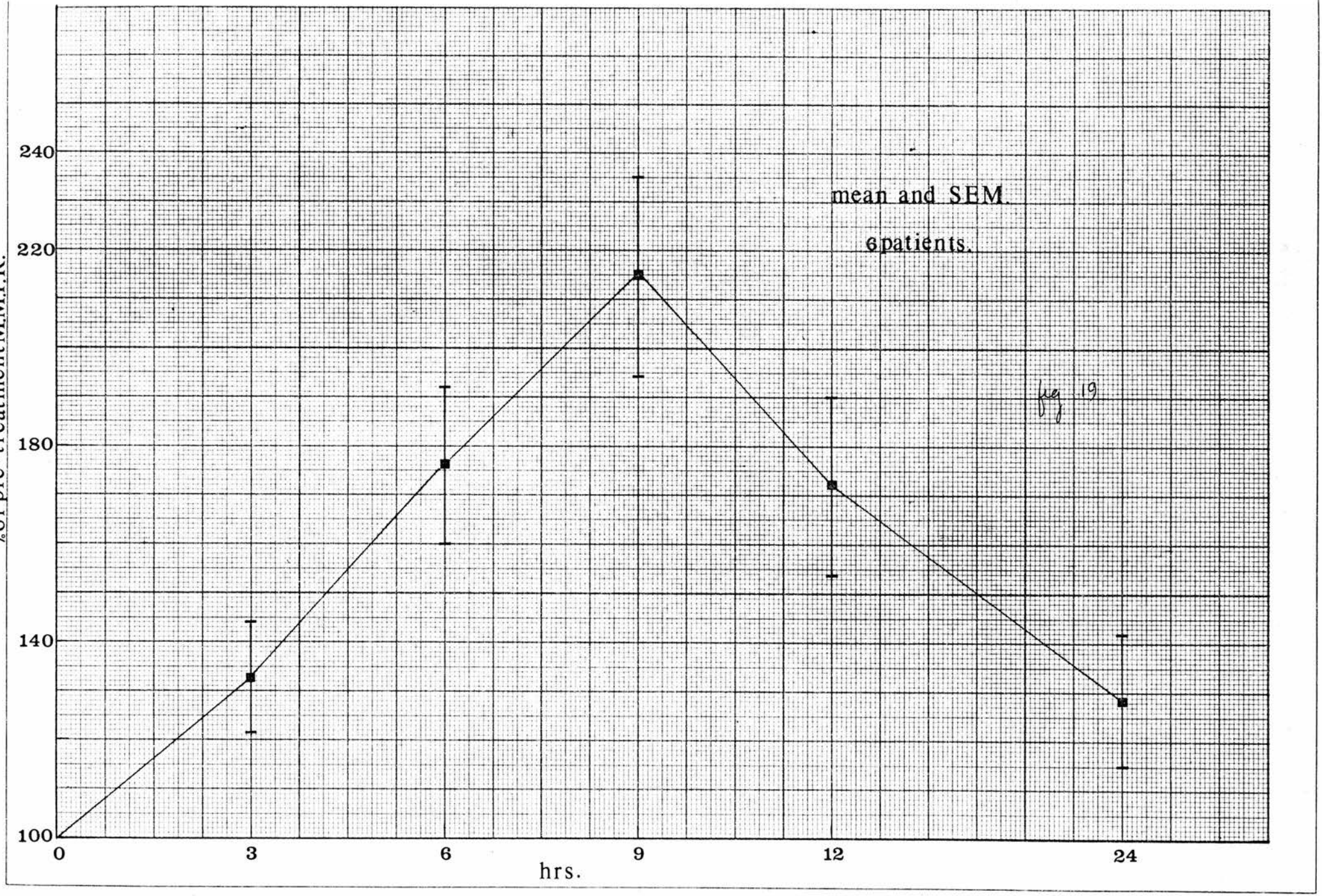

mean and S.E.M.
6 patients.
fig 4
% of pre-treatment SGaw.
220
180
140
100
0
6
12
24
hrs.

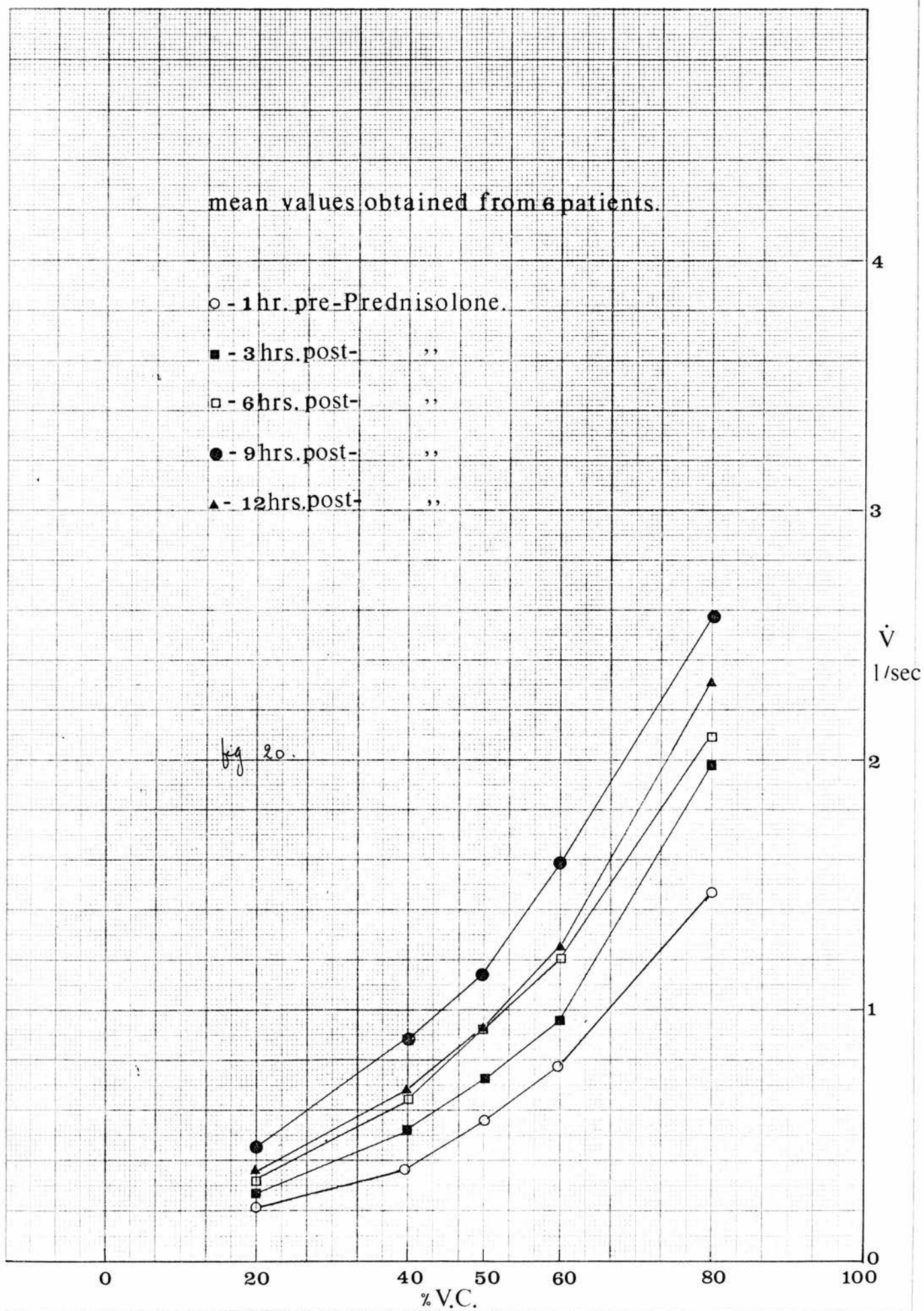
pre-treatment levels.

Three hours after Prednisolone administration both the M.E.F.R. and the M.M.F.R. were significantly greater than before durg administration ($P < 0.05$; $P < 0.05$); improvement reaching a peak at nine hours, after which a decline occurred. At nine hours the mean M.E.F.R. was 176% of the pre-treatment value and the mean M.M.F.R. was 215.5% (Fig.18,-20.) Individual patients showed parallel changes as shown in Fig.21-23. The maximum expiratory flow volume curves for subjects S.D., M.E., and R.M. are representative of the whole group. Only four curves are reproduced on each graph for the sake of clarity. When airway obstruction was severe the peak flow was reach early on in the vital capacity and then the rate of flow fell off quickly, making the curve concave to the volume axis throughout. Following therapy, the curves became more convex upward and airflow at any given lung volume increased. Flow was also plotted against the absolute lung volume obtained from helium dilution measurements. Fig.24-26 show this for patients S.D., M.E., and R.M.

Therefore these six patients, both individually as well as a group, showed a similar pattern of response. A statistically significant improvement was detectable within three hours of Prednisolone administration. The peak effect was reached within nine to twelve hours, after which there was a return towards pre-treatment levels. The mean change in P.E.F.R., $F.E.V._1$, M.E.F.R.


mean and SEM.
6 patients.
fig 18
% of pre-treatment M.E.F.R.
200
180
140
100
0
3
6
9
12
24
hrs.


mean and SEM.
6 patients.
fig 19
% of pre-treatment M.M.F.R.
240
220
180
140
100
0
3
6
9
12
24
hrs.


mean values obtained from 6 patients.
○ - 1 hr. pre-Prednisolone.
■ - 3 hrs. post- ,,
□ - 6 hrs. post- ,,
● - 9 hrs. post- ,,
▲ - 12 hrs. post- ,,
fig 20.
V̇
l/sec
0
1
2
3
4
0
20
40
50
60
80
100
% V.C.

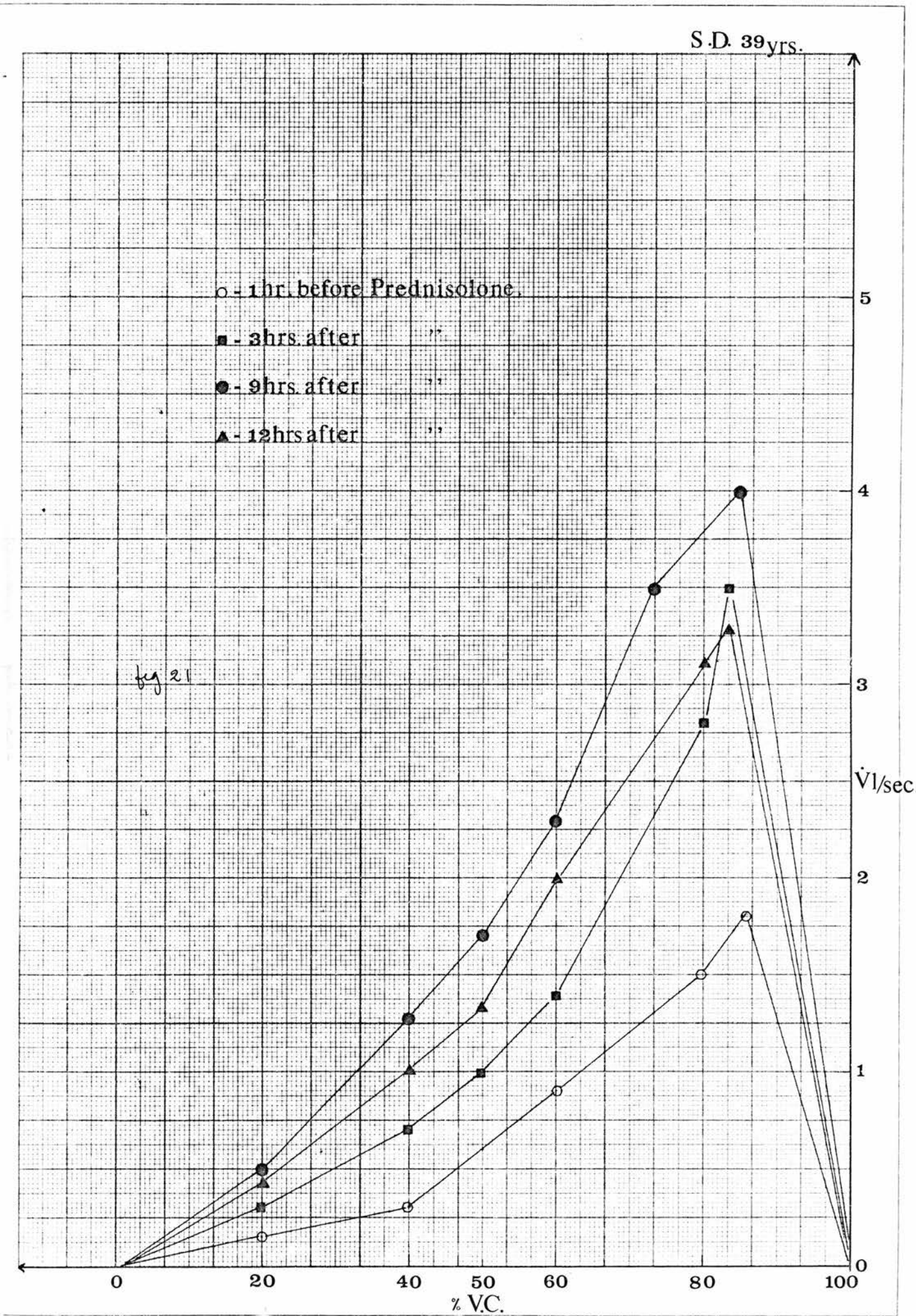

S.D. 39yrs.
o - 1hr. before Prednisolone.
■ - 3hrs. after ''
● - 9hrs. after ''
▲ - 12hrs after ''
5
4
3
2
1
0
V̇l/sec.
0
20
40
50
60
80
100
% V.C.

fig 21

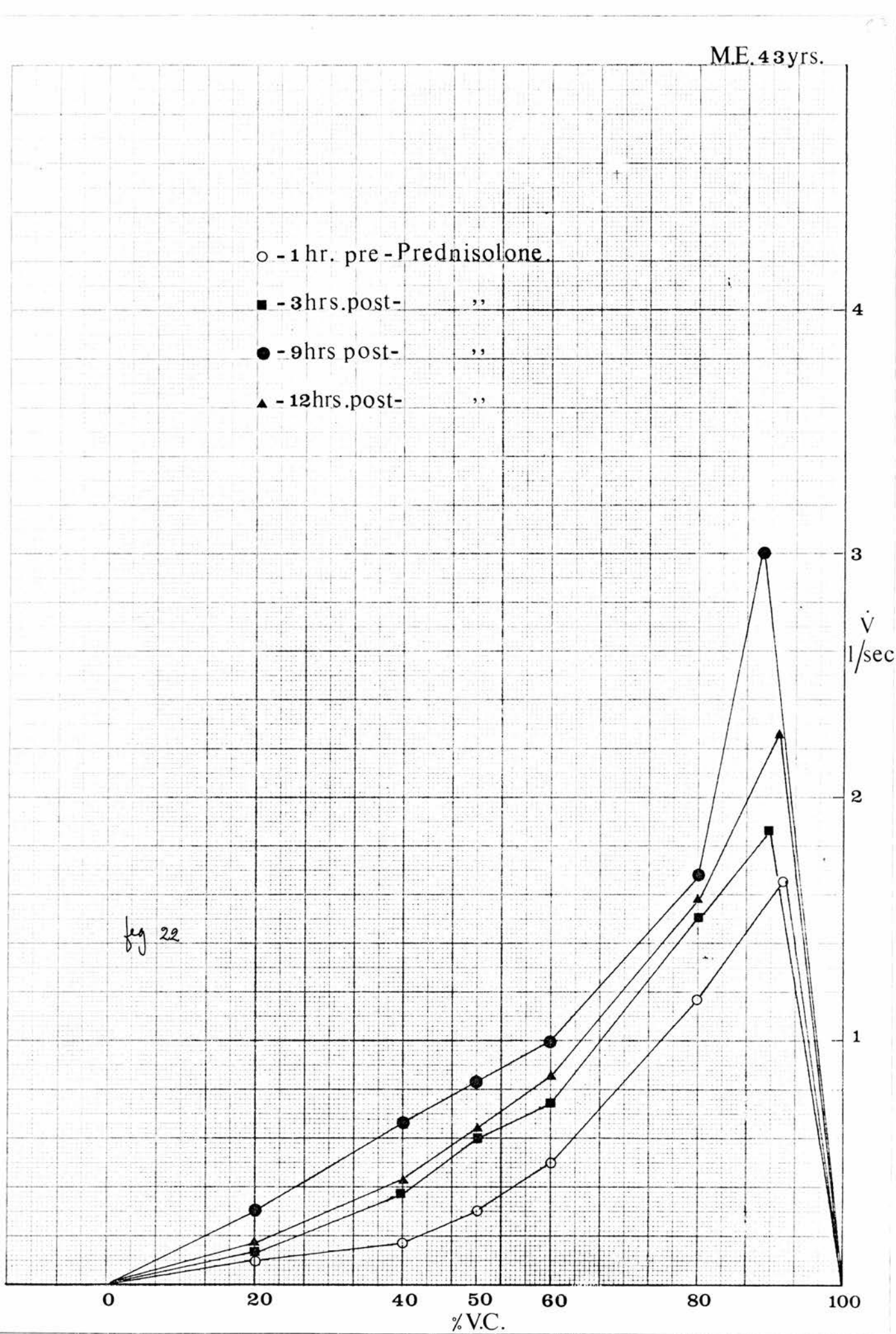

M.E. 43yrs.
○ - 1 hr. pre - Prednisolone.
■ - 3hrs.post- ,,
● - 9hrs post- ,,
▲ - 12hrs.post- ,,
4
3
2
1
V̇
l/sec
0
20
40
50
60
80
100
% V.C.

fig 22

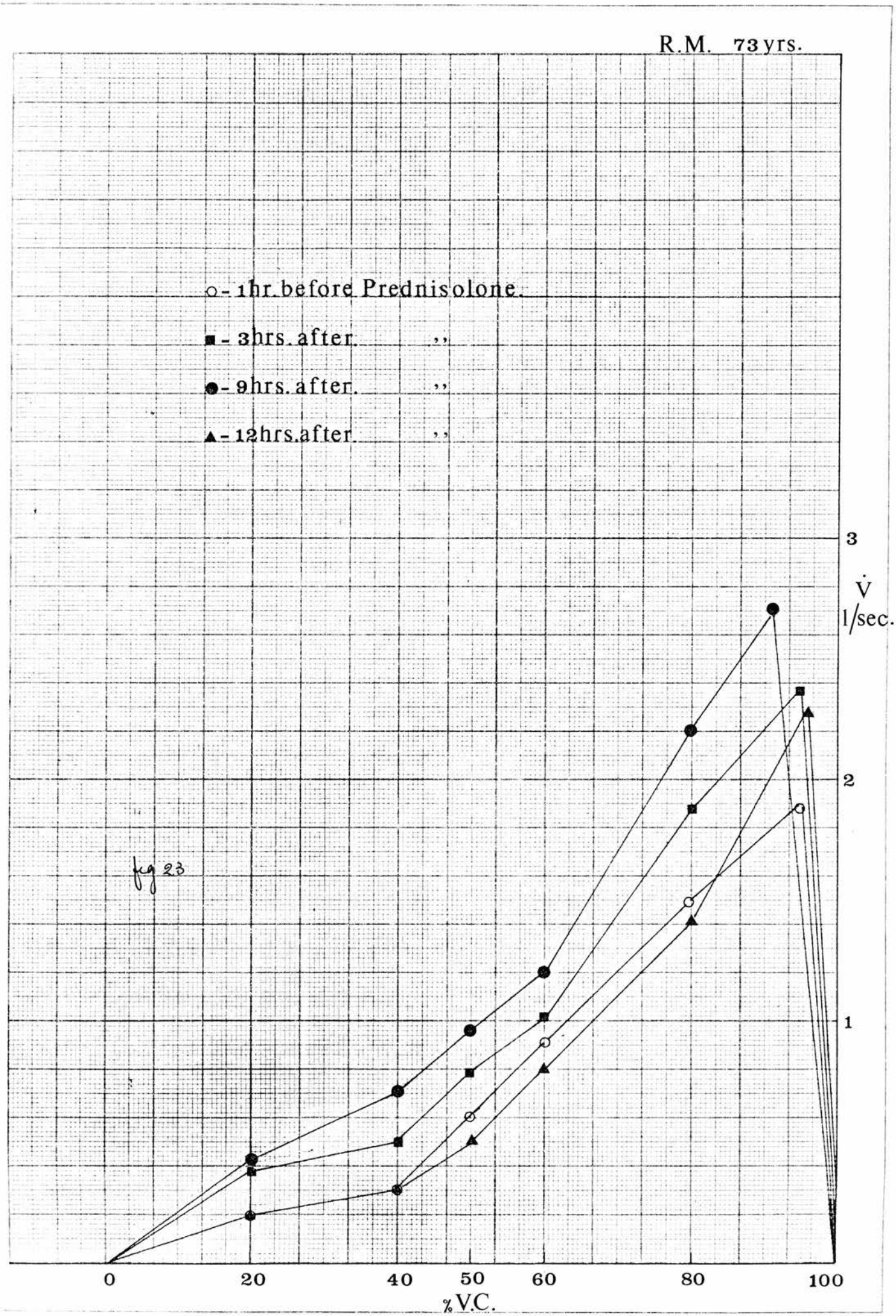

R.M. 73 yrs.
○ - 1hr. before Prednisolone.
■ - 3hrs. after ,,
● - 9hrs. after ,,
▲ - 12hrs. after ,,
3
2
1
V̇
l/sec.
0
20
40
50
60
80
100
% V.C.

fig 23

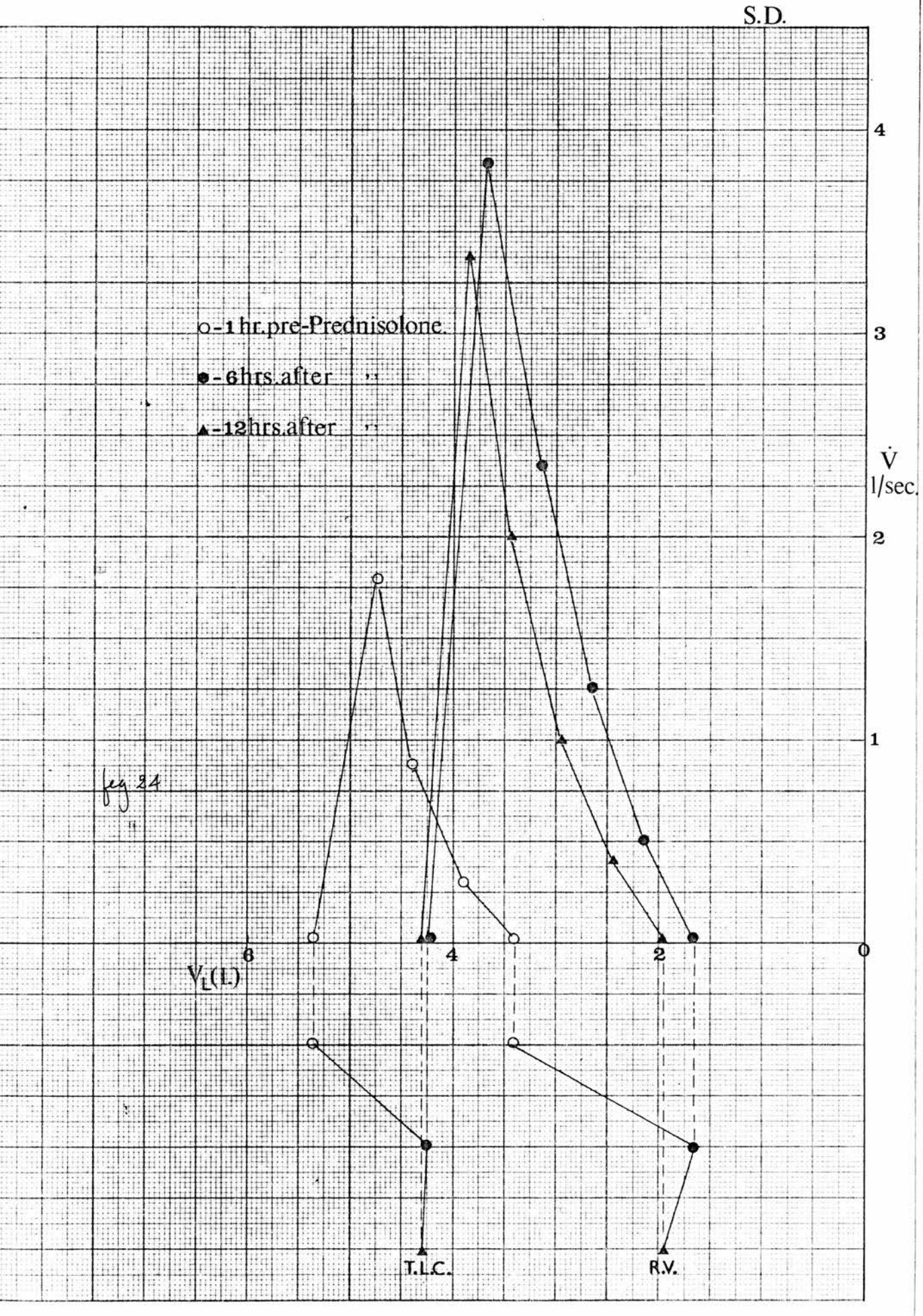
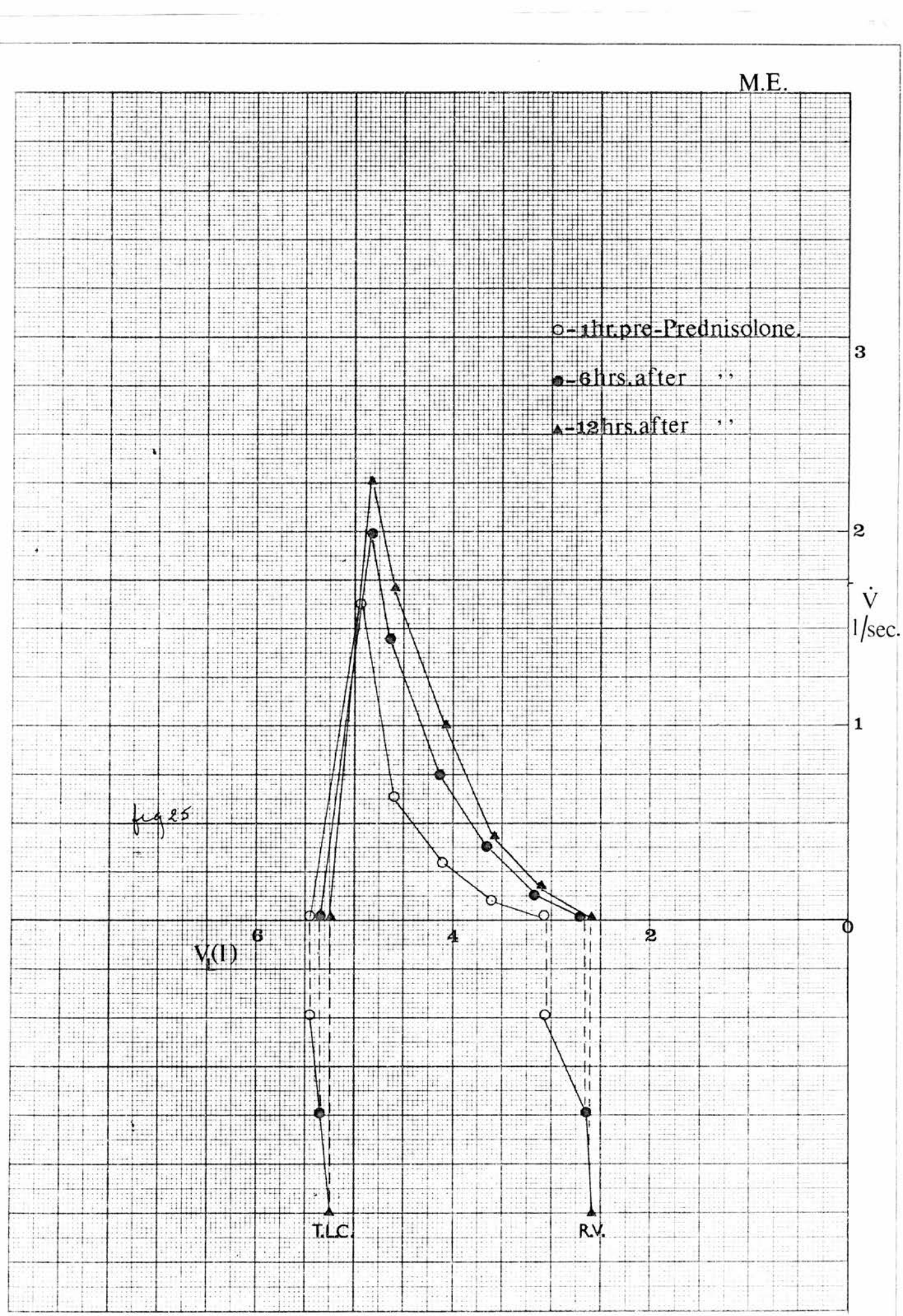
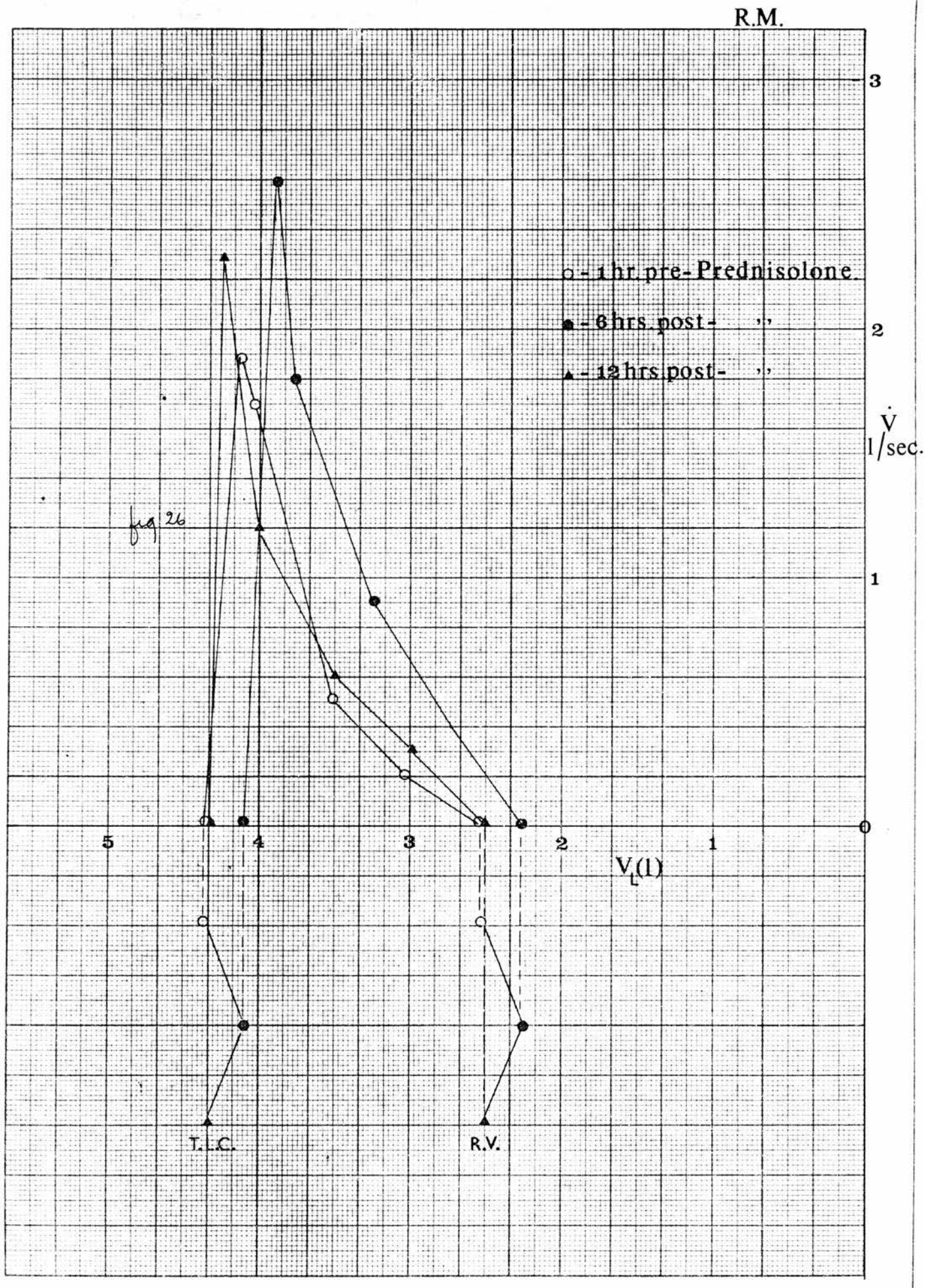

S.D.
○-1 hr.pre-Prednisolone.
●-6hrs.after
▲-12hrs.after
V̇ l/sec.
4
3
2
1
0
6
4
2
V_L(L)
T.L.C.
R.V.

fig 24


M.E.
○-1Hr.pre-Prednisolone.
●-6hrs.after ''
▲-12hrs.after ''
3
2
1
0
V̇
l/sec.
6
4
2
V(l)
T.L.C.
R.V.


R.M.
3
2
1
0
V̇
l/sec.
○ - 1 hr. pre-Prednisolone
● - 6 hrs. post- ,,
▲ - 12 hrs. post- ,,
fig 26
5
4
3
2
1
V_L(l)
T. L. C.
R.V.

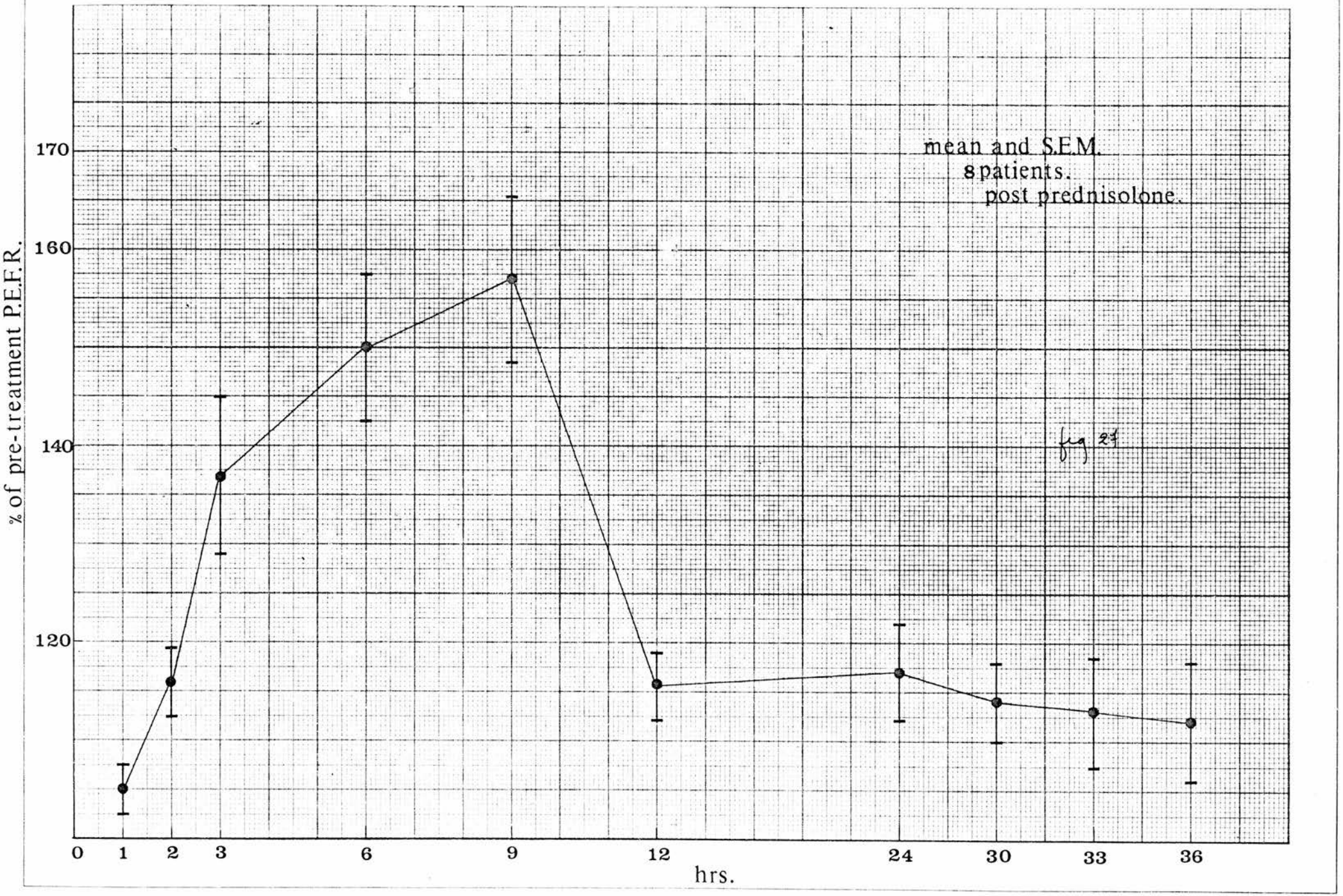
and SGaw was still statistically significant twenty-four hour after the drug had been given ($P < .005$; $P < 0.05$; $P < 0.05$;:$P < 0.05$). The mean change in F.V.C., R.V./T.L.C. and M.M.F.R. was however no longer significant by this time. The mean change in P.E.F.R. and $F.E.V._1$, had returned to non-significant levels by thirty-six hours. SGaw was however still markedly improved by this time in four patients, M.E., M.J., S.D. and B.R. These patients had values of 161%, 141%, 192% and 176% respectively, of their pre-treatment measurements. No statistical analysis was attempted on the measurements obtained at this time as patient M.T. failed to carry out this test because of an acute onset of breathlessness.

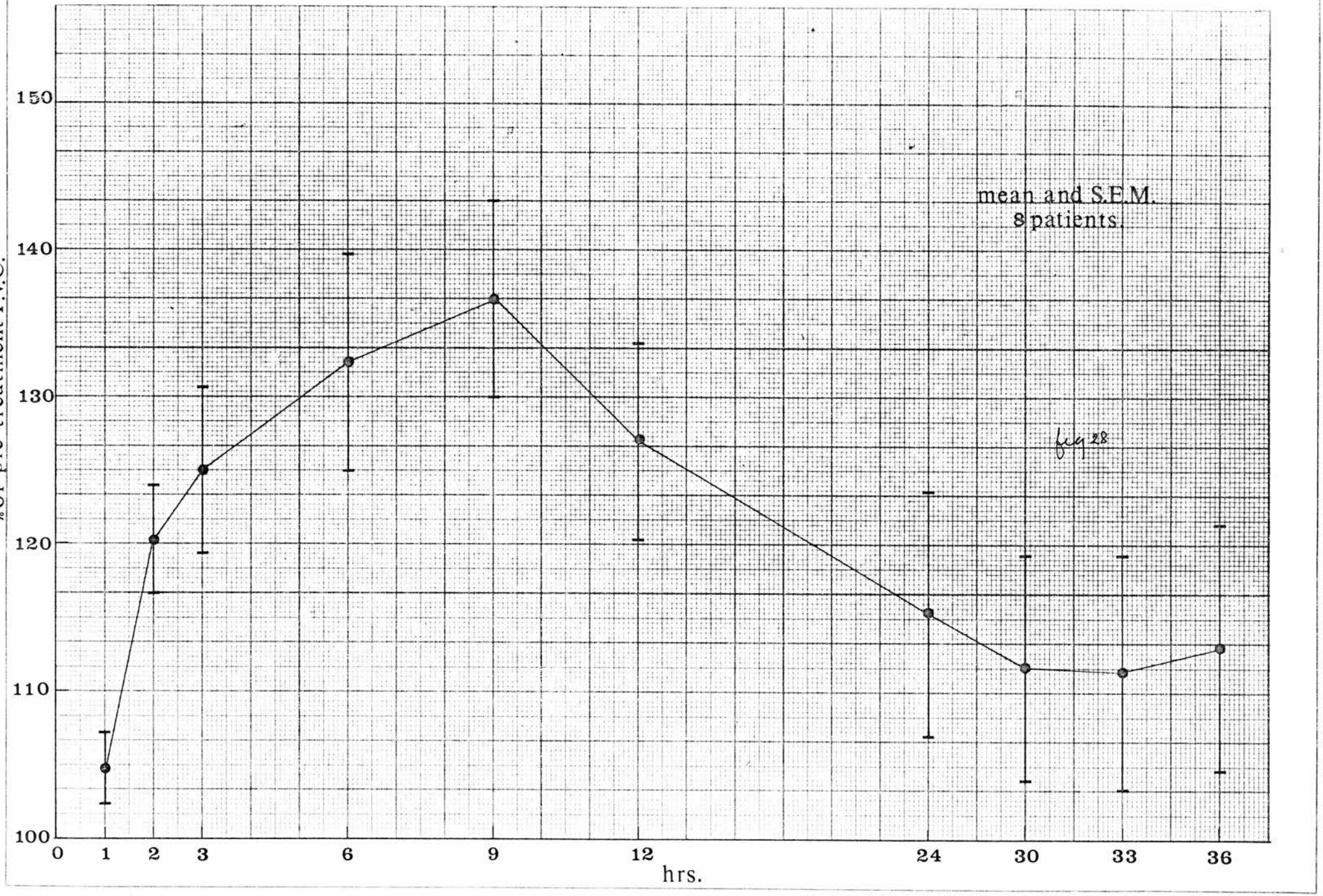
Stage II

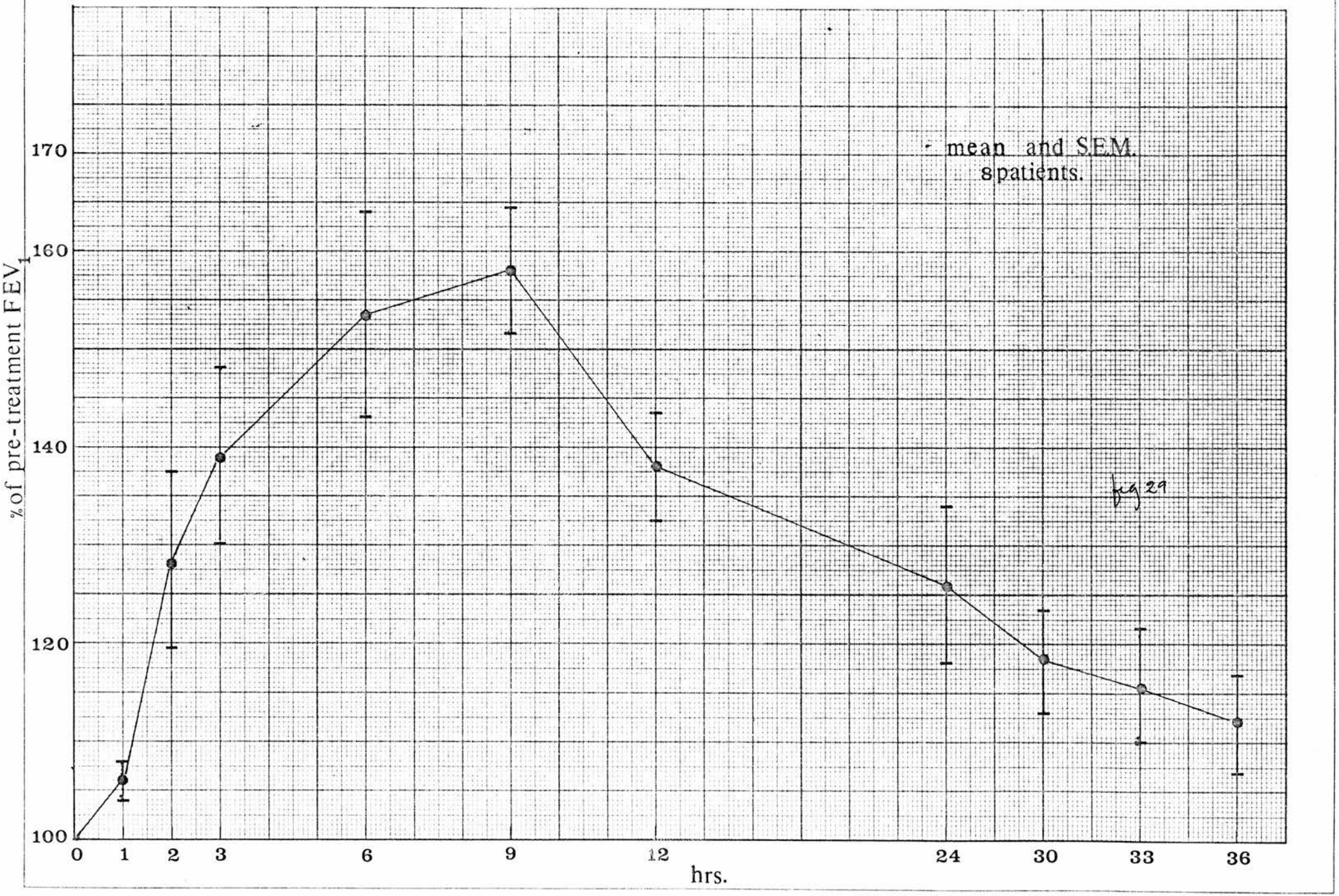
Of the twelve patients initially admitted to the study only eight managed to complete it. M.R. improved spontaneously within a day of being admitted to hospital whilst patient A.G. and L.R. became acutely breathless soon after admission. Patient B.W. was able to complete the first two days of the trial but despite having had 40 mg Prednisolone orally, developed an acute attack of asthma eight hours after the drug had been given. The results presented in this part of the study hence refer to the first eight patients in Table VI . As patients G.W. and H.B. were under the age of consent it was felt that arterial blood should not be withdrawn from them.

In this part of the study the FEV_1, FVC and PEFR were measured hourly during the first three hours following the Prednisolone administration in addition to the measurements performed at times similar to the previous stage. This was done in an attempt to establish whether change could be detected at an earlier time than that found in the first six patients. Body plethysmographic measurements were also carried out more frequently. Pulmonary gas exchange was studied on two occasions, at 0800 hours of the third day, i.e. an hour before Prednisolone was given to the patients, and at 1800 hours of the same day, when the peak effect was expected to be present. The effect of an intravenous injection of Hydrocortisone sodium succinate was followed hourly for twelve hours using a Wright's peak flow meter on the fifth day of the study.

In the group as a whole statistically significant improvement in the FEV_1 could be detected one hour after Prednisolone administration (P 0.025). Although both the F.V.C. and the P.E.F.R. showed an improvement at this time, this was not statistically significant. Significant improvement in both tests did however occur two hours after the drug had been given (P 0.005; P 0.001). In the group as a whole, the peak effect in all three parameters occurred at nine hours, as shown in Fig.27-29. However, in some patients the peak effect was detectable at six hours(Values in Appendix). The difference between the measurements of these tests performed six and nine hours after Prednisolone administration was not statistically


mean and S.E.M.
8 patients.
post prednisolone.
fig 2
% of pre-treatment P.E.F.R.
170
160
140
120
0
1
2
3
6
9
12
24
30
33
36
hrs.


150
140
130
120
110
100
% of pre-treatment F.V.C.
0
1
2
3
6
9
12
24
30
33
36
hrs.
mean and S.E.M.
8 patients.
fig 28


- mean and S.E.M.
8 patients.
fig 29
% of pre-treatment FEV_1
170
160
140
120
100
0
1
2
3
6
9
12
24
30
33
36
hrs.

significant. A parallel change was observed in the relaxed vital capacity measurement as shown in Fig. 30 ; a significant change was observed after an hour (P 0.05). This measurement was generally greater than the F.V.C. (Table X).

Vtg and Raw decreased and SGaw increased to significant levels when they were first measured, three hours after the drug had been given (P 0.01; P 0.005; P 0.005). The maximum effect on Raw, Vtg and SGaw, in the group as a whole, was found to occur at nine hours as shown in Fig. 31,32. However, there were individual variations; thus the lowest Raw was found at twelve hours in four patients (H.B., G.W., S.J., and M.V.), this was also true for the Vtg and SGaw. The mean values measured nine and twelve hours after Prenisolone administration were in fact not significantly different.

Pulmonary gas exchange was studied in six of the eight patients, in one of these, M.N., collection and analysis of expired gas was not successful because of breakdown in equipment. Although R values were on the high side, ranging between 0.88 and 1.20, the pre-treatment and post-treatment values were comparable, as shown in Table XI. Mean pre-treatment R. value was 1.04, the corresponding post-treatment value was 1.05. The arterial PO_2 rose in all patients and the alveolar-arterial oxygen difference decreased as shown in figures and tables XII both changes being significant (P 0.005; P 0.001). Dead space:tidal volume ratio and $PaCO_2$ showed little change, as can be seen from Tables XIII, XIV . Table XV shows the change in

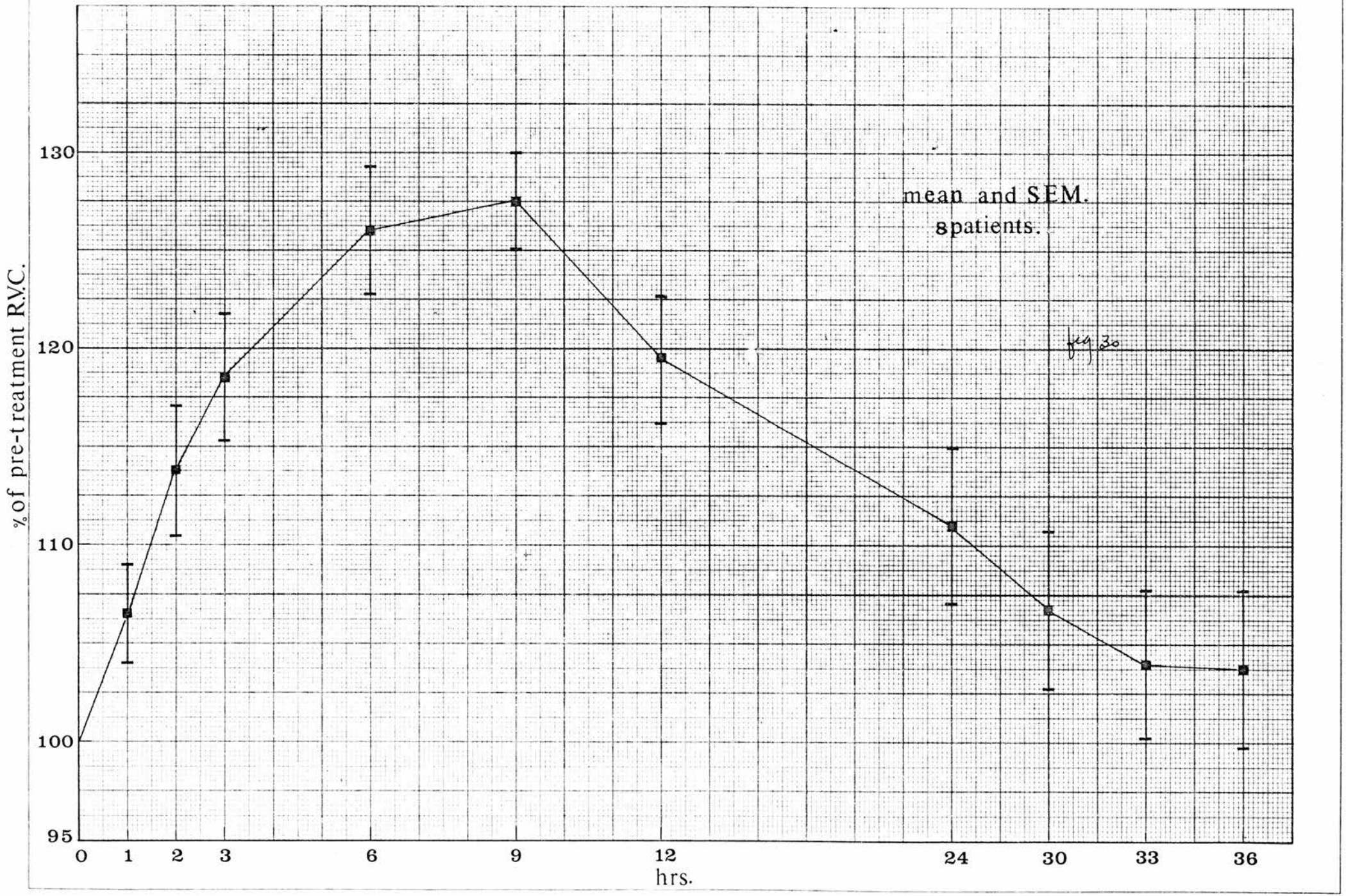
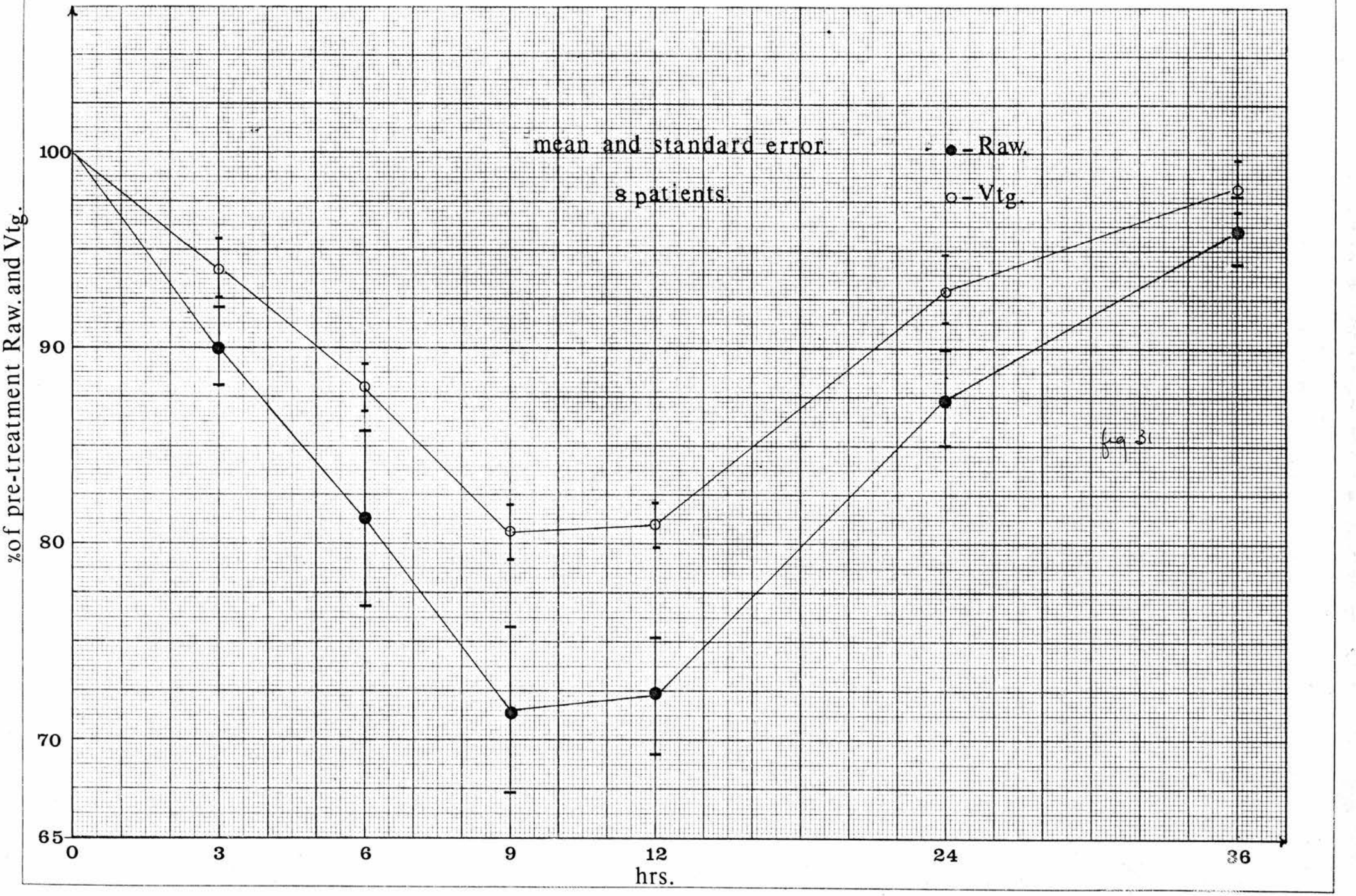

mean and SEM.
8 patients.
fig 30
% of pre-treatment R.V.C.
130
120
110
100
95
0
1
2
3
6
9
12
24
30
33
36
hrs.

TABLE X.

R.V.C./F.V.C. %

Patient	0 hr.	1 hr.	2 hr.	3 hr.	6 hr.	9 hr.	12 hrs.	24 hrs.	30 hrs.	33 hrs.	36 hrs.
B.H.	113	113	107	107	106	110	103	104	104	100	100
K.H.	110	109	109	109	104	104	100	110	110	111	105
M.V.	136	159	110	110	106	105	105	106	104	103	100
M.N.	105	102	106	108	106	103	108	109	102	102	100
A.L.	107	103	103	106	106	101	103	103	108	100	100
F.G.	124	124	115	123	129	123	113	136	121	121	113
G.W.	104	112	103	100	102	103	107	107	116	117	113
S.J.	109	106	102	102	103	103	112	108	108	104	104
Mean:	114	116	107	108	108	104	106	110	109	107	104


mean and standard error.
8 patients.
● – Raw.
○ – Vtg.
% of pre-treatment Raw. and Vtg.
100
90
80
70
65
0
3
6
9
12
24
36
hrs.
fig 31

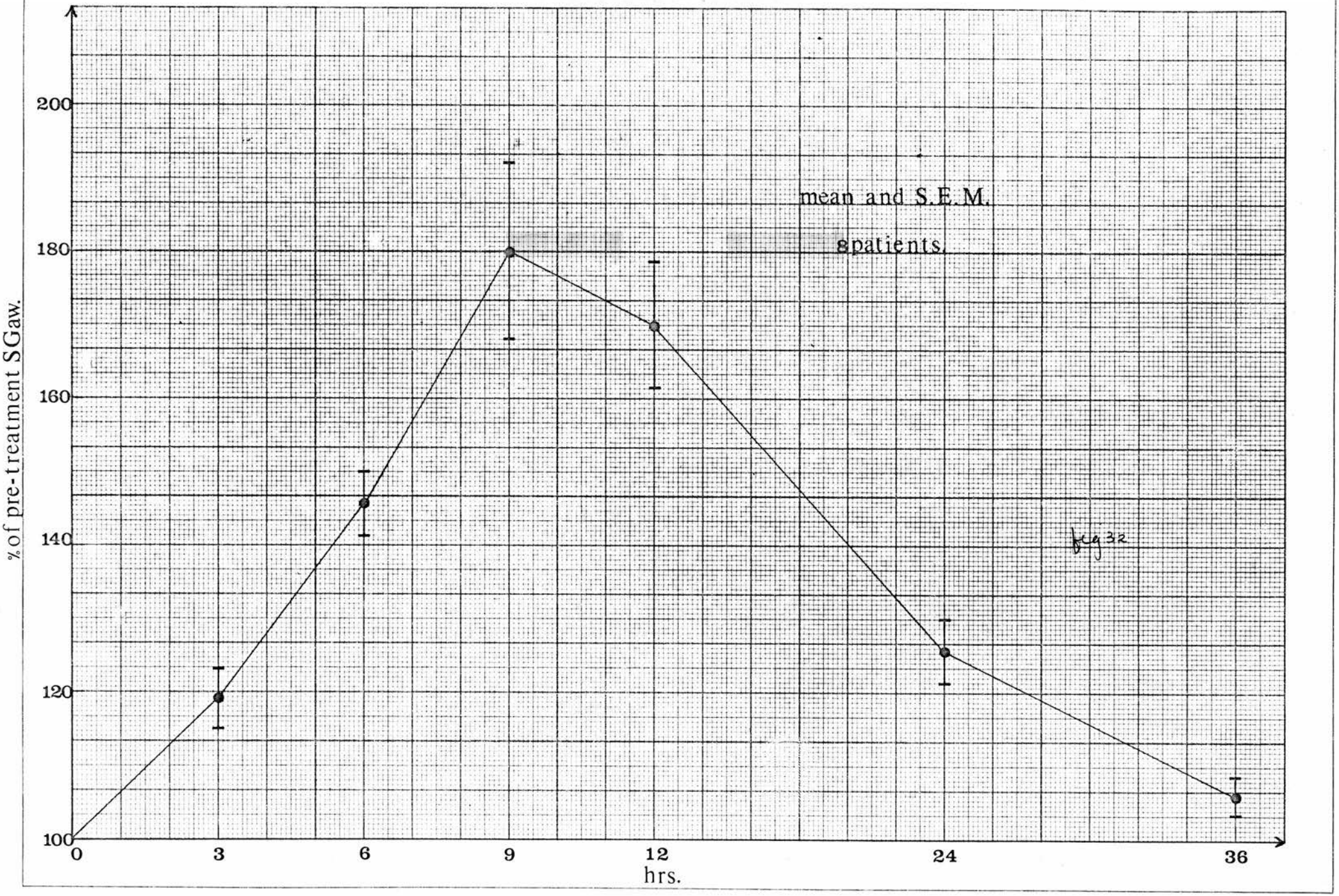

mean and S.E.M.
8 patients.
Fig 32
% of pre-treatment SGaw.
200
180
160
140
120
100
0
3
6
9
12
24
36
hrs.

TABLE XI

$\dot{V}CO_2$, $\dot{V}O_2$ and R values

Patient	Pre-Prednisolone			Post-Prednisolone		
	$\dot{V}CO_2$	$\dot{V}O_2$	R	$\dot{V}CO_2$	$\dot{V}O_2$	R
K.H.	197	207	0.95	179	203	0.88
M.V.	206	173	1.19	184	180	1.02
A.L.	249	230	1.08	325	254	1.20
F.G.	271	275	0.98	202	215	0.94
S.J.	232	226	1.02	245	225	1.09

TABLE XII

$(A-a)DO_2$ (mmHg)

Patient	Pre-Prednisolone	Post-Prednisolone	Predicted
K.H.	27	11	11
M.V.	36	26	13
A.L.	29	20	8
F.G.	36	25	12
S.J.	32	18	12

TABLE XIII

Dead Space:Tidal Volume ratio

Patient	Pre-Prednisolone	Post-Prednisolone	Predicted
K.H.	46%	48%	31%
M.V.	49%	45%	33%
A.L.	42%	40%	29%
F.G.	41%	40%	32%
S.J.	44%	39%	33%

Predicted values from Mellemgaard K (1966) Acta physiol. scand. 67;10.

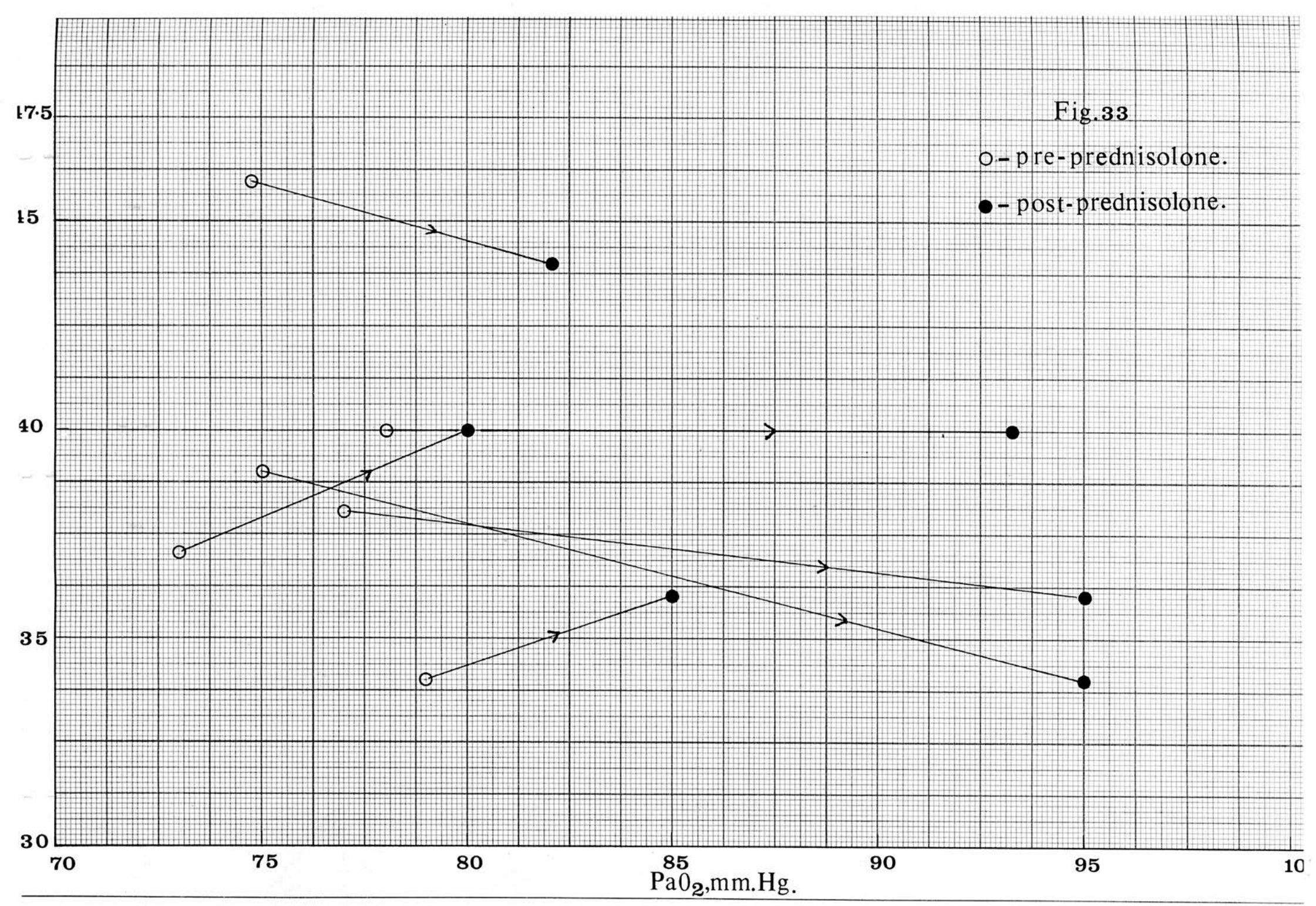


Fig.33
○ – pre-prednisolone.
● – post-prednisolone.
17·5
15
40
35
30
70
75
80
85
90
95
10
Pa0₂,mm.Hg.

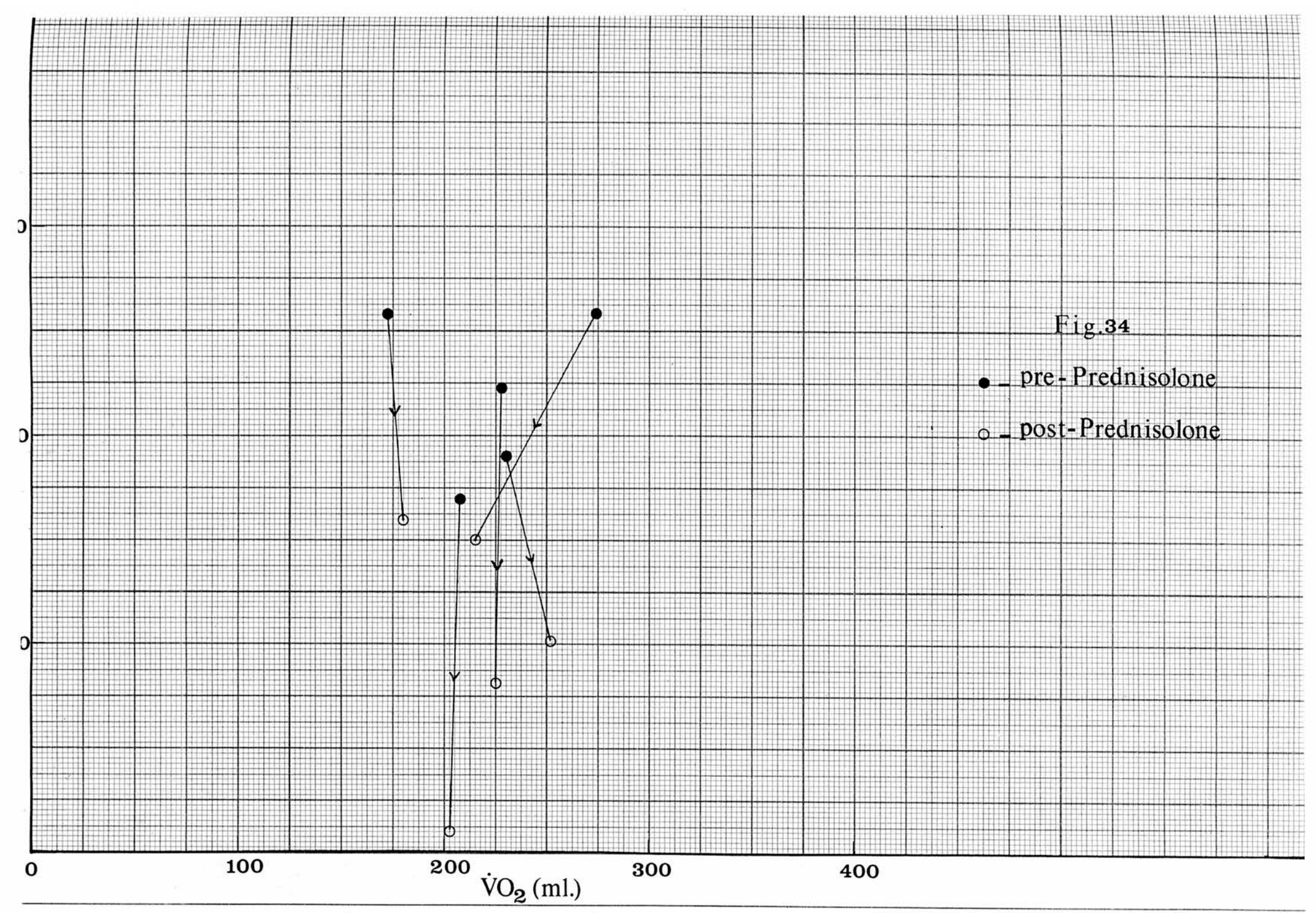


Fig.34
● – pre-Prednisolone
○ – post-Prednisolone
0
100
200
300
400
$\dot{V}O_2$ (ml.)

TABLE XIV

Arterial blood gases and pH

Patient	Pre-Prednisolone			Post-Prednisolone		
	PaO_2	$PaCO_2$	pH	PaO_2	$PaCO_2$	pH
K.H.	78	40	7.45	92	40	7.44
M.V.	79	34	7.47	85	36	7.46
A.L.	77	38	7.46	95	36	7.47
F.G.	73	37	7.47	80	40	7.46
S.J.	75	39	7.45	95	34	7.48
M.N.	74	46	7.44	82	44	7.44

TABLE XV

Venous-admixture effect

Patient	Pre-Prednisolone	Post-Prednisolone.
K.H.	9 - 12%	3 - 4%
M.V.	10 - 12%	7 - 9%
A.L.	11 - 16%	4 - 7%
F.G.	12 - 16%	9 - 12%
S.J.	13 - 18%	6 - 8%

TABLE XVI

Alveolar Ventilation

Patient	Pre-Prednisolone	Post-Prednisolone
K.H.	4.25 l	3.90 l
M.V.	5.23 l	4.40 l
A.L.	5.65 l	7.79 l
F.G.	6.15 l	4.50 l
S.J.	5.40 l	6.20 l

venous admixture effect; this was also significantly decreased ($P < 0.01$).

Following the administration of 200 mg of Hydrocortisons intravenously, in the group as a whole, the P.E.F.R. was significantly increased one hour later ($P < 0.05$). The overall peak effect occurred at five hours after the injection. There were however, individual variations. Thus in patients H.B., M.N. and F.G. the maximum change occurred at four hours and in patients M.N., S.J., and M.V., this took place at six hours. Figure 35 shows the mean effect of hydrocortisone on PEFR and Figure 36 compares the effect of placebo tablets, prednisolone and hydrocortisone, on the same test.

The reversibility tests to adrenaline and atropine are shown in Tables XVII - XX. Both adrenaline and atropine produced statistically significant improvement in FEV_1 ($P < 0.001$; $P < 0.001$). The change in FEV_1 produced by adrenaline was markedly and significantly greater than that produced by atropine, ($P < 0.001$). Similar changes were found in the FVC.

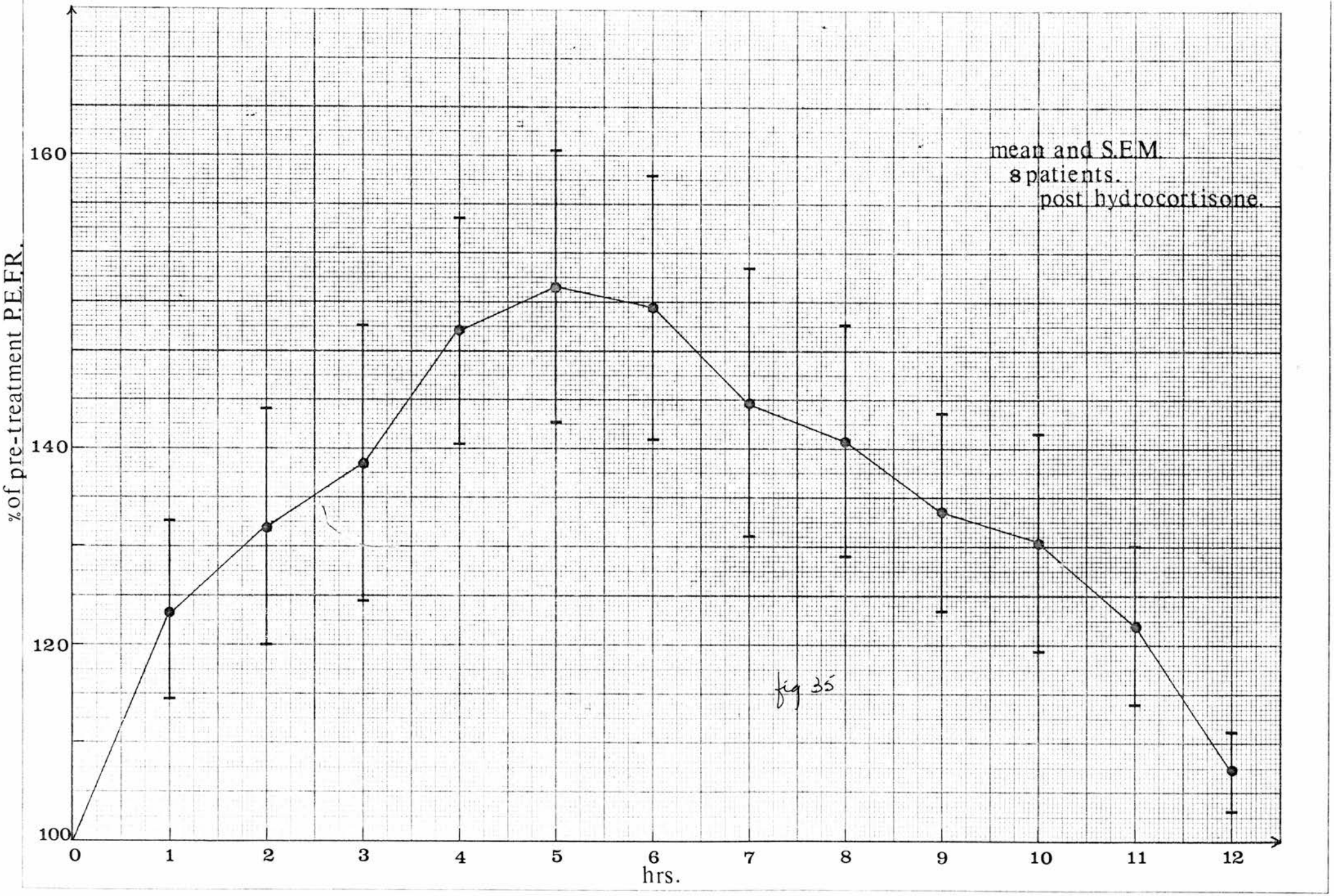

mean and S.E.M.
8 patients.
post hydrocortisone.
% of pre-treatment P.E.F.R.
160
140
120
100
0
1
2
3
4
5
6
7
8
9
10
11
12
hrs.

fig 35

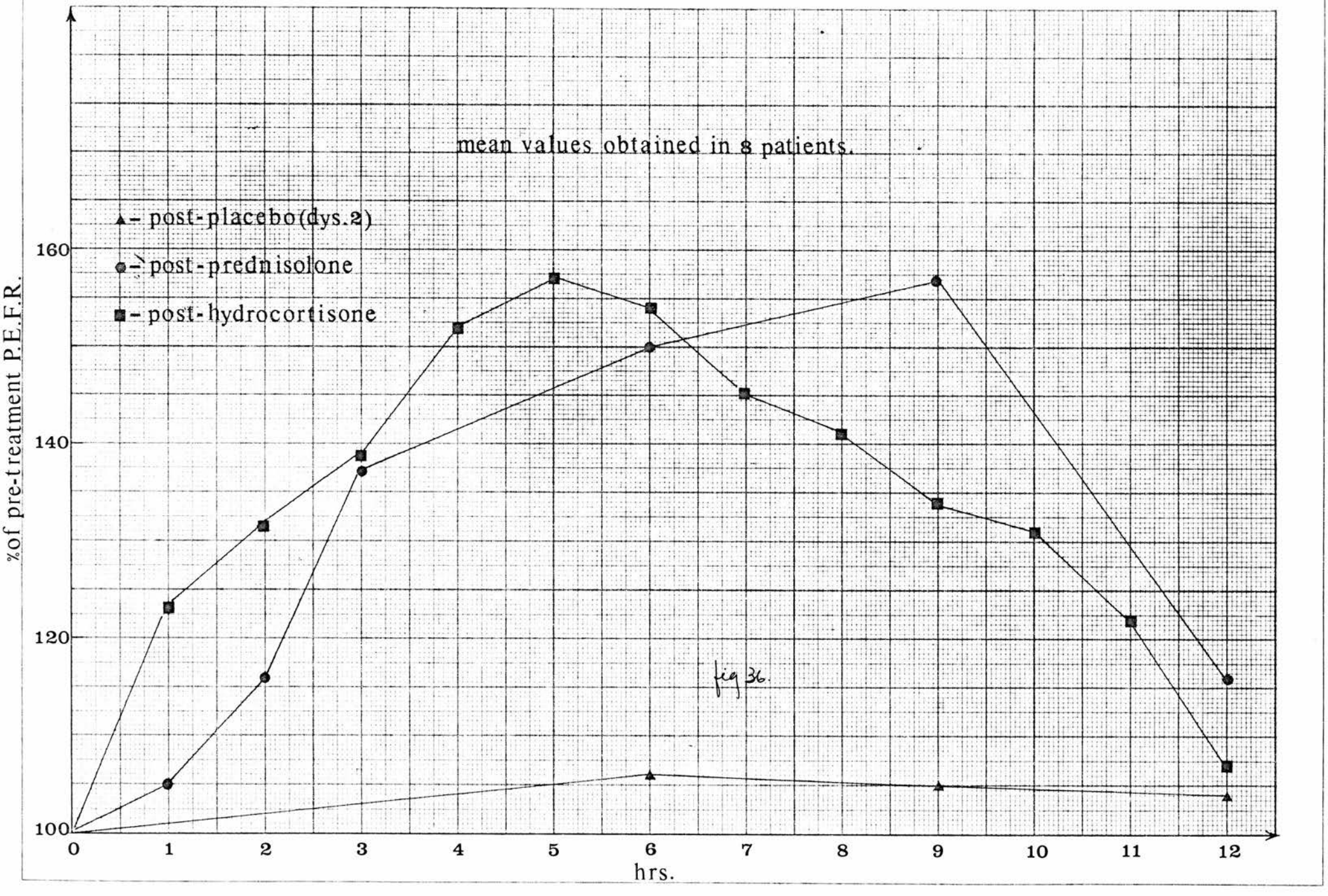

mean values obtained in 8 patients.
▲ - post-placebo(dys.2)
● - post-prednisolone
■ - post-hydrocortisone
%of pre-treatment P.E.F.R.
160
140
120
100
0
1
2
3
4
5
6
7
8
9
10
11
12
hrs.

fig 36.

TABLE XVII

FEV_1 reversibility to Adrenaline

	Pre-treatment	Post-treatment
M.T.	650 ml	3000 ml
S.D.	980 ml	1790 ml
B.R.	1040 ml	1650 ml
M.E.	820 ml	2060 ml
M.J.	1030 ml	2150 ml
R.M.	500 ml	1630 ml
B.H.	1350 ml	2450 ml
K.H.	750 ml	2000 ml
M.V.	750 ml	1350 ml
M.N.	2150 ml	3800 ml
A.L.	1800 ml	2300 ml
F.G.	1000 ml	1730 ml
G.W.	780 ml	1100 ml
S.J.	900 ml	1850 ml

TABLE XVIII

FVC reversibility to Adrenaline

	Pre-treatment	Post-treatment
M.T.	1800 ml	3400 ml
S.D.	1270 ml	2850 ml
B.R.	2450 ml	3200 ml
M.E.	2200 ml	2650 ml
M.J.	1530 ml	2700 ml
R.M.	1630 ml	1950 ml
B.H.	2200 ml	2650 ml
K.H.	2050 ml	2500 ml
M.V.	1025 ml	2075 ml
M.N.	3700 ml	4650 ml
A.L.	2950 ml	3075 ml
F.G.	2600 ml	3450 ml
G.W.	1700 ml	2300 ml
S.J.	1950 ml	3150 ml

TABLE XIX

FEV_1 reversibility to Atropine

	Pre-treatment	Post-treatment
M.T.	650 ml	2650 ml
S.D.	1030 ml	1270 ml
B.R.	1150 ml	1350 ml
M.E.	820 ml	2000 ml
R.M.	950 ml	2000 ml
M.J.	1000 ml	1900 ml
B.H.	1550 ml	1975 ml
K.H.	720 ml	1100 ml
M.V.	600 ml	925 ml
M.N.	2375 ml	3100 ml
A.L.	2000 ml	2400 ml
F.G.	800 ml	1250 ml
G.W.	750 ml	850 ml
S.J.	1150 ml	1450 ml

TABLE XX

FVC reversibility to Atropine

	Pre-treatment	Post-treatment
M.T.	1730 ml	2880 ml
S.D.	1500 ml	2680 ml
B.R.	2375 ml	2650 ml
M.E.	2300 ml	2460 ml
M.J.	1390 ml	2430 ml
R.M.	1350 ml	2050 ml
B.H.	2525 ml	3100 ml
K.H.	1900 ml	2480 ml
M.V.	900 ml	1300 ml
M.N.	4125 ml	4925 ml
A.L.	2850 ml	2900 ml
F.G.	2575 ml	2700 ml
G.W.	1550 ml	1850 ml
S.J.	2300 ml	2800 ml

DISCUSSION.

Sir John Floyer, in his book, 'Treatise on Asthma' (1698), wrote, "The Asthma is a long Disease, and it requires a long Observation to give a true Account of its Symptoms, Changes and various Causes, which common Patients cannot nicely observe". Floyer's observation is of course perfectly correct, and his suggestion that "a long Observation" is necessary for the understanding of asthma perhaps applies most appropriately when the therapeutic value of drugs is being assessed in this condition.

It is common knowledge that it is difficult to evaluate the effectiveness of any therapeutic measure because of the psychological effect of the new procedure itself and the increased attention that the patient frequently receives. When corticosteroid therapy is used the evaluation is perhaps all the more difficult because of the frequent effect of this drug on mood. The difficulty of drug evaluation in such a variable and complex disease as asthma is illustrated by the fact that the Medical Research Council in 1956 concluded, on the basis of a controlled trial, that corticosteroids have no long term value in the treatment of chronic asthma. The report is based on 96 patients, 49 of whom were given Cortisone acetate and the rest placebo tablets; 19 of the patients failed to complete the trial for various reasons. Assessment was carried out fortnightly by means of a physical examination, an evaluation of exercise tolerance using five arbitrarily defined grades, an

arbitrary assessment of incapacity for work and a single measurement of vital capacity, over a period of thirty-six weeks. Almost all the patients were also receiving bronchodilator and other drugs during the study.

It is essential that a homogeneous group of patients be selected when the value of a drug is to be assessed in bronchial asthma, in order to ensure that results obtained in individual patients are comparable. Asthmatic patients often show changes in the severity of their disease either spontaneously, following hospital admission, or as a response to placebo preparations. These patients often exhibit significant day to day, as well as, diurnal variation in airway obstruction.

Definite day to day fluctuations in tests of pulmonary function have been demonstrated in patients with chronic airway obstruction by various workers, (Spicer et al, 1962; Beerel et al, 1963; Freedman, 1963). McDermott, (1966) pointed out that airway resistance in normal subjects may have cyclical changes throughout the day. She found a decrease in airway resistance of about 10% in the morning (between 10 a.m. and 3 p.m.) which was followed by a slight increase in the evening (from 3 p.m. to 11 p.m.). Zuidema, (1965) measuring airway resistance by an interrupter technique found a similar diurnal variation in ten asthmatic patients. Zedda and Sartorelli, (1971) using a body plethysmograph reported that bronchitic and asthmatic patients showed an increase inairway resistance in the

afternoon. On the other hand, Guyatt and his co-workers (1967) failed to find any significant variation during the day, or from day to day in their study on normal subjects. Lewinsohn et al, (1960) demonstrated relatively large spontaneous variations in FEV_1 and FVC between 6 a.m. and 10 p.m., with lowest values occurring early in the morning. Fuleihan and Abboud, (1968), however, found no significant change in TLC, RV, FEV_1 and FVC between 8 a.m. and 4.30 p.m. in their patients with airway obstruction.

Hume and Gandevin, (1957) and Hume and Rhys Jones, (1960) described a 'response curve' in asthmatic patients, where, during an acute episode, there is slight improvement following isoprenaline therapy, the response increasing as the patient's clinical condition improves and finally decreasing again as the patient's clinical state approaches normal. The bell-shaped response curve of Hume and Gandevia was however not reproduced in Pain and Read's study (1963). An important point emphasised by the latter workers is that the degree of improvement also depends on whether the patient's condition is improving or deteriorating when the initial pre-treatment FEV_1 is measured.

Great care was taken to ensure that the patients selected for the present study had a stable degree of airway obstruction. Any significant degree of diurnal variation, spontaneous improvement or placebo effect was excluded by performing measurements at identical times during the day in which the patients were on placebo tablets,

as well as when they received the actual drug. Although minor fluctuations in the various parameters could be observed during the placebo days, these were not significantly different from the pre-treatment values. During these two days, three patients improved spontaneously and a similar number developed acute asthma and were therefore excluded from the study on grounds of instability.

It is often both difficult and hazardous to base the interpretation of the therapeutic response to a drug in bronchial asthma by employing isolated tests of pulmonary function. Similarly, it is frequently misleading to make subjective assessments of the degree of breathlessness or exercise tolerance without performing objective pulmonary tests. It was for these reasons that the effects of corticosteroids in the patients investigated in this study were carefully monitored using a wide range of pulmonary function tests.

All the patients were screened for Respiratory tract infection. They all had three sputum specimens negative on culture for ordinary pathogens, and sputum which was macroscopically mucoid. There was no concomitant cardio-pulmonary disease in any of the patients, an electrocardiogram and a chest x-ray taken at the beginning of the study were all normal.

It has been demonstrated that the clearance of corticosteroids from the plasma maybe abnormal in patients with either renal or hepatic dysfunction (Libberman and Teich, 1953; Brown et al, 1954; Willar-

dson et al, 1955: Wallach and Simons, 1958; Peterson, 1960), Venous congestion of the liver in cats has been shown to lead to decreased efficiency in the inactivation of deoxycorticosterone, cortisone, cortisol and aldosterone, which may last for as long as nine months after the onset of congestion (Yates, 1958; Yates, Urquhart and Herbst, 1958). Hench had reported the observation that patients with rheumatoid arthritis who developed jaundice often showed remarkable improvement in their symptoms. This phenomenon he later attributed to a decrease in the rate of inactivation of adrenocorticosteroids by a deranged liver (Hench, 1952). Peterson, (1959) reported a plasma half-life for prednisoloneof 200 minutes in normal subjects and 240 minutes for patients with hepatic cirrhosis, the corresponding values for hydrocortisone being 80 - 100 minutes and 300 minutes. Mugent and his co-workers found very similar values for prednisolone; 214 minutes in normal males, 241 minutes in patients with hepatic disease and 223 minutes in patients with renal insufficiency.

In all the patients studied, there was no evidence of hepatic or renal disease. Estimations of serum urea and electrolytes, plasma bilirubin and serum alanine aminotransferase and alkaline phosphatase were all normal (Table Hyperthyroidism has also been shown to enhance hydrocortisone turnover through increased formation of conjugated A-ring reduced products, (Levin and Doughaday, 1955; Brown et al, 1958). None of the patients studied had clinical evidence of increased thyroid activity.

Evidence is available that a number of drugs are capable of activating pituitary-adrenal secretion. Amongst these are chlorpromazine (Egdahl and Richards, 1956), reserpine (Egdahl, Richards and Hume, 1956) and thyroxine analogues (Melby et al, 1960). There have also recently beenreports that certain drugs can enhance the hepatic metabolism of corticosteroids. Thus Werk and his colleagues (1964), Conney and his associates, (1965) and Jubiz et al, (1970) pointed out that the anticonvulsant diphenylhydantoin enhanced hepatic microsomal hydroxylation enzyme activity, resulting in an increased clearance rate of corticosteroids both in rats and in human subjects. Their work has been supported by that of Haque et al, (1972), who found that diphenylhydantoin hastens removal of dexamethasone from the plasma mainly by increasing its conversion to more polar metabolites. Burstein and Klauber, (1965) reported that barbiturates too increased the clearance rate of corticosteroids.

Brooks et al, (1972) have recently studied the effect of phenobarbitone therapy on corticosteroid metabolism in eleven patients with bronchial asthma. The previous work had been done on normal subjects or patients on long term anticonvulsants. Brooks and his co-workers found a mean decrease in half life of 44% and an increase in metabolic clearance rate of 88%, of the intravenously administered dexamethasone following the administration of 120 mg of phenobarbitone in four daily divided doses for three weeks. Three prednisolone-dependent patients deteriorated clinically and showed an increase in blood eosinophilia and a fall in the FEV_1 and MMFR follow-

ing phenobarbitone. When barbitone was stopped, these changes were reversed. The patients in the present study, therefore, received no other drugs besides corticosteroids during the trial. It was ensured in this way, that as far as possible, no external factors interfered with corticosteroid metabolism, and the changes observed in pulmonary function could reasonably be attributed to the corticosteroids administered.

The rate of removal of hydrocortisone from the bloodstream of normal subjects has been reported to be faster in children than in adults (Done and Kelly, 1956) and faster in the adult than in the aged (Tyler et al, 1955). It has been suggested that this is due to the different metabolic rates present at the different stages of life. Collins et al, (1970) on the other hand, reported finding no statistically significant difference in the handling of intravenous hydrocortisone between young and elderly healthy individuals. Age however appeared to have no effect on the time course of response of corticosteroids in the asthmatic patients studied in this investigation. Thus two fourteen year old patients and two patients who were over seventy years old had a similar response to that of the middle age adult patients.

Although various time intervals have been suggested as elapsing between the administration of corticosteroids and the onset of improvement in patients with bronchial asthma, no systematic physiological studies have as yet been carried out. These time-intervals

have been variously reported as two to three hours (Cope, 1972), five to nine hours(Schwartz, 1950) and twenty-four to forty eight hours and longer (Herxheimer, 1966). The relief provided by corticosteroids has also been described as immediate, (Saporia, 1966). It is not surprising that conflicting results of this nature have been reported, because the degree of severity of the disease, the patients studied, the drugs given and the dosages and routes of administration have been widely different. All too often, subjective clinical observation seems to have been relied on when conclusions were being drawn, instead of systematic physiological assessment. Porter and his colleagues (1970), who were studying the effects of corticosteroids on the distribution of histamine in the blood of asthmatic children, reported seeing very rapid clinical improvement, in two patients two to three minutes after the administration of a single corticosteroid dose. Indeed, so rapid was the effect that the authors commented that it "seemed to be psychological rather than pharmacological". Glick and Freedman, (1969) using intramuscular corticotrophin in patients with acute asthma have reported significant changes in P.E.F.R. ($P < 0.001$) at the time of the first measurement, six hours after the injection.

In the patients studied the earliest effect produced by the administration of prednisolone that was statistically significant was the change in FEV_1 and the change in relaxed vital capacity that occurred in the second part of the study. These changes occurred one hour after the drug had been given. In these patients, the changes in FVC and

P.E.F.R. became statistically significant at the next time they were measured. Specific conductance was also signficantly improved when first measured, three hours after the drug had been administered The mean peak effect of all tests for both groups of patients occurred nine hours after prednisolone had been given. Thereafter, there was a deterioration towards pre-treatment levels in all tests. The changes in P.E.F.R. and FEV_1 were still statistically significant when these were measured thirty-three hours after administration of prednisolone in the second group of patients ($P < 0.05$; $P < 0.05$), but had fallen to non-significant levels by thirty-six hours. The change in FVC was not significant when measured twenty-four hours after the drug had been given. However specific conductance when last measured, thirty-six hours after treatment, was still significantly increased in the second group of patients ($P < 0.05$). In contrast the mean change in P.E.F.R. was significantly increased at the time of the first measurement, one hour after the intravenous injection of hydrocortisone, the peak effect being attained in five hours. The mean change in P.E.F.R. was no longer statistically significant at the time of the last measurement, twelve hours after the injection ($P < 0.10$).

Payne et al, (1967) writing about the investigation of bronchial asthma, stated: "The inability to reproduce patterns of airway responsiveness to test medications in the same subjects at different times illustrates the complex nature of the biological system being measured..... In addition, failure to duplicate individual re-

sponse patterns at different times should not cause dismay". The fact that consistent changes in tests of pulmonary function have been demonstrated in this study following the administration of corticosteroids, must be attributed to careful initial selection and rejection of patients who failed to meet the strict criteria laid down. No patient was admitted to the study whose clinical history did not suggest that stable airway obstruction was present during the period immediately prior to hospitalization and none were allowed to complete the study if the disease showed evidence of significant improvement or deterioration during the first two days of the trial. Collins et al, (1970) have recently reported failure to detect significant improvement in patients with asthma following intravenous hydrocortisone assessing response by measurement of the P.E.F.R. However, the patients they studied were acutely ill, whereas in the present investigation such patients were excluded.

The different time-course responses of prednisolone and hydrocortisone in the subjects studied could perhaps be best ascribed to the different routes of adminstration used and the fact that these two corticosteroids are known to be metabolized at different rates. Absorption of orally administered corticosteroids is thought to occur by passive diffusion chiefly from the proximal half of the small intestine since for any given corticosteroid, absorption in terms of weight per unit time is directly proportional to the concentration, (Schedl, 1965). One of the earliest indications that adrenocortical hor-

mones could be absorbed from the intestines was Osler's report in 1896 of a patient with Addison's disease who showed signs of improvement after oral administration of a glycerol extract of hog adrenal glands. Many years later, Freyberg, (1950) first showed that cortisone is absorbed from the gastro-intestinal tract, when he described its effectiveness in the treatment of rheumatoid disease. In contrast with the parenteral administration of corticosteroids whose absorption depends on their water solubility, the rate of absorption of orally administered corticosteroids appears to be more related to their lipid solubility; since as the number of hydroxyl groups increases, absorption becomes slower. The pore size in the small intestine is only four A° units and the corticosteroid molecule is thus too big to simply flow through the pores. It would appear likely that some change must occur in the lipoidal surface of the cell membrane in order for the steroid molecule to pass through, (Di Palma, 1971).

Mean changes in P.E.F.R. following oral prednisolone became statistically significant one hour later than they did when intravenous hydrocortisone was administered. However, although it might be tempting to conclude that this difference could be solely ascribed to the slower absorption of the prednisolone, data is now available that absorption and biological activity are not necessarily directly related. Indeed, Schedl, (1965), has shown that sometimes they may be inversely related; thus progesterone, one of the best absorbed steroids is almost inactive orally, and triamcinolone, which

is the most poorly absorbed compound is quite active clinically when given by the oral route.

The different times when maximum effect was achieved using the two corticosteroids and the different duration of action is very probably due to their different biological activities and rate of metabolic breakdown. Collins et al, (1970) reported a plasma half-life of 125 - 135 minutes when intravenous hydrocortisone was administered to a number of patients with acute asthma. The plasma 11-O.H.C.S. level reached a maximum after 60 minutes. Nelson et al, (1952) had previously published similar figures for orally administered hydrocortisone in a normal subject. Prednisolone is known to be more slowly removed from the circulation than hydrocortisone. Its half-life is on an average double that of hydrocortisone in normal subjects (Slaunwhite and Sandberg, 1956; Ely et al, 1956; Sandberg and Slaunwhite, 1957; Nugent et al, 1959; Di Palma, , 1971). It appears likely that it is the longer persistence in the plasma of free unconjugated, and therefore presumably pharmacologically active, prednisolone which accounts for its longer activity. Using isotope labelled prednisolone it has been found that all its metabolites are excreted within 48 hours of its administration.

There are some conflicting reports about how corticosteroids are metabolically dealt with in asthmatic patients. Dwyer et al, (1967) found that steroid treated patients with acute asthma achieve a low plasma cortisol response to intravenous hydrocortisone. The

metabolic clearance rate of hydrocortisone was however normal in those patients who had not previously received corticosteroids. Schwartz et al, (1968) reported finding a more rapid plasma clearance of hydrocortisone in asthmatic patients who showed no clinical response to corticosteroids. It is not known whether their patients had a significant hepatic or renal dysfunction or whether they were taking other drugs as well. On the other hand, Collins et al, (1970) in a well controlled trial failed to find any statistically significant difference in the handling of intravenous hydrocortisone between normal subjects and asthmatic patients. Plasma 11-O.H.C.S. levels were also unaffected by whether the asthmatic patients had been receiving corticosteroids or not.

There seems to be reason to believe that some of the biological effects of corticosteroids represent indirect rather than direct actions, (Liddle, 1961). In general, the pharmacological and therapeutic effectiveness of a drug is a function of its concentration within the body at a given moment. This however does not appear to be the case with corticosteroids, where a significant latent period exists between the time of maximum concentration in the plasma or tissues and the time of their peak effect (Nelson et al, 1952). Thus, although it would be expected from previous studies that the maximum concentration would be achieved one hour after the injection of hydrocortisone, the mean peak effect in the eight asthmatic patients studied occurred five hours after the drug had been administered. The beneficial therapeutic effect of corticosteroids would appear to have persisted for a long time after the plasma levels of hydrocor-

tisone would have been expected to return to baseline values.

The effects of corticosteroids on tests of pulmonary function in the asthmatic patients studied in the present investigation appear to follow a similar time course to that of other biological effects of corticosteroids. Thorn and his co-workers (1953a) reported that the metabolic and clinical effects of a single dose of intramuscular conrtisone were evident in three to four hours, although peak activity usually occurred eight to twelve hours after the injection and the effective duration extended over a period of twenty-four hours or slightly longer. Renal excretion of electrolytes has been shown to be definitely affected within two to four hours of the administration of intramuscular, (Fourmann et al, 1952) as well as intravenous, (Thorn et al, 1953b) desoxycortisone. Fourmann and his co-workers found that potassium loss in the urine reached a maximum twelve hours after the injection. Hills and his co-workers first noted the fall in the number of circulating eosinophils following A.C.T.H., and this soon became a standard test for assessing corticosteroid activity. Nelson et al, (1952) found the maximum change in circulating eosinophils four to eight hours after the administration of 200 mg of oral hydroxycorticosterone. This lagged behind peak steroid levels by three to seven hours. Measurements were only carried out one, four and eight hours after the drug had been given. Cope, (1972) reported a maximum eosinopaenic effect occurring eight hours after the oral administration of 200 mg of hydrocortisone acetate.

Glenn et al, (1957) studied the effect of corticosteroids on the production of liver glycogen on twenty-four hour fasted, adrenalectomized rats. They found that following the injection of 1 mg. of hydrocortisone, either subcutaneously or intravenously, the maximum effect could be detected about eight hours later, at a time when there was an insignificant amount of hormone in the blood. The hyperglycaemic effect of corticosteroids follows a similar time course. Thus West, (1958) reported that 5 mg of oral methylprednisolone produced its peak effect eight hours later, and with the same dose of oral prednisolone, maximum effect occurred between four and eight hours afterwards. Walton et al, (1970) described the effect of various doses of methylprednisolone on blood glucose in four normal subjects. Irrespective of the dose used the onset of the effect occurred between two and four hours; the first glucose estimation being performed two hours after the drug had been given. They found however, that the peak measurable effect was affected by the amount of steroid given, being greater and on the whole coming later with increasing dosage. In general, the peak effect occurred between six and ten hours, and the duration was between sixteen and twenty-two hours.

Corticosteroids have now been used in bronchial asthma for over twenty years. Carryer and his associates were the first to use intramuscular cortisone in three patients with asthma in 1950 and intravenous hydrocortisone was first used in this condition by Burrage and Irwin, (1955), having been used in an oral form the

previous year by Schwartz. Prednisolone and prednisone were originally introduced by Herzog and his colleagues in 1955. Their therapeutic value in bronchial asthma was demonstrated by Barach et al, in the same year. Very little however is known with any certainty of their possible modes and site of action in bronchial asthma.

Goth, (1966) put forward the hypothesis that the anti-allergic effect of corticosteroids is simply another manifestation of their non-specific anti-inflammatory action. However, as pointed out by Aviado and Carrillo, (1970) direct proof of this hypothesis is lacking. It has been suggested that the anti-allergic action is achieved by increasing the stability of various membranes, such as those of endothelial and smooth muscle cells and of lysosomes, as well as possibly reducing enzyme activity, such as that of histidine decarboxylase (Brocklehurst, 1968). Both prednisolone and hydrocortisone have been reported as stabilizing lysosomes thus retarding the release of inflammatory enzymes both in vitro and the living cell, (Weismann, 1971).

It has been suggested that corticosteroids inhibit the formation of antibodies (Bjornboe et al, 1951; Gabrielsen and Good, 1967). In the passively immunized rabbit cortisone does not influence the level of circulating antibodies, however, suppression of formation of new antibodies has been reported in the actively immunized rabbit, (Germuth et al, 1951).

The effects of corticosteroids on the metabolism of the lymphocyte have been studied in detail. The synthesis of nucleic acid and protein is depressed and glucose utilization is decreased. The thymus loses intracellular potassium and gains sodium. These changes are probably secondary to a more fundamental action of corticosteroids of which very little is known at present. Despite the changes in lymphoid tissues (Hechter and Johnson, 1949; Santisteban and Dougherty, 1954; Claman, 1972), the corticosteroids do not significantly suppress anti-body synthesis in man, although they do so in animals, (Larson and Tomlinson, 1951). Huffman and Ellis, (1969) immunized asthmatic children with diphtheria and tetanus toxoid and typhoid/paratyphoid and influenza vaccines. Assays were performed for specific anti-body responses. They showed that corticosteroids did not interfere with the synthesis of circulating anti-body.

Inhibition of the formation or storage of histamine has also been reported, (Carrillo and Aviado, 1968). Cortisone strongly inhibits the rate of histamine binding in the rat skin (Schayer et al, 1954) and the formation of histamine in lung tissue, (Gefland, 1951 Beall, 1965). Noah and Brand, (1957) found marked falls in blood histamine levels in asthmatic patients who were given therapeutic doses of prednisolone. However, the method then employed for estimating histamine levels was rather inaccurate. More recently Konoshita, (1963) has reported that high blood histamine levels encountered in status asthmaticus decreased to normal levels in 4 out of 6 patients, who were given corticosteroids. Pepys, (1971) suggested that corticosteroids would block 'inducible histamine'

produced by histidine decarboxylase. The restoration of histamine to tissues which have been depleted of it is thereby delayed.

Corticosteroids could also sensitize the β receptors in the airways, thus lower the receptor-threshold to the action of catecholamines. The adrenal glucocorticoids seem to act with catecholamines as a functional unit. It has been established that in the absence of these steroids the receptor-threshold for catecholamines may be elevated, at times to the point of complete unresponsiveness (Ramey and Goldstein), 1957).

Suggestions for other possible mechanisms have included a direct relaxant action on smooth muscle. Lefcoe, (1956) reported that hydrocortisone added to an isolated organ bath produced relaxation of guinea-pig tracheal muscle. Cinelli et al, (1964) showed that cortisone diminished the response to acetylcholine, and hence inhibition of acetylcholine induced bronchoconstriction could be yet another way in which corticosteroids might act.

Aviado and Carrillo, (1970) basing their studies on sensitized and non-sensitized animals, concluded that the two most important mechanisms appear to be the inhibition of formation or storage of histamine and a direct action of corticosteroids on bronchial smooth muscle. They showed that in rats the action of corticosteroids consists not only of relaxation but also of a reduction in the reactivity of the airways to cigarette smoke (Aviado and Carrillo,

1969). However, they failed to reproduce similar local effects in dogs (Carrillo and Aviado, 1970). This emphasizes that corticosteroids probably have different modes of action in various species, underlines the need for great care when extrapolating from the animal experiment to the human situation.

Studies have recently been carried out on the effect of corticosteroids on two leucocyte membrane enzymes, leucocyte adenyl cyclase and adenosine triphosphatase, of normal and asthmatic children, (Coffey et al, 1972). It was found that adenosine triphosphatase activity was increased in asthmatic patients and that this increase was reversed when corticosteroids were administered. Hydrocortisone was found to stimulate adenyl cyclase and inhibit both adenosine triphosphatase and phosphodiesterase. Coffey et al, suggest four possible mechanisms for the action of corticosteroids in asthma; direct simulation of adenyl cyclase, restoration of responsiveness of adenylcyclase to catecholamines which was found to be decreased in asthmatic patients, inhibition of adenosine triphosphatase activity and inhibition of phosphodiesterase.

Not only is the site and mode of action of corticosteroids in bronchial asthma unknown, but there is also uncertainty as to the exact site of airway obstruction in patients with bronchial asthma (Macklem, 1971). Hogg et al, (1968, 1970) have shown at postmortem examination that the major site of obstruction in lungs with bronchitis and emphysema, as well as in those with bronchiolitis,

pulmonary complications of fibrocystic disease, and bronchiectasis, was in bronchioles 2 mm in diameter and less. No mention is made of asthmatic lungs in their studies. Campbell, Martin and Riley, (1957), based their work on a mathematical analysis of the factors tending to open and close the airways during a forced expiration. They measured the intrathoracic pressure at which maximum expiratory flow occurs by means of an oesophageal balloon and concluded that critical narrowing first occurs in the large airways in asthma. There has recently been some confirmation of Campbell's findings by Gayrard (1968). Crofton and Douglas, (1969) remark that bronchoscopy does not suggest any crude variation in bronchoconstriction among the large bronchi in the asthmatic patients they have studied.

Although it has yet to be proved possible to determine the precise location of the narrowing that occurs during a spontaneous or provoked attack of asthma, some indication can be obtained from the changes that take place in mechanical function. A number of workers have shown that in asymptomatic patients, the distribution of ventilation remains uneven despite the fact that tests such as the measurement of Raw and FEV_1 are normal (McFadden and Lyons, 1969; Woolcock et al, 1969; Levine et al, 1970). They assumed that this was due to regional differences in time constants of small lung units and indicated residual abnormality in the small airways. Woolcock et al, (1969) regard the small airways in adult lungs as a "silent zone", in that obstruction within them causes little abnor-

mality in tests which are specifically designed to detect it until the degree of obstruction is quite advanced. It is now accepted that changes in Raw reflect predominantly changes in large airways (Green, 1964), whereas the FEV_1 is determined mainly by the elastic recoil of the lung and the resistance of the airways upstream from the equal pressure point, (Macklem and Mead, 1967).

McFadden and Lyons, (1969) measured the resistance of airways during forced expirations upstream and downstream from equal pressure points, (Mead et al, 1967) combining the equal pressure point concept with measurements of isovolume pressure-flow curves, in asthmatics during recovery from acute attacks. Downstream resistance was measured at the point that flow limitation was reached. They found that both upstream and downstream resistances were increased, indicating that both large and small airways are involved. However, their data showed that the principle area of obstruction appeared to be in the upstream pathways; i.e. from alveoli to the equal pressure points. Peripheral airway obstruction may cause equal pressure points to be displaced upstream (Macklem et al, 1965), with the result that downstream resistance is increased because the downstream segment is lengthened and not because there is intrinsic abnormalities in the segment, (Macklem, 1971). Cade et al, (1971) studying lung mechanics during provocation of asthma with metacholine showed that both the larger as well as the smaller airways were involved, but the response of the larger airways was faster and of a shorter duration than the response of the smaller airways. The

characteristic finding of plugging of the smaller airways by viscid plugs of mucus in lungs of patients dying in status asthmaticus (Spencer, 1968; Dunnill, 1971), indicates that in the more prolonged and severe type of asthma it must also be assumed that many bronchioles are obstructed.

There is therefore probably more than one site of airway obstruction. Thus there is evidence that in remission considerable obstruction may be present in peripheral airways, (McFadden and Lyons 1969; Woolcock et al, 1969; Levine et al, 1970), whereas, during an acute attack there is bronchographic evidence that central airways are narrowed (Dulfano and Hewetson, 1966; Epstein et al, 1948). The relative contribution that the larger and the smaller airways make, either singly or in combination, to the obstruction of the flow of air in the various stages of asthma remains to be determined. Although, the present study throws very little light on the mode of action of corticosteroids in asthma, the results indicate that obstruction was present both in the larger airways as shown by a marked reduction in SGaw and M.E.F.R., which are thought to reflect mainly upper airway changes, as well as in the peripheral airways as shown by the changes in M.M.F.R., a test, most determined by the smaller airways. The improvement is obvious from the maximum flow volume curves plotted against percentage of vital capacity (Fig. 21 - 23). However, the changes of flow rate at the actual vital capacity are larger than this representation suggests. When the same maximum expiratory flow volume curves are plotted against an absolute volume scale, which shows the decrease in TLC and RV after treatment (Fig. 24, 25 and 26,)the degree of improvement that has occurred is

even greater. Such a representation is also more accurate physiologically. As no volume displacement body plethysmograph was available absolute lung volumes were obtained from separate measurements of helium dilution methods as suggested by (Bouhuys et al, 1969). As can be seen from figures 24 - 26, parts of the lung which contributed little or nothing to flow before treatment made significant contributions after the prednisolone have been given.

Although the Vtg of the asthmatics studied was signficantly greater than the F.R.C. measured by closed circuit helium dilution, the difference between the two measurements was not very big. There have been a number of studies in which lung volumes in asthmatic patients have been measured by both methods, (Meisner and Hugh Jones, 1968; Herzog et al, 1968; Corbeel, 1968; Woolcock et al, 1971). These have ingeneral shown marked differences between the two methods. The patients on which these measurements were carried out had however acute asthma or asthma of a much more severe degree than that of the patients presented in this study. Woolcock et al, (1971) have suggested that the differences obtained between plethysmographic measurements and those obtained by helium dilution, probably depend on the development of non-communicating regions in asthma. In the present investigation, great care was taken to ensure that dilution of the helium was complete, by asking the patients to perform three relaxed vital capacity manoeuvres before the final helium reading was taken. Studies comparing plethysmographic with prolonged gas dilution methods of measuring

lung volumes have shown good agreement in patients with chronic airway obstruction (Tierney and Nadel, 1962; Ross et al, 1961). Thus in Tierney and Nadel's work the mean differences between Vtg and F.R.C. in a number of emphysematous patients was 990 ml when the open circuit N_2 dilution method for measuring F.R.C. was performed over seven minutes, but fell to 130 ml when this was prolonged to between twelve and eighteen minutes. This bears out Bedell's (1956) original suggestion that gas dilution methods, unless prolonged do not accurately measure the lung volume in some patients with chronic airway obstruction.

Throughout the group of patients studied in the present investigation the changes produced by the administration of corticosteroids on body plethysmographic measurements and flow volume curves were consistent in timing and degree with those produced in the FEV_1 and P.E.F.R. Although P.E.F.R. is an effort dependent manoeuvre, present results demonstrate that it is as sensitive an index of change as the more complicated measurements, provided the full co-operation of the patient in producing a maximal effort is ensured on each occasion.

The administration of prednisolone resulted in a consistent and significant improvement in PaO_2, $(A-a)DO_2$ and venous admixture effect. There was no significant correlation between PaO_2 and airway obstruction as measured by the FEV_1, P.E.F.R. or SGaw. A similar lack of correlation has been found by Rees, Millar and

Donald (1968) in their study of patients in status asthmaticus and by Shibel and Moser (1970) in patients with chronic airway obstruction. Alveolar ventilation showed no significant change. The changes in V_D/V_T ratio were small or negligible in all 5 patients studied. In a study of chronic asthmatic patients treated with isoprenaline and aminophylline, Tai and Read, (1967) reported a similar lack of change in V_D/V_T ratio, despite a marked difference in $(A-a)DO_2$. They claimed that in these particular circumstances, $(A-a)DO_2$ is a more sensitive index of change in ventilation-perfusion distribution.

Two of the patients, (H.K. and J.S.) attained normal PaO_2 values despite spirometric and plethysmographic evidence of persisting airway obstruction. Similar findings have been reported by Walabhji(1968) and Stanescu and Teculescu (1970) in some of the asthmatic patients they studied. Fulcihan and his co-workers (1967) studying chronic bronchitic patients who had been treated with betamethasone found significant improvement in PaO_2 and venous admixture effect with no change in FEV_1 and alveolar ventilation. Such an improvement in PaO_2 is probably due to a more uniform distribution of ventilation in relation to perfusion.

It is to be hoped that this work is not merely an interesting physiological exercise but that it may also have some important clinical connotations and perhaps contribute in a small way to the management of a disease which Thomas Willis (1677) described as "Asthma morbus maxime terribilis".

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(A) Introduction

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Bronchitic Patients

NAME N.A. AGE 61 yrs. WARD 8A DATE 19.5.71.

Chronic Bronchitis.

Predicted	TEST	0800hrs.	1500hrs	2100hrs	0800hrs	1500hrs.	2100hrs.	0800hrs.	1200hrs.	1500hrs.	1800hrs	2100hrs.	0900hrs.	2100hrs.
3.00	F.E.V.	1050	1250	900	1050	1200	1100	1200	1300	1250	1300	1225	1100	1200
4.050	F.V.C.	2050	2950	2000	2300	2700	2300	2900	3100	3100	3000	2750	2500	2800
525	P.F.R.	115	140	130	115	135	145	155	160	160	150	165	155	145
6.00	T.L.C.		6.020			6.590		6.100		7.120		7.050	6.800	
3.500	V.C.		3.100			2.750		2.600		3.850		3.250	3.300	
3.350	P.R.C.		4.780			4.540		4.700		4.570		4.600	4.350	
2.500	R.V.		3.570			3.840		3.800		3.270		4.800	3.500	
42%	R.V./ T.L.C.		53%			59%		59.5%		46%		54%	52%	
	Raw		3.5			3.02		3.67		3.02		3.20	3.67	
	Vtg		4.9			5.48		5.49		5.48		5.90	5.48	
	Gaw		0.385			0.331		0.272		0.331		0.312	0.272	
	SGaw		0.058			0.060		0.049		0.060		0.053	0.049	

NAME M.A. AGE 43 yrs. WARD 8A DATE 30.3.71

Chronic Bronchitis.

Predicted	TEST	0800hrs.	1500hrs	2100hrs.	0800hrs	1500hrs.	2100hrs.	0800hrs.	1200hrs.	1500hrs.	1800hrs	2100hrs.	0900hrs.	2100hrs.
3.60	F.E.V.	850	800	850	850	750	750	700	750	750	750	650	775	725
4.60	F.V.C.	2000	1950	1950	1600	2000	1900	1650	1500	1600	1550	1480	1700	1600
575	P.F.R.	155	140	150	150	160	160	185	145	155	160	155	160	150
6.30	T.L.C.		6.83			6.50		6.90		6.67		6.73	6.95	6.95
4.15	V.C.		2.10			2.15		2.45		2.55		2.60	2.47	
3.35	F.R.C.		5.55			5.43		5.65		5.25		5.28	5.65	
2.15	R.V.		4.73			4.35		4.55		4.12		4.13	4.47	4.50
34%	R.V./ T.L.C.		69%			67%		66%		62%		62%	64.5%	65%
	Raw		4.58			4.48		4.90		4.90		4.40	4.48	4.48
	Vtg		5.76			5.61		5.78		5.78		5.33	5.56	5.56
	Gaw		0.218			0.223		0.204		0.204		0.230	0.220	0.220
	SGaw		0.038			0.039		0.035		0.035		0.043	0.039	0.039

Appendix.

Table 1.

Individual body plethysmographic values obtained from twenty-six normal subjects.

	Raw ($cmH_2O/l/sec$)	Gaw ($l/sec/cmH_2O$)	Vtg. (l)	SGaw ($l/sec/cmH_2O/lVTG$)
Females				
Non-smokers				
1.	1.25	0.80	3.30	0.242
2.	0.96	1.04	4.20	0.247
3.	1.41	0.71	2.93	0.242
4.	1.20	0.83	3.22	0.257
5.	1.03	0.97	3.73	0.260
6.	1.20	0.83	2.95	0.281
7.	1.15	0.87	3.15	0.276
8.	0.87	1.12	3.45	0.333
ales				
Non-smokers				
9.	0.97	1.03	4.98	0.206
10.	0.97	1.03	4.73	0.218
11.	1.14	0.88	3.97	0.222
12.	0.98	1.02	3.78	0.270
13.	1.02	0.98	3.16	0.310
14.	0.92	1.09	4.66	0.234
15.	1.09	0.92	3.72	0.247
16.	1.12	0.89	4.60	0.193
17.	1.21	0.83	3.84	0.21
18.	1.30	0.77	3.80	0.202
19.	1.25	0.80	4.45	0.180
20.	1.25	0.80	3.62	0.220

Appendix.

Table 1.

cont.

	Raw ($cmH_2O/l/sec$)	Gaw ($l/sec/cmH_2O$)	Vtg. (l)	SGaw ($l/sec/cmH_2O/Vtg$)
Males				
Non-smokers				
21.	0.85	1.17	4.51	0.260
Males				
Smokers				
22.	1.44	0.69	3.50	0.198
23.	1.38	0.72	3.99	0.180
24.	1.60	0.63	3.50	0.180
25.	1.21	0.83	3.40	0.243
26.	1.54	0.65	4.05	0.160

Appendix.

Table (II)

Individual values obtained from 10 normal subjects on five different days. Analysis of variance in Table III in text.

SUBJECT	Vtg. (l)	Raw ($cmH_2O/l/sec$)	Gaw $l/sec/cmH_2O$	SGaw $l/sec/cm\ H_2O/l/vtg$
1. E.M.K.F.	4.10	1.00	1.00	0.240
	4.30	0.92	1.09	0.254
	4.23	0.95	1.05	0.248
	4.35	0.91	1.09	0.250
	4.18	0.93	1.07	0.255
2. P.G.	3.30	1.24	0.81	0.240
	3.50	1.19	0.84	0.240
	3.43	1.18	0.84	0.245
	3.37	1.27	0.78	0.231
	3.28	1.24	0.80	0.243
3. L.C.	2.85	1.52	0.66	0.230
	3.00	1.30	0.77	0.258
	2.91	1.28	0.78	0.268
	3.15	1.23	0.81	0.257
	2.97	1.25	0.80	0.269

Appendix

cont. Table II

SUBJECT	Vtg. (l)	Raw ($cmH_2O/l/sec$)	Gaw $l/sec/cmH_2O$	SGaw $l/sec/cm/H_2O/l/vtg$
4. M.G.	3.40	1.20	0.84	0.240
	3.20	1.30	0.770	0.240
	3.40	1.22	0.82	0.241
	3.62	1.19	0.84	0.232
	3.35	1.24	0.80	0.238
5.F.M.	3.97	1.14	0.88	0.222
	3.88	1.09	0.92	0.238
	3.86	1.10	0.90	0.233
	4.00	1.12	0.89	0.223
	3.79	1.09	0.91	0.240
6. G.D.	4.63	1.02	0.98	0.210
	4.83	0.91	1.10	0.228
	4.68	0.88	1.14	0.244
	4.68	0.92	1.09	0.234
	4.50	0.88	1.14	0.252
7. J.R.S.	3.22	1.00 0	1.00	0.310
	3.19	0.93	1.08	0.338

Appendix

cont.

Table (II)

SUBJECT	Vtg. (l)	Raw ($cmH_2O/l/sec$)	Gaw $l/sec/cmH_2O$	Sgaw $l/sec/cm/H_2O/l/vtg$
7. J.R.S.	3.00	1.10	0.91	0.302
	3.19	1.02	0.98	0.340
	3.21	1.04	0.96	0.300
8. R.C.B.	4.40	0.84	1.19	0.270
	4.38	0.79	1.27	0.290
	4.68	0.85	1.18	0.252
	4.55	0.83	1.20	0.266
	4.55	0.97	1.03	0.226
9. A.T.P.	3.69	1.10	0.91	0.247
	3.78	1.02	0.98	0.260
	3.60	1.13	0.89	0.248
	3.83	1.06	0.94	0.246
	3.71	1.16	0.87	0.234
10.D.B.	3.80	1.03	0.97	0.254
	3.71	0.97	1.03	0.278
	3.70	1.04	0.96	0.260
	3.77	0.94	1.06	0.288
	3.93	0.94	1.06	0.270

Appendix.

Experiment 2.

English Translation of experiment by R. Menzies (Tentamen Physiologicum Inaugurale de Respiratione; Edinburgh, 1790).

A strong and healthy man, 5ft. 8ins. tall, measuring 3ft. 3ins. round the thorax, was securely placed in the barrel ABCD (Figure 4), which was filled with water at a temperature of 90°F. up to that part of the man's neck which was most convenient for measuring the rise and fall of water. This was found to be 1.25 ins. His arterial pulsation, both before and after immersion was at the rate of 64 or 65 per minute, his respiration 14 or 14½ per minute, as had been frequently noted before. This remained constant for the two hours or more during which he was in the barrel. All this time he did not suffer any discomfort in breathing in and out or in any other respect. Indeed, throughout the experiment, the rise/fall of the water was found to remain constant, viz. 1.25 ins. When the man breathed in deeply he inhaled as much air as caused the water to flow over the edge of the cylinder. As the area of the cylinder was 55.41 sq. ins. and that of the man's neck 18; 55.41 - 18 x 1.25 = 46.76 c. ins. gives the volume of air normally breathed in by the man. This experiment was repeated three times, with practically the same result. I considered it necessary to carry out the experiment to test his respiration by means of the bag in case, for some reason or other, errors might have been committed.

NAME M.T. AGE 41 WARD 8A DATE 17.11.70.

Predicted	TEST	0800hrs.	1500hrs	2100hrs	0800hrs	1500hrs.	2100hrs.	0800hrs.	1200hrs.	1500hrs.	1800hrs	2100hrs.	0900hrs.	2100hr
3.51	F.E.V.				700	715	750	800	800	1000	1300	1150	850	700
4.62	F.V.C.				1950	1900	2000	2100	2550	2850	3750	3700	2500	1950
575	P.F.R.				80	60	60	75	115	130	140	135	100	75
6.40	T.L.C.					7.90		8.01		8.27		8.00	7.075	coughing and wheezing
4.25	V.C.					2.10		2.42		2.92		3.55	2.65	
3.35	F.R.C.					7.10		7.15		6.75		6.50	5.76	
2.15	R.V.					5.80		5.59		5.35		4.45	4.425	
34%	R.V./ T.L.C.					73%		69%		65%		50%	63%	
	Raw					5.320		5.320		3.320		3.690	4.380	
	Vtg					7.558		7.558		7.250		6.937	6.640	
	Gaw					0.187		0.187		0.301		0.271	0.228	
	SGaw					0.025		0.025		0.041		0.039	0.034	

NAME S.D. AGE 39 yrs. WARD 8 DATE 4.11.71

dicted	TEST	0800hrs.	1500hrs	2100hrs.	0800hrs	1500hrs.	2100hrs.	0800hrs.	1200hrs.	1500hrs.	1800hrs	2100hrs.	0900hrs.	2100hrs.
2500	F.E.V.	1060	950	1000	1100	975	1250	1250	1250	1550	1800	1300	1250	1200
3500	F.V.C.	1270	1500	1300	1400	1450	1500	1550	1500	2500	2700	2100	2000	1850
410	P.F.R.	160	145	140	120	165	180	180	180	305	325	270	250	200
4.450	T.L.C.		5.710			5.700		5.360		4.240		4.280	4.325	4.590
2.90	V.C.		1.950			1.850		1.950		2.575		2.325	2.300	2.100
2.30	F.R.C.		4.360			4.500		4.310		2.390		2.530	2.525	3.290
1.55	R.V.		3.760			3.850		3.410		1.655		1.955	2.025	2.490
34.8%	R.V./ T.L.C.		68%			67.5%		63.5%		39%		46%	47.2%	54%
	Raw		6.144			5.580		5.890		3.380		3.670	3.810	3.860
	Vtg		4.450			4.450		4.290		2.50		2.690	2.776	3.439
	Gaw		0.162			0.179		0.169		0.295		0.272	0.262	0.269
	SGaw		0.036			0.040		0.039		0.118		0.101	0.094	0.075

NAME B.R. **AGE** 62 yrs. **WARD** 8A **DATE** 20.11.71

Predicted	TEST	0800hrs.	1500hrs	2100hrs.	0800hrs	1500hrs.	2100hrs.	0800hrs.	1200hrs.	1500hrs.	1800hrs	2100hrs.	0900hrs.	2100hrs.
2600	F.E.V.	1400	1300	1050	1500	1400	1150	1500	1800	1850	1950	1750	1700	1700
3800	F.V.C.	2250	2500	2300	2600	2300	2250	2700	3100	3160	3400	2900	3000	2950
525	P.F.R.	200	210	195	230	215	210	225	250	255	295	275	260	250
5.750	T.L.C.		5.800			6.150		6.300		6.370		6.050	6.100	6.100
3.250	V.C.		2.600			3.050		3.100		3.530		3.200	3.200	3.100
3.350	F.R.C.		4.250			4.200		4.280		4.130		3.980	4.100	4.200
2.500	R.V.		3.200			3.100		3.200		2.840		2.850	2.900	3.000
43%	R.V./ T.L.C.		55.5%			50.5%		51%		45%		47.2%	47.4%	49.2%
	Raw		3.52			3.68		3.40		2.06		1.62	2.22	2.22
	Vtg		4.31			4.35		4.64		4.24		3.54	4.17	4.12
	Gaw		0.282			0.272		0.294		0.484		0.615	0.454	0.454
	SGaw		0.065			0.063		0.063		0.114		0.174	0.109	0.111

NAME M.E. **AGE** 43 yrs. **WARD** 8 **DATE** 19.7.71

Predicted	TEST	0800hrs.	1500hrs	2100hrs	0800hrs	1500hrs.	2100hrs.	0800hrs.	1200hrs.	1500hrs.	1800hrs	2100hrs.	0900hrs.	2100hrs
2750	F.E.V.	825	775	850	600	725	800	850	950	1150	1250	1075	1050	1000
3400	F.V.C.	2125	2150	2200	1900	2150	2000	2100	2000	2850	3100	2600	2450	2500
445	P.F.R.	110	90	105	125	110	95	120	135	175	180	170	155	130
4.900	T.L.C.		5.66			5.30		5.45		5.39		5.24	5.30	5.29
3.250	V.C.		2.36			2.23		2.33		2.72		2.56	2.55	2.56
2.330	F.R.C.		4.02			3.73		3.92		3.47		3.43	3.58	3.48
1.650	R.V.		3.30			3.07		3.12		2.67		2.60	2.75	2.73
34%	R.V./ T.L.C.		58%			58%		57.5%		50%		49.5%	52%	51.5%
	Raw		6.38			6.24		6.01		4.03		4.03	4.16	4.16
	Vtg		4.263			4.104		4.22		3.538		3.538	3.807	3.80
	Gaw		0.156			0.160		0.166		0.248		0.248	0.240	0.24
	SGaw		0.036			0.039		0.039		0.070		0.070	0.063	0.06

NAME M.J. AGE 76 yrs. WARD 8 DATE 6.5.72

Predicted	TEST	0800hrs.	1500hrs	2100hrs.	0800hrs	1500hrs.	2100hrs.	0800hrs.	1200hrs.	1500hrs.	1800hrs	2100hrs.	0900hrs.	2100hrs.
1.8	F.E.V.	950	1030	1050	1000	1050	800	800	1050	1330	1500	1150	1100	900
2.2	F.V.C.	1650	1530	1800	1450	1800	1700	1700	2000	2350	2650	2100	2100	1900
320	P.F.R.	160	180	170	170	180	185	165	210	240	265	220	230	185
4.0	T.L.C.		4.180			3.970		4.200		4.150		4.200	4.300	4.300
2.05	V.C.		2.250			1.720		1.900		2.300		2.200	2.000	1.800
2.3	F.R.C.		2.560			2.700		2.650		2.500		2.600	2.550	2.650
1,95	R.V.		1.930			2.250		2.300		1.850		2.000	2.300	2.500
49%	R.V./ T.L.C.		45%			57%		55%		45%		48%	53.5%	52.5%
	Raw		5.03			5.31		5.28		3.67		3.67	4.11	4.11
	Vtg		2.876			3.07		2.968		2.763		2.763	2.675	2.675
	Gaw		0.198			0.188		0.189		0.272		0.272	0.243	0.243
	SGaw		0.068			0.061		0.064		0.098		0.098	0.090	0.090

NAME R.M. AGE 73 yrs. WARD 8 DATE 12.5.71

elicted	TEST	0800hrs.	1500hrs	2100hrs	0800hrs	1500hrs.	2100hrs.	0800hrs.	1200hrs.	1500hrs.	1800hrs	2100hrs.	0900hrs.	2100hrs.
1.80	F.E.V.	625	700	500	800	825	750	800	1100	1000	1100	1000	1150	800
2.30	F.V.C.	1500	1600	1650	1800	1850	1600	1800	2050	1950	2000	1950	2050	1750
320	P.F.R.	80	60	60	105	110	95	125	150	150	160	140	155	110
4.15	T.L.C.		4.170			4.270		4.375		4.100		4.340	4.650	4.440
2.25	V.C.		1.70			1.80		1.850		1.850		1.850	1.950	1.900
2.30	F.R.C.		2.770			2.970		2.900		2.880		2.940	3.200	3.140
1.90	R.V.		2.470			2.470		2.525		2.250		2.490	2.700	2.540
46%	R.V./ T.L.C.		59%			58%		58.5%		55%		58.7%	58%	57.5%
	Raw		4.308			4.167		4.343		4.167		4.343	4.133	4.133
	Vtg		3.006			3.246		3.221		3.221		3.107	3.417	3.417
	Gaw		0.232			0.239		0.230		0.239		0.230	0.242	0.242
	SGaw		0.077			0.074		0.071		0.074		0.074	0.071	0.071

NAME H.N. AGE 24 yrs. WARD 8A DATE 14.10.70

redicted	TEST	0800hrs.	1500hrs	2100hrs	0800hrs	1500hrs.	2100hrs.	0800hrs.	1200hrs.	1500hrs.	1800hrs	2100hrs.	0900hrs.	2100hrs.
2.67	F.E.V.	2550	3000	3150	2850	3000	2900							
3.10	F.V.C.	3200	3850	3800	3500	3850	3550							
400	P.F.R.	350	380	380	360	365	370							
4.30	T.L.C.		4.41			4.13								
2.90	V.C.		3.37			3.45								
2.30	F.R.C.		2.57			2.08								
1.40	R.V.		1.04			0.68								
33%	R.V./ T.L.C.		24%			16%								
	Raw													
	Vtg													
	Gaw													
	SGaw													

NAME B.S. AGE 47 yrs. WARD 8A DATE

Predicted	TEST	0800hrs.	1500hrs	2100hrs	0800hrs	1500hrs.	2100hrs.	0800hrs.	1200hrs.	1500hrs.	1800hrs	2100hrs.	0900hrs.	2100hrs.
3400	F.E.V.	3000	3150	3200	3400	3385	3125							
4300	F.V.C.	4050	4000	4050	4200	4125	3950							
562	P.F.R.	495	540	535	580	580	575							
6.00	T.L.C.		6.25											
4.30	V.C.		3.86											
2.50	F.R.C.		4.92											
1.70	R.V.		2.39											
28%	R.V./ T.L.C.		38%											
	Raw		2.52											
	Vtg		5.36											
	Gaw		0.39											
	SGaw		.072											

NAME D.M. AGE 51 yrs. WARD 8 DATE 1.3.71

redicted	TEST	0800hrs.	1500hrs	2100hrs	0800hrs	1500hrs.	2100hrs.	0800hrs.	1200hrs.	1500hrs.	1800hrs	2100hrs.	0900hrs.	2100hrs.
2.25	F.E.V.	680	550	500										
2.65	F.V.C.	1280	1100	975										
370	P.F.R.	120	95	70										
3.72	T.L.C.		4.20											
2.12	V.C.		2.50											
2.02	F.R.C.		2.30											
1.60	R.V.		2.70											
43%	R.V./ T.L.C.		41%											
	Raw		5.95											
	Vtg		3.52											
	Gaw		0.17											
	SGaw		.048											

(1) M.T. 41 yrs.

MAXIMUM EXPIRATORY FLOW VOLUMES CURVES.

	0800 hrs.	1200hrs.	1500hrs.	1800hrs.	2100hrs.		0900hrs.	2100hrs.
% VC	Flow in litres.							
80	0.56	0.62	0.94	1.33	1.04		0.62	
60	0.45	0.45	0.73	1.02	0.84		0.52	
50	0.41	0.40	0.65	0.92	0.62		0.48	
40	0.38	0.38	0.50	0.82	0.73		0.38	
20	0.25	0.25	0.40	0.61	0.52		0.25	
M.E.F.R % V.C.	1.1 100%	1.52 91%	2.34 91%	2.5 91%	2.5 95%		1.65 94%	

MAXIMUM EXPIRATORY FLOW VOLUMES [illegible]RVES.

(2) S.D. 30 yrs.

	0800 hrs.	1200hrs.	1500hrs.	1800 [illegible]	2100hrs.	0900hrs.	2100hrs.
% VC	Flow in litres.						
80	1.50	2.80	3.10	3.56	3.20	2.10	1.30
60	0.90	1.40	2.00	2.30	2.00	1.40	0.60
50	0.60	1.00	1.40	1.70	1.33	1.00	0.50
40	0.30	0.70	1.00	1.28	1.08	0.60	0.30
20	0.15	0.30	0.50	0.50	0.44	0.30	0.20
M.E.F.R.	1.8	3.5	3.84	4.0	3.4	2.74	2.0
% V.C.	86%	83.5%	83.5%	85%	84.5%	95%	95%

MAXIMUM EXPIRATORY FLOW VOLUME CURVES.

(3) B.R. 62 yrs.

	0800 hrs.	1200hrs.	1500hrs.	1800 hrs	2100hrs.	0900hrs.	2100hrs.
% VC	Flow in litres.						
80	2.00	2.80	2.80	3.80	3.80	2.80	2.40
60	1.20	1.40	1.40	2.60	2.00	1.60	1.57
50	1.00	1.20	1.20	1.60	1.60	1.20	1.20
40	0.80	0.80	0.80	1.20	1.20	0.60	0.60
20	0.40	0.40	0.40	0.60	0.60	0.40	0.40
M.E.F.R.	4.20	4.80	4.80	5.40	5.20	5.00	4.40
% V.C.	94%	92%	92%	90%	93%	93%	96%

(4) M.E. 43 yrs. MAXIMUM EXPIRATORY FLOW VOLUMES CURVES.

	0800 hrs.	1200hrs.	1500hrs.	1800 hrs.	2100hrs.	0000hrs.	2100h
% VC	Flow in litres.						
80	1.17	1.50	1.45	1.67	1.57	1.28	1.4
60	0.50	0.75	0.75	1.00	0.86	0.71	0.77
50	0.30	0.60	0.60	0.80	0.64	0.50	0.60
40	0.17	0.37	0.37	0.67	0.43	0.43	0.43
20	0.10	0.13	0.13	0.30	0.14	0.14	0.13
M.E.F.R.	1.67	1.86	2.2	3.0	2.28	2.0	2.1
% V.C.	92%	90%	89%	89%	91%	95%	96%

MAXIMUM EXPIRATORY FLOW VOLUMES CU. ES.

(5) M.J. 76 yrs.

	0800 hrs.	1200hrs	1500hrs.	1800hrs.	2100hrs	0900hrs.	2100hrs.
% VC	Flow in litres.						
80	2.12	2.25	2.25	2.80	2.88	2.45	1.00
60	0.70	0.75	1.00	1.34	1.00	1.02	0.50
50	0.47	0.50	0.76	0.94	0.75	0.55	0.37
40	0.24	0.37	0.50	0.67	0.50	0.30	0.25
20	0.12	0.13	0.13	0.27	0.12	0.22	0.13
M.E.F.R	3.30	4.25	4.75	5.20	4.75	4.22	3.75
% V.C.	93%	94%	93%	91%	91%	92%	93%

MAXIMUM EXPIRATORY FLOW VOLUMES CURVES.

(6) M.R. 73 yrs.

	0800 hrs.	1200hrs	1500hrs.	1800hrs.	2100hrs.	0900hrs.	2100hrs.
% VC	Flow in litres.						
80	1.53	1.88	2.10	2.20	1.40	1.40	1.33
60	0.90	1.00	1.30	1.20	0.80	0.70	0.80
50	0.60	0.80	1.10	0.96	0.60	0.50	0.50
40	0.30	0.50	0.70	0.70	0.30	0.30	0.30
20	0.20	0.38	0.40	0.40	0.20	0.20	0.20
M.E.F.R.	1.90	238	2.30	2.70	2.30	1.80	2.16
% V.C.	95%	95%	89%	91%	96%	95%	95%

Individual results obtained in second stage of study.

Pred. Spirometric measurements from Cotes, J. Lung Function,

Blackwell Scientific Publications, 1968.

1 H.B. 14 yrs. 1.11.71.

		PLACEBO				PLACEBO				PREDNISOLONE							PLACEBO			
Predicted	TEST	0900	1500	1800	2100	0900	1500	1800	2100	0900	1000	1100	1200	1500	1800	2100	0900	1500	1800	2100
420	PFR	240	230	260	270	240	280	275	260	270	270	320	320	345	350	290	280	300	290	280
2850	FEV_1	2000	2100	1700	1800	1700	1500	1800	1750	1700	1800	2250	2250	2350	2500	2300	2000	2100	2000	1875
3300	FVC	2450	2600	2300	2400	2225	1950	2300	2300	2300	2300	2700	2700	2700	3000	2900	2500	2500	2600	2600
	VC	2500	2500	2400	2500	2300	2400	2400	2400	2600	2600	2900	2900	2850	3300	3100	2600	2600	2600	2600
	Vtg	3.20	2.98	3.15	3.20	3.10	3.25	3.30	3.09	3.15			2.92	2.86	2.64	2.64	3.10			3.30
	Raw	2.65	2.74	2.70	2.68	2.72	2.68	2.70	2.74	2.72			2.45	2.13	2.10	1.86	2.25			2.65
	Gaw	.370	.360	.370	.370	.360	.370	.370	.360	.360			.404	.470	.476	.540	.450			.380
	SGaw	.115	.120	.177	.115	.116	.114	.112	.117	.114			.139	.164	.180	.203	.145			.115

2. K.H. 38 yrs. 30.4.72.

		PLACEBO				PLACEBO				PREDNISOLONE							PLACEBO			
	TEST	0900	1500	1800	2100	0900	1500	1800	2100	0900	1000	1100	1200	1500	1800	2100	0900	1500	1800	2100
380	PFR	85	85	85	95	100	110	90	100	100	100	105	125	150	170	120	135	120	130	130
2420	FEV_1	600	500	600	650	750	750	800	650	700	750	850	1000	1350	1250	1000	1000	950	975	850
2800	FVC	1500	1400	1400	1450	1900	2100	2000	2075	2000	2200	2200	2200	2500	2700	2300	2000	2000	1900	2000
	VC	2350	1900	2050	2000	2325	2300	2300	2200	2200	2400	2400	2400	2600	2800	2300	2200	2200	2100	2200
	Vtg	3.76	3.50	3.53	3.45	3.58	3.72	3.56	3.68	3.68			3.68	3.24	2.78	2.86	3.45			3.53
	Raw	3.62	3.52	3.71	3.83	3.72	3.62	3.73	3.58	3.56			3.26	3.10	2.83	2.90	3.36			3.62
	Gaw	.276	.284	.269	.268	.268	.276	.268	.279	.280			.306	.322	.353	.345	.297			.276
	SGaw	.073	.081	.076	.075	.074	.074	.075	.075	.076			.083	.099	.127	.120	.086			.078

3. M.V. 50 yrs. 2.12.71.

	PLACEBO				PLACEBO				PREDNISOLONE							PLACEBO			
TEST	0900	1500	1800	2100	0900	1500	1800	2100	0900	1000	1100	1200	1500	1800	2100	0900	1500	1800	2100
PFR	95	110	105	115	120	115	110	105	110	115	130	145	145	160	120	130	140	135	135
FEV_1	625	650	450	700	750	575	650	650	700	700	775	850	975	975	900	800	850	850	850
FVC	1200	975	900	1100	1025	1000	900	900	1100	1100	1500	1700	1975	2000	1900	1800	1800	1800	1850
VC	1450	1500	1500	1450	1500	1450	1450	1500	1500	1750	1650	1875	2100	2100	2000	1900	1875	1850	1850
Vtg	4.39	4.26	4.36	4.39	4.26	4.34	4.18	4.26	4.38			4.38	4.12	3.78	3.78	4.28			4.36
Raw	6.01	5.86	5.74	5.88	5.86	5.75	5.64	5.86	5.88			5.54	5.36	4.82	4.20	5.18			5.74
Gaw	0.166	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17			0.18	0.18	0.20	0.20	0.19			0.17
SGaw	0.037	.039	.039	.387	.039	.039	.042	.040	.038			.041	.045	.054	.054	.045			.039

No. 4 M.N. 44 yrs 28.10.71

	PLACEBO				PLACEBO				PREDNISOLONE							PLACEBO			
TEST	0900	1500	1800	2100	0900	1500	1800	2100	0900	1000	1100	1200	1500	1800	2100	0900	1500	1800	2100
PFR	345	340	360	370	350	360	330	365	350	360	380	465	535	495	380	370	350	355	360
FEV_1	2300	2375	2200	2100	2300	2100	2250	1850	2100	2250	2575	2900	3300	3250	2950	2300	2200	2150	2100
FVC	4200	4000	4000	3800	4100	3900	4000	3800	4000	4100	4800	4925	5000	5100	4800	4400	4100	4100	4200
VC	4300	4100	4000	4100	4100	4150	4150	3900	4200	4200	5100	5300	5250	5200	4800	4200	4200	4200	4200
Vtg	4.60	4.25	4.50	4.55	4.45	4.70	4.40	4.50	4.50			4.20	4.00	3.50	3.60	3.80			4.10
Raw	4.20	3.90	4.00	4.18	4.15	4.10	4.20	4.00	4.20			3.80	3.20	2.40	3.20	3.50			4.00
Gaw	0.24	.250	.250	.240	.240	.240	.240	.250	.240			.263	.310	.420	.310	.285			.250
1/Gaw	.052	.058	.056	.052	.054	.051	.054	.056	.053			.062	.077	.119	.080	.075			.060

No. 5. A.L. 25 yrs. 4. 11.71

		PLACEBO				PLACEBO				PREDNISOLONE							PLACEBO			
	TEST	0900	1500	1800	2100	0900	1500	1800	2100	0900	1000	1100	1200	1500	1800	2100	0900	1500	1800	2100
400	PFR	215	190	220	215	185	195	225	220	210	225	275	300	320	345	250	260	270	270	260
2700	FEV_1	1600	2050	1800	1700	1700	1550	1750	1800	1800	1800	2050	2500	2550	2700	2200	2200	2100	2100	2250
3100	FVC	2600	2900	2700	2800	2900	3000	2700	2900	2800	2900	3400	3550	3550	3650	3300	3300	3100	3100	3200
	VC	3000	3000	2900	2900	3000	3100	2900	3000	3000	3000	3500	3750	3750	3700	3400	3400	3350	3100	3200
	Vtg	3.82	3.64	3.76	3.76	4.01	3.82	3.94	3.78	3.82			3.36	3.18	3.18	3.26	3.64			3.82
	Raw	4.25	4.10	4.22	4.17	4.26	4.15	4.18	4.10	4.14			3.26	2.20	2.20	2.53	3.17			3.64
	Gaw	.235	.243	.237	.239	.234	.240	.239	.243	.241			.306	.454	.454	.395	.315			.274
	SGaw	.061	.066	.063	.063	.058	.062	.060	.064	.063			.091	.143	.143	.121	.086			.072

6. F.G. 43 yrs. 27.3.72

		PLACEBO				PLACEBO				PREDNISOLONE							PLACEBO			
Pred.	TEST	0900	1500	1800	2100	0900	1500	1800	2100	0900	1000	1100	1200	1500	1800	2100	0900	1500	1800	2100
525	PFR	115	130	120	125	130	125	115	100	120	120	120	135	155	155	125	120	120	105	100
2900	FEV_1	700	550	800	650	950	1000	700	600	700	700	700	720	775	950	850	650	650	600	600
3800	FVC	2300	2600	2650	2200	2650	2400	2300	2100	2500	2500	2600	2600	2850	2950	3100	2200	2300	2310	2300
	VC	3500	3500	3400	3000	3450	2850	3450	3100	3100	3100	3000	3200	3675	3625	3500	3000	2800	2800	2600
	Vtg	4.33	4.28	3.98	4.16	4.26	4.28	4.28	4.32	4.28			3.87	3.64	3.41	3.41	3.98			4.28
	Raw	3.60	3.71	3.72	3.65	3.71	3.71	3.71	3.64	3.71			3.45	3.34	3.10	3.10	3.65			3.72
	Gaw	.270	.269	.268	.273	.269	.269	.269	.274	.269			.289	.299	.323	.323	.273			.268
	SGaw	.062	.063	.067	.065	.063	.062	.062	.063	.063			.074	.082	.094	.060	.068			.062

7. G.W. 24.3.72

Pred.	TEST	PLACEBO 0900	1500	1800	2100	PLACEBO 0900	1500	1800	2100	PREDNISOLONE 0900	1000	1100	1200	1500	1800	2100	PLACEBO 0900	1500	1800	2100
480	PFR	155	165	155	150	150	130	165	135	155	165	180	300	300	310	210	220	160	160	165
2350	FEV_1	950	1100	1000	1200	775	1000	750	1150	1200	1300	2200	2350	2400	2200	2000	2000	1350	1250	1250
2600	FVC	1800	2300	2150	2300	975	2200	1600	2300	2400	2500	3100	3250	3250	3200	3000	2900	2500	2400	2400
	VC	2500	2500	2500	2400	1400	2300	2300	2450	2500	2800	3200	3250	3300	3300	3200	3100	2900	2800	2700
	Vtg	3.40	3.12	3.06	3.25	3.36	3.18	3.21	3.16	3.28			3.16	2.87	2.64	2.58	2.86			3.16
	Raw	3.71	3.56	3.68	3.64	3.66	3.66	3.68	3.63	3.62			3.35	3.18	2.25	2.18	3.12			3.27
	Gaw	0.27	0.28	0.27	0.27	0.27	0.27	0.27	0.27	0.27			.298	0.31	0.45	0.46	0.32			0.30
	SGaw	.079	.089	.088	.083	.080	.085	.084	.085	.082			.094	.108	.168	.177	.112			.094

8. S.J. 47 yrs. 1.5.72.

Pred.		PLACEBO				PLACEBO				PREDNISOLONE							PLACEBO			
	TEST	0900	1500	1800	2100	0900	1500	1800	2100	0900	1000	1100	1200	1500	1800	2100	0900	1500	1800	2100
500	PFR	245	215	240	230	195	260	255	230	240	290	310	335	390	425	290	300	290	300	300
2800	FEV_1	1175	1150	900	1075	900	1350	1175	1050	1100	1300	1575	1550	1625	1950	1600	1550	1550	1500	1400
3460	FVC	2300	2000	2000	1900	2250	2240	2250	1900	2200	2600	2750	2850	3000	3000	2600	2500	2500	2500	2500
	VC	2350	2400	2350	2200	2600	2700	2200	2200	2400	2750	2800	2900	3100	3100	2900	2700	2700	2600	2600
	Vtg	4.26	3.88	3.86	4.12	3.84	4.16	4.24	4.06	4.24			3.84	3.66	3.34	3.26	3.86			4.16
	Raw	4.11	3.92	3.96	4.10	3.92	4.12	4.04	3.96	3.92			3.56	3.42	3.02	2.94	3.56			3.96
	Gaw	.243	.255	.252	.243	.255	.242	.247	.252	.255			.280	.292	.331	.340	.280			.252
	SGaw	.057	.065	.065	.058	.066	.058	.058	.062	.060			.073	.08	.099	.104	.072			.060

9. B.W. 38 yrs. 27.1.72

		PLACEBO				PLACEBO				PREDNISOLONE							PLACEBO			
Pred.	TEST	0900	1500	1800	2100	0900	1500	1800	2100	0900	1000	1100	1200	1500	1800	2100	0900	1500	1800	2100
550	PFR	215	220	205	205	190	170	120	120	120	135	135	135	120						
3400	FEV_1	1600	1825	1550	1550	1350	1300	950	1000	1000	1000	1000	950	950						
4200	FVC	3500	3250	3125	3200	3200	3155	2900	3050	3100	3150	3000	3000	3000						
	VC	3800	3500	3400	3350	3300	3355	3250	3450	3315	3300	3150	3200	3175						
	Vtg	4.67	4.78	4.60	4.60	4.93	4.88	4.78	4.85	4.93			4.86	4.86						
	Raw	4.73	4.51	4.85	4.85	5.16	4.94	4.51	5.24	5.16			4.77	4.77						
	Gaw	.211	.221	.206	.206	.193	.202	.221	.190	.193			.209	.209						
	SGaw	.045	.046	.044	.044	.039	.041	.046	.039	.039			.043	.403						

Acute attack of dyspnoea.

10. G.A. 68 yrs. 18.3.72

Pred.	TEST	PLACEBO 0900	1500	1800	2100	PLACEBO 0900	1500	1800	2100	PREDNISOLONE 0900	1000	1100	1200	1500	1800	2100	PLACEBO 0900	1500	1800	2100
475	PFR	140	135	135	115															
2250	FEV_1	540	575	500	500															
3150	FVC	2100	1950	1500	1400															
	VC	2650	2450	1875	1750															
	Vtg	3.95	4.63	4.63	4.82															
	Raw	4.33	4.87	4.87	5.24															
	Gaw	.230	.205	.205	.190															
	SGaw	.058	.044	.044	.039															

An acute attack of wheezing.

11. L.R. 63 yrs. 4.4.72.

Pred.	TEST	PLACEBO 0900	1500	1800	2100	PLACEBO 0900	1500	1800	2100	PREDNISOLONE 0900	1000	1100	1200	1500	1800	2100	PLACEBO 0900	1500	1800	2100
475	PFR	350	310	265																
2500	FEV_1	1950	1855	1850																
3340	FVC	2875	2600	2650																
	VC	3050	2960	2900																
	Vtg	3.80	3.95	3.95																
	Raw	4.70	4.78	4.78																
	Gaw	.210	.209	.209																
	SGaw	.055	.053	.053																

12. M.R. 32 yrs. 10.5.72

Pred.	TEST	PLACEBO 0900	1500	1800	2100	PLACEBO 0900	1500	1800	2100	PREDNISOLONE 0900	1000	1100	1200	1500	1800	2100	PLACEBO 0900	1500	1800	2100
390	PFR 375	420	460	460																
2350	FEV_1 2275	2550	2550	2600																
2900	FVC 3400	3500	3500	3450																
	VC 3550	3500	3500	3600																
	Vtg 3.45	3.30	3.30	3.42																
	Raw 1.86	1.52	1.52	1.81																
	Gaw .537	.657	.657	.552																
	SGaw .155	.199	.199	.161																

PEFR post - Hydrocortisone.

ent.	0hr.	1hr.	2hrs.	3hrs.	4hrs.	5hrs.	6hrs.	7hrs.	8hrs.	9hrs.	10hrs.	11hrs.	1
H.	270	285	285	300	300	370	370	350	325	335	290	280	26
.H.	140	245	280	315	300	340	325	325	300	275	280	240	180
M.V.	145	150	150	155	165	170	190	180	175	170	170	170	155
M.N.	385	430	450	465	485	480	510	470	465	430	425	420	400
A.L.	255	300	320	310	340	340	315	305	305	300	280	280	280
F.G.	110	115	130	130	150	145	125	120	120	115	110	110	90
G.W.	175	190	190	210	280	300	290	265	265	240	265	230	100
S.J.	280	425	460	490	500	510	525	445	445	420	390	350	290